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Associations between sedentary time, physical activity and cardiovascular health in six-year-old children born to mothers with increased cardiometabolic risk

Running head: Child physical activity and CV health

Original Research

Abstract

Purpose: To assess associations between sedentary time (ST), physical activity (PA), and cardiovascular health in early childhood.

Method: Cross-sectional study including 160 children (age 6.1 years (SD 0.5), 86 boys, 93 maternal BMI ≥ 30kg/m^2 and 73 gestational diabetes) assessed for pulse wave velocity (PWV), echocardiography, ultra-high frequency 48-70 MHz vascular ultrasound, and accelerometery.

Results: Boys had 385 (SD 53) min/day ST, 305 (SD 44) min/day light PA, 81 (SD 22) min/day moderate-to-vigorous PA (MVPA). Girls had 415 (SD 50) min/day ST, 283 (SD 40) min/day light PA, 66 (SD 19) min/day MVPA. In adjusted analyses, MVPA was inversely associated with resting heart rate (β=-6.6; 95%CI -12.5,-0.7), and positively with left ventricular mass (β=6.8; 1.4-12.3), radial intima-media thickness (IMT, β=11.4; 5.4-17.5), brachial IMT (β=8.0; 2.0-14.0), and femoral IMT (β=1.3; 0.2, 2.3). MVPA was inversely associated with body fat percentage (β=-3.4; -6.6, -0.2), diastolic blood pressure (β=-0.05; -0.8,-0.1), femoral (β=-18.1; -32.4,-0.8) and radial (β=-13.4; -24.0,-2.9) circumferential wall stress in boys only. ST and PWV showed no significant associations.

Conclusions: In young at risk children, MVPA is associated with cardiovascular remodelling, partly in a sex-depended way, likely representing physiological adaptation, but ST shows no association with cardiovascular health in early childhood.

Introduction

Beneficial effects of physical activity on cardiovascular (CV) health are extensively reported in adulthood. Physical activity triggers physiological cardiac and vascular remodelling, [1–4] impacts traditional CV risk factors, [5,6] and lowers all-cause CV mortality. [7–9] Current preventive guidelines recommend physical activity prescription in adults of all ages. [10,11]

The World Health Organization recommends an average of 60 min/day of moderate-to-vigorous physical activity across the week in children from 5 years of age. [11] Previous observational and interventional studies reported positive effects of moderate-to-vigorous physical activity on child health, however, associations with different aspects of child CV health were inconsistent, particularly during early childhood. [12–14] This could be partially attributed to the wide range of studied age groups and methodological discrepancies, but nonoptimal quality of evidence, including a subjective physical activity assessment, could also play a role. [12] The effect of light physical activity on child CV risk and circulatory system, however, is less understood and not addressed in the current World Health Organization guidelines. [11] Finally, the unfavourable effect of sedentary time on child CV health has been frequently documented, but the lack of high-quality data warrant further studies. [15]

The evidence linking sedentary time and physical activity with heart morphology in children is limited to adolescents and young athletes, while the effect of physical activity in younger children is less understood. [16–20] Associations between objectively measured sedentary time, physical activity, and child arterial morphology and function remain the matter of research, as previous studies reported conflicting results. [21]

Previous studies reported early increase in left ventricular mass, arterial wall thickness, and arterial stiffness in children and adolescents with obesity, hypertension, kidney disease, and type 1 diabetes. [22–24] Early cardiac and vascular remodelling related to nonoptimal cardiometabolic health in otherwise healthy children, their role as subclinical markers of CV diseases, and finally the potential to reverse unfavourable remodelling with physical activity during childhood are important public health concerns to address.

In this study of 6-year-old children (N=160) born to mothers with increased risk of cardiovascular disease (pre-gestational BMI ≥ 30 kg/m^2 or history of gestational diabetes) we aimed to assess associations between objectively measured sedentary time, light and moderate-to-vigorous physical activity, traditional cardiometabolic risk factors, cardiac morphology, arterial wall layers thickness, and arterial stiffness.

