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Title

Associations between objectively measured physical activity intensity across childhood and measures of sub-clinical atherosclerosis in adolescence: the European Youth Heart Study

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Abbreviations:

Carotid Intima media thickness (cIMT), Cardiovascular disease (CVD), Physical activity (PA), European Youth Heart Study (EYHS), carotid compliance (CC), Young's elastic modules (YEM),

Key words: Intima media thickness, carotid stiffness, metabolic syndrome, exercise

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Abstract

Objectives: There is paucity in prospective studies investigating the association between carotid sub-clinical atherosclerosis across childhood. Therefore the aim was investigate the association between physical activity (PA) intensity across childhood and sub-clinical atherosclerosis in adolescence.

Study design: This was a prospective study of a sample of 254 children (baseline age 8-10 y) with a six year follow-up. The cumulative exposure and the change in minutes spend in moderate-and-vigorous and vigorous PA intensity were measured using the Actigraph activity monitor. Sub-clinical atherosclerosis progression was expressed as carotid intima thickness (cIMT), carotid arterial stiffness and secondarily as a metabolic risk z-score. The summed z-score included a homoeostasis model assessment score of insulin resistance (HOMA-IR), triglycerides, total cholesterol to high-density lipoprotein ratio, inverse of cardio-respiratory fitness, systolic blood pressure and the sum of four skinfolds.

Results: No associations were observed between PA intensity variables and cIMT or carotid arterial stiffness ($p>0.05$). Neither change in PA intensity nor accumulated minutes of moderate-and-vigorous PA intensity was associated to the metabolic risk z-score in adolescence ($p>0.05$). However, a significant inverse association was observed between accumulated minutes of vigorous PA and the metabolic risk z-score in adolescence independent of gender, and biological maturity (std. beta= -0. 19 $p=0.01$).

Conclusion: Accumulation of or changes in minutes spend at higher PA intensities across childhood was not associated to measures of sub-clinical atherosclerosis in the carotid arteries in adolescence. Our observations suggest that a high volume of vigorous PA across childhood independently associated with lower metabolic CVD risk in adolescence.

Introduction

Increased carotid intima thickness (cIMT) and arterial stiffness in adults are associated to future cardio vascular disease (CVD) events independent of conventional risk factors (1, 2). The physical activity (PA) level declines across childhood into adolescence (3). Little is known about how physical activity across childhood affects arterial health later in life as no studies, to the best of our knowledge, have investigated the longitudinal association between PA from childhood to adolescence and adolescent carotid arterial stiffening and cIMT. Several cross-sectional studies between arterial health and physical activity (PA) have been conducted in children, but the observations have been inconsistent (4-8). The vast majority of these studies have assessed PA using self-report. Self-reported PA is susceptible to non-differential misclassification and is particularly vulnerable to recall bias in childhood (9). This would thus introduce a regression dilution bias and PA should therefore be assessed objectively.

The purpose of the study is to investigate the longitudinal associations between PA intensity across childhood sub-clinical atherosclerosis in adolescence. More specifically, the primary aim of the study is to investigate the association between cumulative exposure of and changes in objectively measured moderate-and-vigorous and vigorous PA across childhood into adolescence and carotid arterial stiffening and cIMT. Secondarily we investigated the association between the change in and cumulative exposure to objectively measured moderate-and-vigorous and vigorous PA from childhood to adolescence and a composite metabolic CVD risk score in adolescence in a sample of Danish children from the European Youth Heart Study (EYHS).

Methods

Participants and design

This is a prospective study using data from the Danish part of EYHS. EYHS is an international population-based mixed longitudinal study that addresses biological, environmental demographic and lifestyle correlates and determinants of cardiovascular disease risk factors in children and adolescents. Detailed description of the EYHS and the sampling procedures has been described in detail elsewhere (10). In 2003-2004 709 9-year old children were randomly sampled and invited to take part in the study. A total of 458 adolescents participated (65% participation). A six-year follow-up was conducted in 2009-2010, where all invitees were re-invited to participate. At follow-up ultrasonography was added to the protocol. At follow-up, a total of 399 subjects agreed to participate. The present study reports on 254 participants (55% of baseline participation) with complete data on exposures, and carotid measures of sub-clinical atherosclerosis. For the secondary analyses fasting blood samples were only available in 205 participants. The study was approved by the Regional Scientific Ethical Committee for Southern Denmark and data was collected according the Helsinki declaration. All participants gave a written informed consent.

