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ORIGINAL RESEARCH

Associations of Cardiovascular Health Metrics in Childhood and Adolescence With Arterial Health Indicators in Adolescence: The PANIC Study

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BACKGROUND: Our aim was to assess the relationships of cardiovascular health metrics, cardiorespiratory fitness, lean mass, and fat percentage with arterial structure and function from childhood to adolescence.

METHODS AND RESULTS: Five hundred four children aged 6 to 9 years were examined in the PANIC (Physical Activity and Nutrition in Children) study at baseline, 2 and 8 years later. The associations of adjusted American Heart Association cardiovascular health metrics (smoking status, body mass index—SD score, moderate-to-vigorous physical activity, diet quality, plasma total cholesterol, systolic blood pressure, plasma glucose categorized into poor, intermediate, and ideal), the American Heart Association cardiovascular health score, cardiorespiratory fitness measured by maximal oxygen uptake in a bicycle exercise test, lean mass and fat percentage with carotid intima–media thickness (cIMT) and pulse wave velocity (PWV) were analyzed cross-sectionally and longitudinally in 277 participants at age 15 to 17 years. Higher American Heart Association cardiovascular health score at baseline was associated with lower PWV at 8-year follow-up (ß, −0.19 [95% CI, −0.32 to −0.05]). Higher body mass index—SD score and systolic blood pressure were associated with higher cIMT (ß, 0.18 [95% CI, 0.05–0.31]); and (ß, 0.13 [95% CI, 0.00–0.25]; respectively) and PWV (ß, 0.20 [95% CI, 0.07–0.34]) and (ß, 0.13 [95% CI, 0.00–0.26]; respectively) at 8-year follow-up. Higher moderate-to-vigorous physical activity was associated with higher cIMT (ß, 0.25 [95% CI, 0.07–0.43]); yet lower PWV (ß, −0.25 [95% CI, -0.44 to -0.06]) at 8-year follow-up. Better cardiorespiratory fitness (ß, 0.29 [95% CI, 0.08–0.51]) and higher lean mass (ß, 0.51 [95% CI, 0.03–0.98]) were associated with higher cIMT after accounting for American Heart Association cardiovascular health score at 8-year follow-up.

CONCLUSIONS: While our results suggest that higher cardiometabolic risk factors in childhood may exert unfavorable effects on arterial health during adolescence, we demonstrated the complexity of relationships between cardiovascular health metrics and arterial health indicators in childhood and adolescence. We found different associations of cardiovascular health metrics with cIMT and PWV in childhood and adolescence, calling for caution when interpreting the results of various cardiovascular risk factors with measures of arterial health, particularly in youth.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01803776.

Key Words: arterial function ■ arterial structure ■ cardiovascular risk ■ pediatrics

In 2010, the American Heart Association (AHA) published national goals and metrics for cardiovascular health promotion by 2020 and beyond, including challenges and opportunities specifically for children.[1] While the primary focus of AHA remains on promoting adult cardiovascular health and the prevention of

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RESEARCH PERSPECTIVE

What Is New?

- Adolescence arterial structure has different associations with childhood cardiometabolic risk factors than arterial function.
- Cardiorespiratory fitness and lean mass have important associations with arterial structure independent of other risk factors.

What Question Should Be Addressed Next?

- There should be an assessment about which of the arterial health indicators are best for childhood and adolescence cardiovascular risk assessment.
- Specific mechanisms for the associations of cardiorespiratory fitness and lean mass with arterial health should be studied.
- The American Heart Association has proposed several cardiovascular health metrics for childhood cardiovascular health promotion, including physical activity and body mass index, but considering the complexity of the interaction between studied risk factors, the refinement of these metrics as indicators of arterial health should be assessed.

cardiovascular diseases (CVD), the importance of promoting cardiovascular health since birth is increasingly recognized.[2] Although evidence of associations between childhood risk factors and adult CVD outcomes is limited,[3] increasing data show that atherosclerosis originates in childhood and is associated with cardiovascular risk factors in childhood and adolescence such as increased blood cholesterol levels, smoking, elevated blood pressure, and adiposity, and atherosclerosis typically progresses over time.[4–6] This understanding emphasizes the need for better methods to identify children and adolescents at increased risk of CVD, prompting the utilization of preclinical markers for CVD such as carotid intima–media thickness (cIMT) and pulse wave velocity (PWV).[7,8]