Material and methods

Study design

This is a cross-sectional analysis of data from a longitudinal observational follow up study. Participants originate from the randomized interventional trial RADIEL (Finnish Gestational Diabetes Prevention Study). Detailed study design and short-term results were previously reported. [25–27] Briefly, women planning a pregnancy or in the first half of pregnancy with pre-pregnancy obesity (BMI ≥ 30 kg/m^2) or with a history of gestational diabetes were prospectively recruited from 2008 to 2011. Participants were randomized into an intervention group, with diet and physical activity counselling, or a control group receiving standard care only. Exclusion criteria were age < 18 years, multiple pregnancy, diabetes diagnosed before pregnancy, use of regular medication affecting glucose metabolism, physical disability, severe psychiatric disorder, current substance abuse and difficulty cooperating due to inadequate language skills.

The cardiovascular 6-year-follow-up was designed as an observational study of mother-child pairs with an equal number of children exposed and unexposed in utero to gestational-diabetes-related metabolic disturbances. Consecutive participants were invited until a prespecified cohort size (~200) was reached (June 2015 - May 2017). Exclusion criteria were a subsequent ongoing pregnancy or haemodynamically significant heart defect in a child. The Helsinki University Hospital Ethics Committee for gynaecology and obstetrics, paediatrics and psychiatry approved the research protocol (20/13/03/03/2015) for the six-year follow-up assessment. Informed written consent was obtained at enrolment separately from mothers and child parents/guardians, and child assent to participate was ascertained orally during the study visits.

Body size and composition

Height and weight were measured with electronic devices (Seca GmbH & Co. KG, Germany) and child BMI Z-scores were calculated in reference to the recent Finnish paediatric dataset. [28] Body composition (lean body mass, fat mass) was assessed by bioelectrical impedance during a separate visit (InBody 720, InBody Bldg, Korea) and using a previously validated equation based on anthropometric measurements obtained at the time of cardiac and vascular examinations. [29] The equation-based values were used in the analysis of cardiac and vascular data. Body fat percentage was calculated as (weight – lean body mass)/weight.

Blood pressure (BP)

Resting BPs were measured in the sitting position from the right arm with cuffs appropriate for child size using oscillometry (Omron M6W, Omron Healthcare Europe B.V., The Netherlands). Child BP Z-scores were generated according to guidelines. [30,31]

Blood tests

Blood samples for plasma glucose and lipids were taken during morning hours in the fasting state. Results from three children with uncertain fasting compliance (concurrently excessively high triglycerides, fasting glucose, and low glycated haemoglobin A1c (HbA_{1C})) were excluded from the analysis. Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were assessed with standard hospital laboratory enzymatic assays (Roche Diagnostics, Basel, Switzerland).

Physical activity

Physical activity was measured with the hip-worn accelerometer (ActiGraph GT3X, ActiGraph, Pensacola, USA) and available in 160 children (80%) due to participants refusal to wear the monitor or monitor not returned to investigators. Caregivers were instructed to ensure monitors working during waking and sleeping hours. Nocturnal sleeping time was eliminated from the analysis based on diaries. Monitors collected data at 30 Hz sample rate. The data were normally filtered, converted into 10 s epoch counts and analysed using Evenson (2008) cut-points for physical activity intensity (sedentary < 100 cpm, light > 100 cpm, moderate > 2296 cpm, vigorous > 4012 cpm; where cpm is count per minute). [32] Valid measurement was defined as at least two weekdays and one weekend day (with a minimum of 480 minutes of recording per day). Non-wear time was set to 30 minutes of consecutive zeros. Light, moderate, vigorous physical activity time and sedentary time was calculated as weighted mean value [(average min/day of weekdays × 5 + average min/day of weekend day × 2)/7] and, in addition, as % of the total wearing time. Recent data on physical activity in Finnish population were used as a reference.[33]

Energy intake

Children energy intake was based on 3-day food records held by their caretaker, and a childcare provider if the child attended day care. Ingredients in the recipes of the day-care meals were inquired from the day-care kitchen. Energy intake was derived from calculations in a nutritional calculation software, AivoDiet (versions 2.0.1.5 and 2.2.0.1, Aivo Finland Oy, Turku, Finland). This software utilizes the food composition database maintained by the Finnish Institute for Health and Welfare (www.fineli.fi).