Carotid arterial properties

The carotid arterial properties were measured using ultrasonography (Model Logic e, 12L-RS probe (5-13 MHz, 12 MHz used) GE Medical) according to guidelines for user procedures (11). Before the measurements, participants rested for 10 minutes in a quiet temperature controlled room. The arterial properties were conducted at the lateral and posterior position of the common carotid artery, 10 mm (cIMT) and 20 mm (for arterial stiffness measures) proximal to the beginning of the carotid bulb on both the right and the left common carotid artery. Carotid IMT was obtained at the far wall of the artery. All examinations were performed by a single trained operator. Intra-reader

coefficients of variation were 5.7 %, 4.5% and 4.5% for IMT, systolic and diastolic diameter, respectively.

Images from seven to eight cardiac cycles were stored offline for quantification of carotid artery diameters and the cIMT. The analyses were performed by a blinded trained reader, using commercially available analysis software (Vascular Research Tools 5, Medical Imaging Applications, LLC). cIMT and carotid artery diameters were obtained from the best quality image. Peak-systolic (DS), end-diastolic (DD) arterial diameter and cIMT were obtained from both positions. The mean of both positions and both sides was used for the subsequent analysis. If the quality of the image in one side was insufficient to obtain data (N=27; 7%), the opposite side was used for analysis. These participants did not differ significantly from the total sample in any of the outcome measures (data not shown).

Brachial systolic and diastolic blood pressures were obtained from the right arm at the end of the examination in a supine position (Welch Allyn Vital Signs monitor 300 series, Kivex, Hoersholm Denmark) by a trained operator using an appropriate cuff size. Brachial pulse pressure (PP) was calculated as systolic minus diastolic blood pressure. The compliance coefficient (CC), and Young's elastic modules (YEM) was calculated as follows (2, 12);

1) $\mathrm{CC} = \pi * (\mathrm{DS}^2 - \mathrm{DD}^2)/(4 * \mathrm{PP})$
2) $\mathrm{YEM} = \mathrm{DD}/(\mathrm{IMT} * \mathrm{CD})$

CVD risk factors and metabolic CVD risk score

Weight and height were measured while the participants were wearing light clothing, without shoes, using standard anthropometric procedures. Skinfold thickness was measured with a Harpenden caliper at the biceps, triceps, subscapular, and suprailiac sites. Blood pressure was measured with a

Dinamap paediatric and adult neonatal vital signs monitor (model XL, Critikron, Inc, Tampa, FL, USA). Five measurements were taken at two-min intervals after resting for five minutes while seated. The mean of the final three measurements was used in the analyses. Cardio-respiratory fitness was determined by the watt-max test - an indirect maximal cycle ergometer test and expressed relative to body weight (watts/kg). The protocol has been described in detail elsewhere (10). Criteria defined for a maximal effort were heart rate of at least 185 beats per minute and a subjective judgment by the test personal that the participant could no longer continue.

After overnight fasting, blood samples were drawn in the morning from the antecubital vein. Samples were aliquoted and separated within 30 min and stored at −22 °C for a maximum of 4 hours. Then it was stored at −80 °C until they were transported to a World Health Organization–certified laboratory in Cambridge, United Kingdom, for analysis. Samples were analyzed for serum glucose, insulin, HDL and triglyceride. Triglyceride was analyzed using the lipase/glycerol kinase/glycerol phosphate oxidase enzymatic method. HDL was analyzed using the homogeneous polyanion/cholesterol esterase/oxidase enzymatic method. Glucose was analyzed using the hexokinase method. Blood lipids and glucose were measured on an Olympus AU600 autoanalyzer (Olympus Diagnostica, Hamburg, Germany). Insulin was analyzed using enzyme immunoassay (micro-titer plate format, Dako Diagnostics, http://www.dako.co.uk). Insulin resistance was estimated according to the homoeostasis model assessment (HOMA) and calculated as the product of fasting glucose (mmol/L) and insulin (μU/mL) divided by 22.5 (13).

For the secondary analysis a continuous metabolic CVD risk z-score was calculated. The z-score was calculated based on a previously published definition, thus included HOMA, triglyceride, total cholesterol to HDL ratio, the sum of four skinfolds, cardio-respiratory fitness (inverted) and systolic blood pressure (14). Standardization in adulthood was done according to the baseline distribution (mean and SD) of each risk factor. As HOMA-IR, triglyceride and the sum of

four skinfolds were positively skewed, they were transformed before standardization using the natural logarithm.