Nonstandard Abbreviations and Acronyms

cIMT	carotid intima–media thickness
CRF	cardiorespiratory fitness
MVPA	moderate-to-vigorous physical activity
PANIC	Physical Activity and Nutrition in Children
PWV	pulse wave velocity
VO_{2peak}	peak oxygen uptake ($mL \times min^{-1}$)

Behaviors linked to cardiovascular health or the risk of CVD often originate in childhood or adolescence.[9] The Strategic Planning Task Force of AHA identified 7 major behavioral and other metrics to establish ideal cardiovascular health in children and adolescents based on scientific evidence.[1] These factors include smoking, body mass index (BMI), physical activity, diet quality, total blood cholesterol, blood pressure, and fasting plasma glucose. While each of these metrics has been found to predict cardiovascular health, recent research has underscored that these childhood cardiovascular risk factors combined serve as the strongest predictor for cardiovascular mortality in midlife.[3] This recognition emphasizes the need for a comprehensive understanding of various childhood indicators of cardiovascular health in the prediction of the development of CVD in later life.

Recent propositions highlight the significance of additional components in evaluating cardiovascular health in children.[10,11] Studies have shown how differences in arterial structure and function in relation to BMI represent combinations of adverse effects of adiposity, adaptive effects of body size, and relatively protective effects of increased skeletal muscle mass.[12] While adiposity is associated with increased cardiovascular risk in both children and adults,[13,14] increased skeletal muscle mass demonstrates neutral or positive associations with cardiovascular health.[12] This distinction prompts a deeper investigation into the effects of different body compositions on cardiovascular health, potentially shedding light on the nuanced interactions between measures of adiposity and cardiovascular risk, with implications for clinical practice and scientific research. Apart from the distinct effects of fat and lean mass on cardiovascular health, in addition cardiorespiratory fitness (CRF) has been proposed as an important additional component of cardiovascular health in adults.[15] Nevertheless, current evidence is not consistent concerning the role of childhood cardiorespiratory fitness in later arterial health.

Here, we investigate the cross-sectional and longitudinal associations of the AHA cardiovascular health score and its components with arterial health in a general population of children followed up for 8 years until adolescence. Additionally, we study whether cardiorespiratory fitness, lean mass, and fat mass are associated with arterial health independent of the AHA cardiovascular health score.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the PANIC study team [https://www.panicstudy.fi]. Cumulative and/or summary research data will be made available upon request to the corresponding author of the article.

Study Design and Participants

The PANIC (Physical Activity and Nutrition in Children) study is a nonrandomized controlled trial (ClinicalTrials.gov NCT01803776) on the effects of a combined physical activity and dietary intervention on cardiometabolic risk factors and other health outcomes in a population sample of children from the city of Kuopio, Finland.[16–18] The Research Ethics Committee of the Hospital District of Northern Savo approved the study protocol in 2006 (Statement 69/2006). The parents or caregivers of the children gave their written informed consent, and the children provided their assent to participation. At 8-year follow-up, not only the caregivers but also the adolescents gave their written informed consent. The PANIC study has been carried out in accordance with the principles of the Declaration of Helsinki as revised in 2008.

A total of 736 children aged 6 to 9 years who started the first grade in 16 primary schools of the city of Kuopio in 2007 to 2009 were invited to participate in the study (Figure 1). Altogether, 512 (70%) children (248 girls, 264 boys) accepted the invitation and participated in the baseline examinations between October 2007 and December 2009. The participants did not differ in sex, age, height—SD score (SDS) or BMI-SDS from all children who started the first grade in the city of Kuopio in 2007 to 2009. Six children were excluded from the study at baseline either owing to their physical disabilities that could hamper participation in the intervention or withdrawal of the families because they had no time or motivation to attend the study. Data from 2 children whose parents or caregivers later withdrew their permission to use these data in the study were excluded.

The study included an intervention and a control arm. Children from 9 schools were allocated to a combined physical activity and dietary intervention group (306 children, 60%) and the children from 7 schools to a control group (198 children, 40%) to avoid contamination in the control group by any health-promotion programs. The children, their parents, or people being responsible for the examination visits or the measurements were not blinded to the group assignment. The first 2 years of the study included more intensive[18] and from 2 to 8 years lighter individualized and family-based physical activity and dietary intervention.[19] In the control group, the children and their parents or caregivers received general verbal and written advice on health-improving physical activity and diet only at baseline with no further lifestyle counseling. Because arterial health was assessed in detail only at 8 years and the intervention had no effect on the outcomes based on the primary statistical review, control and intervention groups were pooled and are not discussed further in this article. Outcome measures by intervention group and timepoint are presented in (Table 1).