Echocardiography and resting heart rate

Children were examined by one experienced paediatric cardiologist (TS) with Vivid 7 (GE Healthcare, Horten, Norway) using a 5 MHz 5S sector transducer. Images were stored in the raw-format and analysed offline by one experienced observer (LL) blinded to maternal and child characteristics with EchoPAC (version 113, GE Healthcare). Images were obtained and measurements performed according to guidelines. [34,35] Cardiac outcome variables include resting heart rate, left ventricular mass and volumes, and left atrial volume. Left ventricular mass and volumes were calculated based on B-mode recordings from parasternal short axis view at the level of mitral valve leaflet tips using Devereux and Teichholz formulas, respectively. [36] Left atrial volume was calculated with the biplane area-length method at ventricular end-systole. Heart rate was recorded in the supine position during echocardiography.

Vascular ultrasound

Ultra-high frequency ultrasound images of arteries (right radial and brachial, femoral and common carotid arteries bilaterally) were obtained by one skilled investigator using 25, 35, and 55 MHz transducers with the Vevo 770 system, and using UHF22, UHF48, and UHF70 (similar centre frequencies) with the Vevo MD system (VisualSonics, Toronto, Canada). Images were analysed offline using Vevo 3.0.0 (Vevo 770) and VevoLab (Vevo MD) software with manual electronic calipers using the leading edge technique to obtain end-diastolic arterial lumen diameter and far-wall intima-media thickness (IMT). [37] Intra-observer coefficients of variations (CV) ranged 1.2–2.9% for LD and 6.9–9.1% for IMT, inter-observer CV ranged 1.5–4.6% for LD and 6.0–8.2% for IMT. Further, common carotid lumen diameter was measured in both peak systole and end-diastole to assess local carotid artery beta-stiffness index and distensibility coefficient. Systolic and diastolic BP for elastic property calculations were recorded during ultrasound imaging in supine position from the right arm with oscillometry (Dinamap ProCare 200, GE) using appropriately sized cuffs. Distensibility coefficient [%/10 mmHg] and beta-stiffness index were calculated using the following formulas:

$$carotid\ artery\ distensibility\ coefficient = 100\ x\ \frac{(CCALAS - CCALAD)/CCALAD}{(SBP - DBP)}$$

$$carotid\ artery\ beta - stiffness\ index = \frac{\ln\left(\frac{SBP}{DBP}\right)}{(CCALDS - CCALDD)/CCALDD}$$

Where CCALAS and CCALAD are common carotid artery lumen area in systole and diastole respectively, CCALDS and CCALDD are common carotid artery lumen diameter in systole and diastole respectively, and SBP and DBP are systolic and diastolic BP. [38] Intra-observer CV was 5.4% for CDC and 5.9% for stiffness index, and inter-observer CV was 11.9% for distensibility coefficient and 12.8% for stiffness index. Mean circumferential wall stress (CWS, kPa) was calculated according to Lamé’s equation as follows:

$$CWS = \frac{(SBP\ + 2\ x\ DBP)}{3} \times \frac{LDD}{2IMT}$$

Where LDD is artery lumen diameter in end-diastole, IMT – intima-media thickness, and SBP and DBP are systolic and diastolic BP. [39]

Pulse Wave Velocity

PWV was measured using mechanosensors (Complior Analyse, Alam Medical, Saint-Quentin-Fallavier, France). [40] Sensors were set at the right carotid, right radial and right femoral arteries to assess central (right carotid-femoral) and peripheral (right carotid-radial) transit times and PWV was then calculated as previously reported. [41] CV for repeat measurements was 3.5% for carotid-femoral PWV and 4.8% for carotid-radial PWV.

Data analysis

Data are presented as mean ± SD, median (interquartile range) or as a count (percentage). All continuous variables were assessed for normal distribution based on histograms and normal Q-Q plots. First, we stratified participants according to moderate-to-vigorous physical activity quartiles, which allowed us to compare CV health in children with different levels of physical activity (1st vs 4th quartile). Independent samples t-test and Mann–Whitney U-test were used, as appropriate. Then associations between sedentary time, physical activity (light, moderate, vigorous, moderate-to-vigorous) and CV health were analysed using multivariable linear regression models: crude (N=160), adjusted for body composition (N=160), and fully adjusted (body composition, age, LDL, HDL, triglycerides, HbA_{1C}, systolic and diastolic BP Z-scores, energy intake, and maternal BMI, N=130). Multicollinearity was assessed with the Variance Inflation Factor (accepted if <3.5). Associations between physical activity and sex in relation to body composition, cardiac and vascular outcomes were analysed with multiple linear regression. Statistical analysis was performed with SPSS, IBM, version 25 and GraphPad Prism version 8.4.3.