Physical activity

PA intensity was assessed using the Actigraph physical activity monitor (Pensacola, USA, FL). The model AM7164 was used in 2003-2004, whereas the models GT3X or model GT1M were used in 2009-2010. Data were extracted using one-minute-epochs for the subsequent intensity analyses. The participants were instructed to wear the monitor for at least five consecutive days and only remove it during showering, bathing and swimming or during night time sleep. The PA variables were adjusted for within-week variation as described previously (15). All activity files were screened using open-source software (Propero v.1.0.18). Consecutive strings of zero >60 min were defined as "activity monitor not worn" and were removed. Subsequently, activity files not meeting the inclusion criteria of three valid days were excluded. A valid day should include at least 9 h 30 min (60% of daily awake time).

PA intensity was expressed as minutes per day spent in different intensity intervals. The minutes were adjusted proportionally to a full day of 13.5 hours (the mean wear time for this population), as described elsewhere (16). The cut points for time spent in moderate-and-vigorous PA (4 > Mets) and vigorous PA (>6 Mets) intensities were determined using published cut points (17). This yielded the following cut points for moderate-and-vigorous PA (>3000 cpm) and vigorous PA (> 5200 cpm).

Other covariates

Soft drink, fruit and vegetable intake (servings/week) and smoking status (yes/no) were obtained using a computerized questionnaire (10). Family history of CVD (parental and maternal) (yes/no)

and parental and maternal educational level were obtained using self-report by the parents. Parental educational level was defined according to the International Standard Classification of Education (ISCED-A) (UNESCO 2011). As the details obtained of the description of education was insufficient, the ISCED level 0, 1 and 2 were grouped, level 3, 4 and 5 were grouped, and level 6, 7 and 8 were grouped into three levels in the analysis. The highest parental educational level of the mother or father was used in the analysis. Biological maturity was subjectively assessed according to Tanner's classification. More specifically the boys rated their biological maturity on the basis of genital and pubic hair development and girls on the basis of breast and pubic hair development using schematic illustrations (18). At baseline TV viewing-time during leisure was obtained by self-report. Two questions were asked about the amount of time viewing TV (before and after school). A summary variable of daily TV viewing time (hours/day) was constructed based on these two questions.

Statistics

Baseline descriptive statistics were calculated for participants with valid data on exposure and outcome and for excluded participants. Exclusion criteria were; 1) drop-out, 2) drop-in and 3) incomplete or invalid data on relevant exposures or outcomes. Group differences were analyzed using independent t-tests, Wilcoxon's rank sum test or chi-squared test when appropriate.

Associations between the outcomes and cumulative exposure to or changes in exposures across childhood were analyzed using multiple linear regression analyses. Analyzing the mean exposure across childhood, we performed an analysis adjusted for gender and biological maturation at follow-up (model 1). Using changes in exposure level we further adjusted for baseline exposure level. We did not observed any gender interaction ($p>0.1$), thus the associations are presented for both gender combined. As none of the potential confounders; parental educational

status, frequency of vegetable, fruit, familiar history of CVD were related to either exposure or outcome (data not shown), they were not included in the models in order to preserve power. Therefore, we additionally adjusted the models for parental soda consumption and TV-viewing time (model 2).

Manual inspections of plots of exposure against outcomes and inspection of components-plus-residual plots did not reveal any non-linear relationships. Variance inflation factors did not reveal any signs of collinearity between covariates. All statistical analyses were performed in STATA 11.2 (STATA Corp. Fort Valton TX) with alpha=0.05 (two-sided).

Results

Baseline characteristics for included and excluded subjects are shown in Table 1. Excluded participants (N=222) did not differ from the included participants, except for the excluded boys who displayed a slightly lower systolic blood pressure ($p<0.05$) and the excluded girls who displayed slightly less accepted PA wear time ($p<0.05$) compared to the included participants. Adolescence outcome measures, mean PA intensity and change herein are described in Table 2. Boys had larger cIMT, carotid compliance, mean PA intensity (moderate-and-vigorous and vigorous) and a steeper decrease PA intensity (moderate-and-vigorous and vigorous) at follow-up compared to girls ($p<0.05$). Drop-in (N=75) did not differ from the included participants in any of the outcomes or PA intensity at follow-up ($p>0.1$), (data not shown).