Results

Child characteristics are presented in Table 1 and Supplemental Table S1. The subcohort included in the analysis (N=160) did not significantly differ from non-participants (N=41) in the physical activity assessment in terms of anthropometrics, body composition, BP, metabolic, or cardiovascular characteristics (Supplemental Table S2). BMI Z-score, systolic and diastolic BP Z-scores were higher in comparison to reference population and every 1 in 4 children was overweight or obese (Table 1). We observed significantly shorter duration of sedentary time and longer duration of physical activity of all intensities in boys than in girls (Table 1, Supplemental Table S3).

Associations between sedentary time, CV risk factors, and circulatory system

Sedentary time was not independently associated with child cardiometabolic profile, arterial IMT, CWS or stiffness (Supplemental Tables S4-5).

Associations between light physical activity, CV risk factors, and circulatory system

Light physical activity [h/day] was inversely associated with LV mass, LV mass index, and LV mass Z-score in girls, but not in boys, after adjusting for child body composition, systolic BP Z-score, energy intake, blood fasting lipids and HbA_{1C}, and maternal BMI (multivariable linear regression models; β=-5.1, p=0.04; β=-3.2, p=0.04; β=-0.5, p=0.03; respectively). Light physical activity displayed no independent statistically significant associations with BPs, metabolic profile, arterial IMTs, CWSs or stiffness parameters (Supplemental Tables S5-6).

Associations between moderate-to-vigorous physical activity and CV risk factors

Lean body mass was higher ($p< 0.001$), body fat percentage lower ($p< 0.05$), systolic BP similar but diastolic BP lower ($p< 0.05$) in children in the 4th quartile of moderate-to-vigorous physical activity duration in comparison to children in 1st quartile (Supplemental Table S6). Moderate-to-vigorous physical activity was inversely associated with body fat percentage in boys, but not in girls, after adjusting for child body composition, systolic BP Z-score, energy intake, blood fasting lipids and HbA_{1C}, and maternal BMI (Table 2). Moderate-to-vigorous physical activity was inversely associated with diastolic BP in boys, but not in girls, when adjusting for child body composition, systolic BP Z-score, energy intake, blood fasting lipids and HbA_{1C}, and maternal BMI (multivariable linear regression model; β=-0.05, *p*=0.02). Moderate-to-vigorous physical activity showed no association with fasting glucose, HbA_{1C} or lipids (Supplemental Table S4).

Associations between moderate-to-vigorous physical activity and cardiac structure and function

Resting heart rate was lower (*p*=0.002), left ventricular mass index higher (*p*=0.006), left ventricular mass Z-score higher (*p*=0.007), and left ventricular diastolic volume higher (*p*=0.01) in children in the 4th quartile of moderate-to-vigorous physical activity duration in comparison to children in 1st quartile. However, we observed no difference in relative wall thickness and left ventricular volume/mass ratio between groups consistent with increased eccentric left ventricular mass being associated with moderate-to-vigorous physical activity duration (Supplemental Table S7). Moderate-to-vigorous physical activity was inversely associated with resting heart rate and positively associated with left ventricular mass after adjusting for child body composition, systolic BP Z-score, energy intake, blood fasting lipids and HbA_{1C}, and maternal BMI in the total child cohort (Table 3).

Associations between moderate-to-vigorous physical activity and arterial IMT and function

Children in moderate-to-vigorous physical activity 4th quartile had thicker femoral, brachial, and radial artery IMT in comparison to children in 1st quartile (*p*=0.02, *p*=0.04, *p*<0.001; respectively), but femoral and radial artery CWS were comparable and brachial artery CWS was lower in 4th quartile (*p*=0.009, Supplemental Table S7).

Moderate-to-vigorous physical activity was associated with femoral, brachial, and radial artery IMTs after adjusting for lean body mass and body fat percentage. Only radial IMT remained significant in the fully adjusted model (Table 4).

Moderate-to-vigorous physical activity was inversely associated with femoral (β=-18.1, *p*=0.01) and radial artery (β=-13.4, *p*=0.01) CWS in boys, but not in girls, when adjusting for child body composition, systolic BP Z-score, energy intake, blood fasting lipids and HbA_{1C}, and maternal BMI (Supplemental Table S8). Moderate-to-vigorous physical activity was not associated with carotid IMT and CWS, nor with central or peripheral PWV.

Discussion

We present associations between objectively measured sedentary time, light and moderate-to-vigorous physical activity, and cardiovascular health in this cross-sectional analysis of six-year-old children born to mothers with increased cardiometabolic risk.

First, we show that associations with child cardiovascular health parameters are mainly observed for moderate-to-vigorous physical activity levels in healthy early childhood. This was related with lower resting heart rate and an eccentric increase in left ventricular mass consistent with physiological adaptation as the underlying mechanism. This is consistent with previously reported observations in adolescents, however, study in young soccer players also showed a tendency to left ventricular concentric remodelling.[16,19] Femoral, brachial, and radial IMT showed weak associations with moderate-to-vigorous physical activity in analyses adjusted for body size and composition. In the fully adjusted models these associations were diluted to non-significant levels, and this could partly be explained by the reduced sample size (N160 vs N130) due to lack of consent for fasting blood sampling in some children. Observed peripheral arterial layer associations are likely, like left ventricular mass, related with physiological remodelling, as we found no evidence for concurrent CWS increase. Further studies in larger group are warranted to verify these observations in young children. We further hypothesize that the extent of cardiac adaptation in the growing child could be determined by duration and quality of physical activity (spontaneous vs. structured, static vs. dynamic components).

Second, we showed moderate-to-vigorous physical activity to be associated with adiposity and diastolic BP in boys, but not in girls. The sex-dependent associations could be related with the dose of physical activity, as boys were significantly more active than girls – a previously reported trend. [33,42] Assuming longitudinal tracking of physical activity from early childhood to adulthood and possible implications for CV health, and public health in general, this trend warrants further studies.[43]

Noteworthy, there is little data on the effect of sedentary time or light physical activity on CV health in early childhood. [19] The present study attempted to address this, but was unable to show any associations between sedentary time, light physical activity and CV health, adiposity or the metabolic profile. We observed, however, a negative association between light physical activity and left ventricular mass in girls, but the clinical significance of this finding is not clear. Sedentary time has been previously linked to unfavourable changes in cardiometabolic health in older children and adolescents [19,44]. The lack of associations in our early childhood study sample could then be related with them emerging later during child development.

We were unable to detect sedentary time or any physical activity related associations with carotid artery IMT or different arterial stiffness measures which seems in contrast with our above mentioned consistent positive associations between moderate-to-vigorous physical activity and left ventricular mass and more peripheral artery wall layer associations. This is similar to previous studies reporting no association between quantitatively measured physical activity and carotid IMT in children of school age.[45,46] A negative association between carotid IMT and time-weighted sports-related metabolic equivalents among 5-year-old children has, however, been reported in a study relying on physical activity data collected by questionnaires with no sustained effect observed at the 8-year-old follow-up. [47] There is then limited and conflicting data on physical activity and vascular form and function in young pre-school and school-aged children with variable applied methodology challenging the comparison between studies. [21] When reviewing the literature, we were unable to identify studies analysing associations between objectively assessed physical activity and carotid and peripheral arterial wall layer thickness in early childhood making this study novel.

The cohort included in this study does not represent the general population. We, however, consider the study population at risk for cardiovascular disease later in life warranting the evaluation of cardiovascular health already during early childhood. The relatively small sample size, with missing blood tests in 15-20% of children, is another limitation. The inclusion of paternal and sibling cardiovascular characteristics, family socioeconomical status, as well as in-depth assessment of more long-term child physical activity prior to study visits could have provided data to improve our analyses. However, due to young age the focus of our assessment was not to study the influence of sport-related physical activity on CV health, but rather focus on CV health relations with objectively assessed spontaneous physical activity during early childhood. The strengths of this study include the comprehensive assessment of cardiovascular risk, cardiac and arterial structure and function, including peripheral vessel imaging using improved ultra-high frequency arterial wall layer imaging methodology specifically validated for this age group combined with objective accelerometery assessed physical activity.