We first analyzed the association between baseline PA exposure and cIMT or the measures of carotid stiffness adjusted for gender, and biological maturity at follow-up. No associations were observed between either baseline moderate-and-vigorous PA nor vigorous PA and adolescence cIMT or any of the measures of carotid stiffness ($p<0.05$).

Table 3 shows the association between cumulative exposure to and change in PA intensity from childhood to adolescence and measures of sub-clinical atherosclerosis in adolescence. No associations were observed between moderate-and-vigorous or vigorous PA and cIMT or any measures of carotid stiffness ($p>0.05$).

The secondary analysis revealed that mean vigorous PA across childhood was significantly associated to adolescence clustered risk z-score in adolescence ($p<0.05$) (Table 3). A one-SD (6.3 min) increment in the cumulative exposure to vigorous PA was associated with a 0.19 SD lower clustered risk z-score in adolescence. Further adjustment for baseline soda consumption and TV-viewing time attenuated the association slightly (std. beta= -0.16, $p=0.03$). Analyzing this association across quintiles of the cumulative exposure to vigorous PA revealed that only the most active participants had a significantly lower metabolic risk z-score in adolescence compared to the least active adjusted for gender, pubertal development, childhood soda consumption and TV-viewing time ($p<0.05$) (Figure 1). No significant associations were observed between the cumulative exposure to or change in moderate-and-vigorous PA and adolescence metabolic CVD risk z-score ($p>0.1$). Baseline vigorous PA was significantly associated to adolescent metabolic CVD risk z-score (beta= -0.06 (95%CI; -0.17 to -0.01) $p<0.05$). A one-SD (10.1 min) increment in vigorous PA (in childhood) was associated with a 0.14 SD lower clustered risk z-score at follow-up ($p<0.05$). Additional adjustment for baseline soda consumption and TV-viewing did not attenuate the association. Baseline moderate-and-vigorous PA was marginally associated with metabolic risk z-score at follow-up (beta=-0.02 (95%CI -0.04 to 0.002) $p=0.07$).

Discussion

In this population based prospective study we did not observe any associations between carotid IMT or arterial stiffness and physical activity, but we observed that a high cumulative exposure to

vigorous PA across childhood was independently associated with a decreased metabolic CVD risk z-score in adolescence. As structural arterial remodeling and stiffening are thought to be products of the cumulative load of CVD risk factors (19) and as CVD factors track from adolescence to adulthood (20, 21) our observations suggest that a large volume of high intensity PA across childhood could be associated to improved health later in life through decreasing metabolic CVD risk in adolescence.

Our observations confirm observations from earlier cross-sectional studies with arterial stiffness (7, 22). Sakuragi et al. observed an association between number of daily steps and carotid-femoral pulse-wave velocity in a population-based sample of 573 children (10.1 years) but the association was attenuated after adjustment for gender, age and systolic blood pressure. Nor did Reed and co-workers observe an association between self-reported PA and pulse-wave velocity (22). Associations between PA and peripheral endothelial function in children have generally been more consistent (4-6). The earliest indication of atherosclerotic progression includes endothelial dysfunction (23) and there are some indications that the association between PA and arterial health differentiates across the arterial tree (22). It is possible that the inconsistencies between studies could be ascribed differences in the measures of arterial health, artery segment (central or peripheral). This needs further attention in future studies.

Our observations are in contrast to longitudinal observations from the Amsterdam Growth and Health Longitudinal study where vigorous PA across adolescence was associated to decreased carotid arterial stiffness in adulthood (12) and an observation from the Cardiovascular Risk in Young Finns Study, were childhood and youth PA were associated with cIMT progression in adulthood (24). Because advanced age is associated with arterial stiffening (25), thus atherosclerotic progression, the discrepancies across studies could be ascribed differences in age at follow-up. Little or no effects of exercise on reduction in cIMT have been observed in healthy

populations (Thijsen). However, Meier and coworkers observed a significant reduction of cIMT following a six month exercise intervention in a sample of overweight and obese children (26). Taken together this suggests that exercise or PA might only have an effect on the carotid properties in high risk populations.