In conclusion, in a young population at risk for cardiovascular disease physical activity behaviours differ between boys and girls. Cardiovascular remodelling seems mainly associated with moderate-to-vigorous physical activity and is consistent with physiological adaptation observable in both left ventricular mass as well as arterial layer thickness already in early childhood. We were, however, unable to show associations between sedentary time or light physical activity and adiposity or cardiovascular health parameters in early childhood.

Table 1. Participant characteristics and accelerometer-derived sedentary time and physical activity.

	All N=160	**Girls** N=74	**Boys** N=86
Age [years]	6.1 ± 0.5	6.1 ± 0.5	6.0 ± 0.5
Height [cm]	118.6 ± 6.7	118.3 ± 6.4	118.9 ± 6.9
Weight [kg]	23.2 (5.0)	23.1 (5.0)	23.5 (5.0)
BMI Z-score	**0.45 ± 0.92** [d] ***	0.51 ± 0.81	0.40 ± 1.00
Overweight (ISO-BMI 25-30) [a]	33 (21%)	12 (16%)	21 (24%)
Obese (ISO-BMI >30) [a]	11 (7%)	2 (3%)	9 (11%)
Lean body mass [kg]	17.1 ± 2.3	16.8 ± 2.3	17.5 ± 2.3
Body fat [%]	16.7 ± 5.2	18.7 ± 5.0	**14.9 ± 4.8** ***
Systolic blood pressure Z-score	**0.42 ± 0.70** [d] ***	0.43 ± 0.58	0.41 ± 0.80
Diastolic blood pressure Z-score	**0.45 ± 0.64** [d] ***	0.45 ± 0.58	0.44 ± 0.69
Fasting glucose [mmol/L] [b]	5.0 ± 0.3	5.0 ± 0.3	5.0 ± 0.4
HbA$_{1C}$ [%]	5.2 ± 0.3	5.2 ± 0.3	5.2 ± 0.3
LDL [mmol/L]	2.4 (0.7)	2.4 (0.9)	2.4 (0.7)
HDL [mmol/L]	1.5 (0.5)	1.5 (0.5)	1.5 (0.4)
Total cholesterol [mmol/L]	4.0 (0.9)	4.0 (1.0)	4.0 (0.9)
Triglycerides [mmol/L]	0.7 (0.4)	0.8 (0.4)	0.7 (0.5)
Sedentary time [min/day]	399 ± 53	415 ± 50	**385 ± 53** ***
Light physical activity [min/day] [c]	295 ± 43	283 ± 40	**305 ± 44** **
Moderate physical activity [min/day]	50 ± 14	45 ± 11	**55 ± 14** ***
Vigorous physical activity [min/day]	22 (16)	21 ± 9	**26 ± 12** **
Moderate to vigorous physical activity [min/day]	74 ± 22	66 ± 19	**81 ± 22** ***
Moderate to vigorous physical activity > 60 min/day [N]	116 (73%)	46 (62%)	**70 (81%)** **

Data presented as mean ± SD, median (IQR), or N (%).

Girls vs. boys t-test, or Fisher's exact test *p* ** < 0.01, *** < 0.001.

BMI indicates body mass index, **HbA$_{1C}$** – glycated haemoglobin A$_{1C}$, **LDL** – low- density lipoprotein, **HDL** – high-density lipoprotein.

[a] ISO-BMI age and sex- specific BMI values corresponding with adult BMI. [28]

[b] Blood results missing in 15-20% of cohort.

[c] Physical activity intensity levels defined by Evenson (2008) cut-points. [32]

[d] p in reference to general population. [28,31]

Table 2. Associations between body fat percentage and moderate-to-vigorous physical activity (MVPA) during early childhood (linear multivariable regression models).

		Model 1	**Model 2**
		N=160	**N=130**
All			
Body fat [%]	*Model adjusted R^2*	0.096	0.14
	MVPA [60 min/day] Beta (95% CI)	-5.2 (-7.9, -2.4)	-4.8 (-7.2, -2.0)
	p-value	**< 0.001**	**0.001**
Girls			
Body fat [%]	*Model adjusted R^2*	-0.012	0.094
	MVPA [60 min/day] Beta (95% CI)	-1.6 (-7.2, 4.1)	-1.3 (-7.5, 4.9)
	p-value	0.6	0.7
Boys			
Body fat [%]	*Model adjusted R^2*	0.098	0.288
	MVPA [60 min/day] Beta (95% CI)	-4.5 (-7.8, -1.3)	-3.4 (-6.6, -0.2)
	p-value	**0.007**	**0.04**

Model 1 – crude

Model 2 – adjusted for lean body mass, age, systolic and diastolic blood pressure Z-score, LDL, HDL, triglycerides, HbA_{1C}, energy intake, maternal BMI.

LBM indicates lean body mass, **MVPA** – moderate to vigorous physical activity

Moderate-to-vigorous PA defined by physical activity Evenson (2008) cut-points. [32]

Table 3. Associations between resting heart rate, left ventricular mass and moderate-to-vigorous physical activity (MVPA) in early childhood (linear multivariable regression models).

		Model 1 **N=160**	**Model 2** **N=130**
All			
Heart rate [beat/min]	*Model adjusted R^2*	0.02	0.12
	MVPA [60 min/day] Beta (95% CI)	-5.0 (-9.4, -0.5)	-6.6 (-12.5, -0.7)
	p-value	**0.03**	**0.03**
Left ventricular mass [g]	*Model adjusted R^2*	0.02	0.37
	MVPA [60 min/day] Beta (95% CI)	5.3 (0.3, 10.3)	6.8 (1.4, 12.3)
	p-value	**0.04**	**0.01**
Girls			
Heart rate [beat/min]	*Model adjusted R^2*	-0.01	0.02
	MVPA [60 min/day] Beta (95% CI)	-1.8 (-9.2, 5.7)	-8.2 (-20.6, 4.1)
	p-value	0.6	0.19
Left ventricular mass [g]	*Model adjusted R^2*	-0.01	0.33
	MVPA [60 min/day] Beta (95% CI)	2.0 (-5.6, 9.6)	7.3 (-2.9, 17.5)
	p-value	0.6	0.16
Boys			
Heart rate [beat/min]	*Model adjusted R^2*	0.03	0.14
	MVPA [60 min/day] Beta (95% CI)	-6.0 (-12.3, 0.3)	-6.8 (-14.8, 1.3)
	p-value	0.06	0.10
Left ventricular mass [g]	*Model adjusted R^2*	0.004	0.31
	MVPA [60 min/day] Beta (95% CI)	4.3 (-3.1, 11.7)	5.1 (-2.9, 13.0)
	p-value	0.25	0.21

Model 1 – crude

Model 2 – adjusted for body composition, age systolic and diastolic blood pressure Z-score, LDL, HDL, triglycerides, HbA_{1C}, energy intake, and maternal BMI.

MVPA indicates moderate to vigorous physical activity

Moderate-to-vigorous PA defined by physical activity Evenson (2008) cut-points. [32]

Body composition (lean body mass, body fat percentage) was assessed with the previously validated equation based on measurements acquired at the day of echocardiography examination. [29]

Table 4. Associations between arterial intima-media thickness (IMT) and moderate-to-vigorous physical activity (MVPA) in early childhood (linear multivariable regression models).