As we did not observe an association between the change in PA across childhood and adolescence metabolic CVD risk, our observations generally confirm previous longitudinal studies (27-29). However, the present study is the first longitudinal study to observe a significant association between the cumulative exposure to vigorous PA in childhood and later metabolic CVD risk. This contradicts previous longitudinal observations in children (27, 30, 31) but is supported by randomized controlled trials reporting on the beneficial effect of exercise metabolic risk factors in high risk children (32, 33). As the cumulative exposure to moderate-and-vigorous PA was not associated with later metabolic CVD risk, this suggests that in order to obtained beneficial effects from habitual PA it has to include a high proportion of vigorous PA. Further, as changes in vigorous PA were not associated with later CVD risk, the observations suggest that a chronic high volume of vigorous PA should be reinforced from an early age to obtain beneficial effects in regard to metabolic CVD risk. This is supported in a recent review by Andersen and coworkers (34).

Strengths of this study include the objective measure of PA, the inclusion of multiple markers of the atherosclerotic progression and the longitudinal design. There are some limitations to the study. First, we used brachial blood pressure for calculation of blood pressure which may overestimate PP in the central arteries, especially in young people (35). This may therefore overestimate our measure of arterial stiffness. This bias would be random as the cohort was homogeneous according to age. Second, the drop-out and participants with incomplete data could have introduced a selection bias. However, they did not differ from the participants in their baseline levels of exposure variables, nor did the drop-in differ from the included participants at follow-up.

Therefore, we do not suspect that selection bias explain our observations. Third, the activity monitor does not capture activities such as bicycling, weight bearing activities and swimming very well. Furthermore a measurement period of ~ 4 days might not represent the participant's true PA activity level. This would introduce a random error and thus attenuate the association between intensity and outcome.

In conclusion, we did not observe any associations between PA across childhood and cIMT or carotid stiffness in adolescence. However, we observed that a high cumulative exposure to vigorous PA was associated with lower metabolic CVD risk in adolescence. This suggests that a chronic high volume of vigorous PA should be reinforced from an early age to prevent later CVD progression.

Acknowledgements

We thank the participants and their families who gave their time to the study.

Table 1 Population characteristics

	Boys		Girls	
	Included	*Excluded*	*Included*	*Excluded*
Number of subjects	107	95	147	109
Age (years)†	9.8 (0.5)	9.8 (0.5)	9.7 (0.4)	9.8 (0.4)
Puberty (%No/Yes) †	100/0	100/0	79/21	75/25
Parental education (%low/middle/high) †	23/59/18	34/50/17	35/43/22	29/64/7*
Fruit (Servings/week)	5.3 (1.8)	5.4 (2.0)	5.4 (1.9)	5.4 (1.9)
Vegetables (Servings/week)	5.0 (2.2)	4.6 (2.4)	5.2 (2.0)	4.9 (2.0)
Soda (Servings/week)	3.2 (2.1)	3.4 (2.3)	3.0 (2.0)	3.4 (2.0)
BMI (kg/m^2)	17.5 (2.5)	17.2 (2.4)	17.3 (2.5)	17.5 (3.0)
Sum of four skinfolds (mm) †	30.8 (14.7)	29.6 (13.5)	38.0 (16.0)	40.8 (21.2)
Systolic BP (mmHg) †	100.6 (6.3)	98.5 (7.0)*	97.7 (7.2)	96.2 (7.3)
Diastolic BP (mmHg)	57.9 (5.2)	57.6 (5.7)	58.1 (5.5)	56.9 (4.5)
Physical activity				
HPA (counts per minute) †	766 (276)	757 (252)	613 (205)	635 (200)
Sedentary time (minutes/day) †	359.3 (66.2)	248.2 (70.6)	373.7 (68.7)	342.1 (76.4)
Moderate-and-vigorous PA (minutes/day) †	40.3 (29.1 to 60.5)	43.7 (29.3 to 61.5)	27.5 (16.4 to 39.3)	29.9 (17.3 to 39.8)
Vigorous PA (minutes/day) †	7.6 (3.8 to 13.6)	7.5 (4.0 to 14.2)	4.7 (2.5 to 7.9)	5.5 (2.8 to 10.0)
Accepted days (days)	4.7 (0.6)	4.5 (0.7)	4.7 (0.6)	4.5 (0.7)*
Daily wear time (hours/day)	13.0 (0.8)	12.9 (1.0)	13.0 (0.8)	13.0 (1.0)
Cardio-respiratory fitness (watt/kg) †	3.31 (0.50)	3.28 (0.49)	2.86 (0.43)	2.75 (0.46)
Blood variables #				
Insulin (µU/dl) †	5.36 (3.90 to 7.12)	5.49 (3.73 to 7.24)	6.43 (4.64 to 8.61)	7.18 (5.03 to 9.06)
Glucose (mmol/L)	5.06 (0.32)	5.09 (0.30)	4.99 (0.33)	4.99 (0.32)
Triglyceride (mmol/L) †	0.57 (0.43 to 0.75)	0.54 (0.42 to 0.71)	0.68 (0.51 to 0.96)	0.65 (0.52 to 0.88)
Cholesterol (mmol/L)	4.49 (0.74)	4.47 (0.65)	4.42 (0.80)	5.00 (0.74)
HDL (mmol/L) †	1.78 (0.38)	1.70 (0.40)	1.56 (0.36)	1.60 (0.34)
LDL (mmol/L)	2.41 (0.66)	2.43 (0.54)	2.50 (0.64)	2.65 (0.59)
Insulin resistance (HOMA score) †	1.20 (0.85 to 1.68)	1.26 (0.84 to 1.68)	1.44 (1.00 to 1.98)	1.63 (1.09 to 2.01)

HPA; Habitual physical activity, BMI; Body mass index, BP; blood pressure, HDL; High density lipoprotein, LDL; Low density lipoprotein, HOMA; homoeostasis model assessment

*p<0.05 for differences between included and excluded,

†p<0.05 for gender differences among the included participants.

N= 205.

Excluded cover lost to follow-up or missing data on follow-up exposure or outcome.

Table 2 Subclinical arthrosclerosis at follow-up, mean PA and change in PA from childhood to adolescence.

	Boys	Girls
*Intima media thickness (mm) **	0.570 (0.023)	0.548 (0.024)
*Carotid compliance (mm^3*kPa^{-1}) **	1.64 (0.39)	1.41 (0.27)
*Young's elastic modules (kPa*mm^{-1})*	228.5 (57.7)	237.5 (49.4)
*Sum of z-scores # **	2.6 (3.6)	4.7 (3.8)
*Cumulative moderate-and vigorous PA (min/day) **	33.4 (24.5 to 43.4)	20.4 (13.7 to 29.9)
*Change in moderate-and vigorous PA (min/day) **	-22.8 (32.6)	-14.8 (18.3)
*Mean vigorous PA (min/day) **	5.6 (3.5 to 9.9)	3.2 (1.8 to 6.3)
*Change in vigorous PA (min/day) **	-6.6 (13.2)	-3.8 (7.6)

Data are mean (SD) or median (interquartile range)

PA (physical activity)

*$p<0.05$ for gender differences

N=205

Table 3 Associations between mean and change in physical activity intensity from childhood to adolescence and sub-clinical atherosclerosis in adolescence

	β (95% CI)	Std. β	P	β (95% CI)	Std. β	P
	Mean			**Change**		
			Vigorous physical activity			
Intima media thickness (mm)	0.0003 (-0.0001 to 0.0008)	0.08	0.17	0.0003 (-0.0003 to 0.0004)	0.12	0.28
Carotid compliance (mm^3*kPa^{-1})	-0.0001 (-0.0007 to 0.0066)	-0.002	0.97	0.0020 (-0.0055 to 0.0098)	0.06	0.59
Young's elastic modules ($kPa*mm^{-1}$)	-0.22(-1.33 to 0.88)	-0.03	0.69	-0.16 (-1.41 to 1.08)	-0.03	0.80
Clustered risk z-score*	-0.11 (-0.19 to -0.03)	-0.19	0.006	-0.06 (-0.15 to 0.03)	-0.16	0.19
			Moderate-and-vigorous physical activity			
Intima media thickness (mm)	0.0001 (-0.0006 to 0.0003)	0.09	0.19	0.0001 (-0.0001 to 0.0003)	0.10	0.34
Carotid compliance (mm^3*kPa^{-1})	-0.0004 (-0.0033 to 0.0023)	-0.02	0.73	-0.0008 (-0.0036 to 0.0019)	-0.06	0.57
Young's elastic modules ($kPa*mm^{-1}$)	-0.01 (-0.53 to 0.38)	-0.02	0.74	-0.08 (-0.45 to 0.29)	-0.04	0.68
Clustered risk z-score*	-0.03 (-0.06 to 0.007)	-0.11	0.13	0.002 (-0.03 to 0.03)	0.01	0.93

The models are adjusted for gender and pubertal development at follow-up.