		Model 1	**Model 2**	**Model 3**
All		N=160	N=160	N=130
Femoral artery	*Model adjusted R^2*	0.03	0.09	0.13
IMT [µm]	*MVPA [60 min/day] Beta (95% CI)*	1.3 (0.2, 2.3)	1.3 (0.2, 2.3)	0.8 (-0.5, 2.2)
	p-value	**0.02**	**0.02**	0.2
Brachial artery	*Model adjusted R^2*	0.04	0.29	0.23
IMT [µm]	*MVPA [60 min/day] Beta (95% CI)*	8.8 (2.0, 15.6)	8.0 (2.0, 14.0)	6.9 (-1.6, 15.4)
	p-value	**0.01**	**0.009**	0.1
Radial artery	*Model adjusted R^2*	0.10	0.16	0.12
IMT [µm]	*MVPA [60 min/day] Beta (95% CI)*	13.0 (6.8, 19.1)	11.4 (5.4, 17.5)	10.2 (1.6, 18.8)
	p-value	**< 0.001**	**< 0.001**	**0.02**
Girls				
Femoral artery	*Model adjusted R^2*	0.03	0.07	0.10
IMT [µm]	*MVPA [60 min/day] Beta (95% CI)*	1.1 (-0.5, 2.7)	1.2 (-0.4, 2.8)	0.9 (-1.5, 3.2)
	p-value	0.2	0.1	0.5
Brachial artery	*Model adjusted R^2*	0.05	0.24	0.22
IMT [µm]	*MVPA [60 min/day] Beta (95% CI)*	10.5 (0.7, 20.2)	10.1 (1.3, 18.9)	6.4(-10.1,18.5)
	p-value	**0.04**	**0.03**	0.6
Radial artery	*Model adjusted R^2*	0.10	0.19	0.15
IMT [µm]	*MVPA [60 min/day] Beta (95% CI)*	14.0 (4.7, 23.5)	13.2 (4.3, 22.1)	6.8 (-8.1, 21.6)
	p-value	**0.004**	**0.004**	0.4
Boys				
Femoral artery	*Model adjusted R^2*	-0.01	0.06	0
IMT [µm]	*MVPA [60 min/day] Beta (95% CI)*	0.5 (-1.0, 2.1)	0.7 (-0.8, 2.2)	0.7 (-1.3, 3.3)
	p-value	0.5	0.3	0.5
Brachial artery	*Model adjusted R^2*	-0.01	0.24	0.13
IMT [µm]	*MVPA [60 min/day] Beta (95% CI)*	2.4 (-7.8, 12.7)	5.2 (-3.8, 14.2)	5.8 (-7.4, 19.1)
	p-value	0.6	0.3	0.4

Radial artery IMT [μm]	*Model adjusted R^2*	0.02	0	0
	MVPA [60 min/day] Beta (95% CI)	6.9 (-2.1, 16.0)	7.3 (-2.0, 16.5)	9.5 (-3.2, 22.1)
	p-value	0.1	0.1	0.1

Model 1 – crude

Model 2 – adjusted for lean body mass, body fat percentage.

Model 3 – adjusted for child age, lean body mass, body fat percentage, HbA_{1C}, LDL, HDL, triglycerides, energy intake, and maternal BMI.

IMT indicates intima-media thickness, **MVPA** – moderate to vigorous physical activity

Moderate-to-vigorous PA defined by physical activity Evenson (2008) cut-points. [32]

Body composition (lean body mass, body fat percentage) was assessed with the previously validated equation based on measurements acquired at the day of echocardiography examination. [29]

Table 5. Associations between arterial circumferential wall stress (CWS) and moderate-to-vigorous physical activity (MVPA) in early childhood (linear multivariable regression models).

		Model 1	**Model 2**	**Model 3**
All		N=160	N=160	N=130
Femoral artery	*Model adjusted R^2*	0.01	0.01	0.02
CWS [kPa]	*MVPA [60 min/day] Beta (95% CI)*	-5.2 (-13.0,2.6)	-4.7 (-12.6,3.3)	-6.9 (-18.0,4.3)
	p-value	0.2	0.3	0.2
Brachial artery	*Model adjusted R^2*	0.03	0.05	0.06
CWS [kPa]	*MVPA [60 min/day] Beta (95% CI)*	-10.0 (-18.3,-1.6)	-8.1 (-16.6,0.4)	-4.1 (-15.6,7.4)
	p-value	**0.02**	0.06	0.5
Radial artery	*Model adjusted R^2*	0.04	0.11	0.06
CWS [kPA]	*MVPA [60 min/day] Beta (95% CI)*	-7.7 (-13.3,-2.1)	-5.9 (-11.5,-0.4)	-5.3 (-13.3,2.7)
	p-value	**0.008**	**0.04**	0.2

Model 1 – crude

Model 2 – adjusted for lean body mass, body fat percentage

Model 3 – adjusted for child age, lean body mass, body fat percentage, HbA_{1C}, LDL, HDL, triglycerides, energy intake, and maternal BMI

CWS indicates circumferential wall stress, **MVPA** – moderate to vigorous physical activity

Moderate-to-vigorous PA defined by physical activity Evenson (2008) cut-points. [32]

Body composition (lean body mass, body fat percentage) was assessed with the previously validated equation based on measurements acquired at the day of echocardiography examination [29]

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