The analysis of change is further adjusted for baseline physical activity intensity.

* N=205

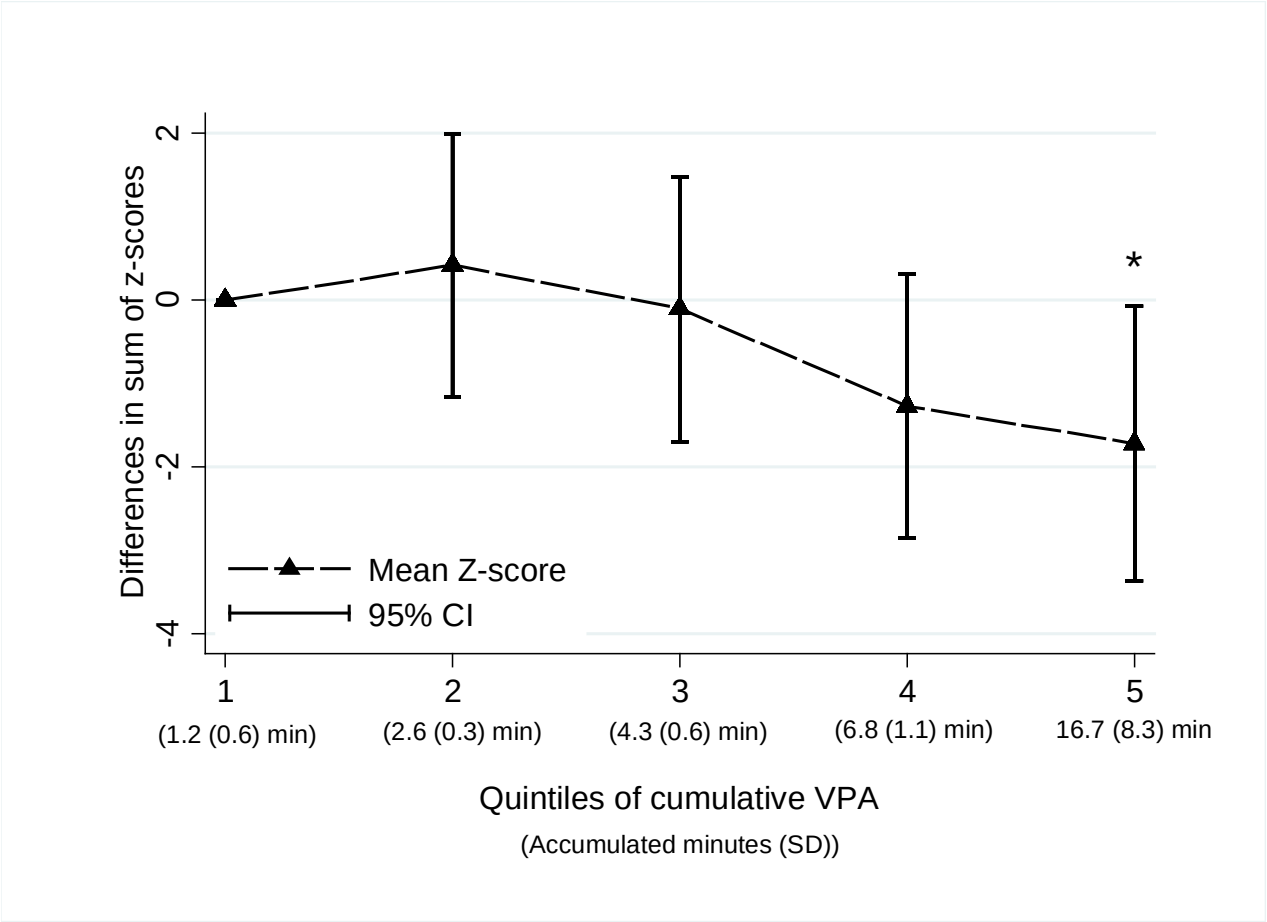

Figure 1: Differences in the sum of metabolic CVD risk z-scores across quintiles of the cumulative exposure to vigorous intensity (minutes) physical activity in childhood and adolescence. *p<0.05 for differences to the least active quintile (1)

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