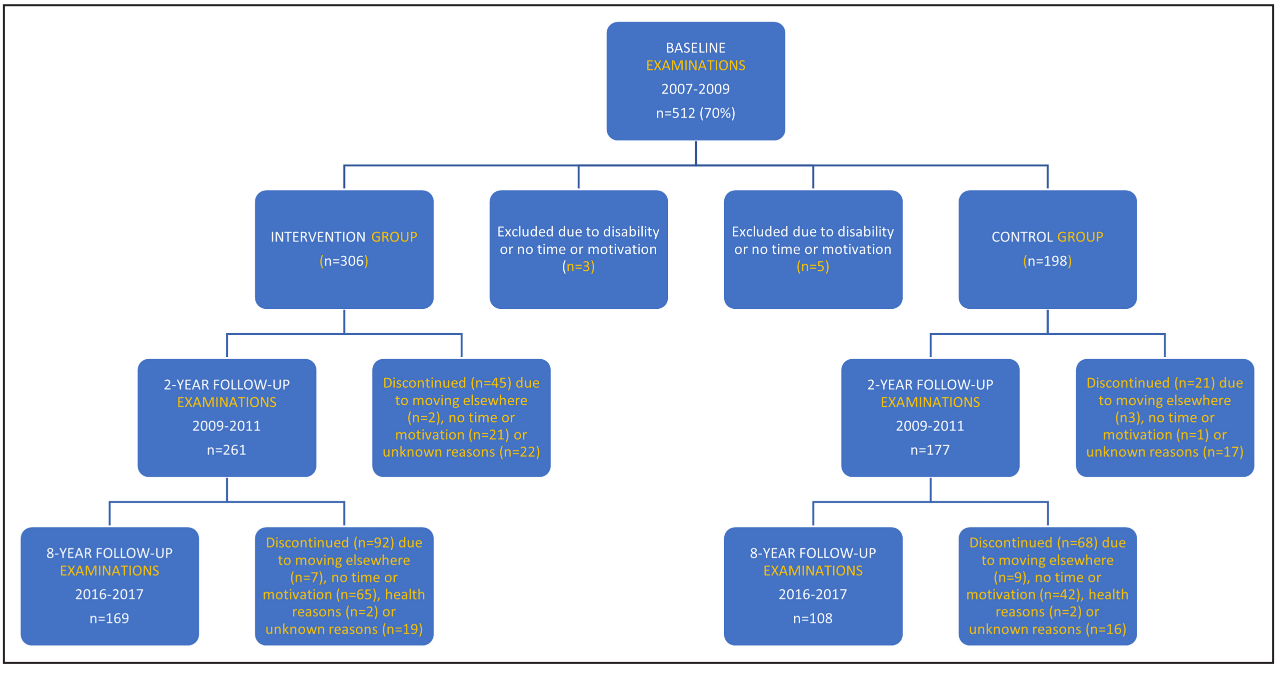

Figure 1. Flow chart of the PANIC study.
PANIC indicates Physical Activity and Nutrition in Children.

Table 1. Study Outcomes by Intervention Group

	Baseline			2-year follow-up			8-year follow-up		
	Intervention N=306	Control N=198	*P* value	Intervention N=261	Control N=176	*P* value	Intervention N=168	Control N=108	*P* value
Arterial health indicators									
Carotid IMT, mm							0.4±0.1	0.4±0.1	0.9
Pulse wave velocity, m/s							5.9±0.7	5.8±0.5	0.3
AHA cardiovascular health score	9.4±1.3	9.2±1.4	0.2	9.2±1.3	9.1±1.4	0.3	11.1±1.5	11.0±1.5	0.7

The values are mean±SD for continuous variables. *P* values are from the Fisher exact test for continuous variables with normal distributions, the Mann–Whitney *U* test for continuous variables with skewed distributions for the comparison of intervention and control. AHA indicates American Heart Association; and IMT, intima media thickness.

Of all 504 children who participated in the baseline examinations and were finally accepted for the study, 438 (87%) attended the 2-year follow-up examinations, and 277 (55%) attended the 8-year follow-up examinations (Figure 1). Those who participated in the 8-year follow-up examinations did not differ in age, BMI-SDS, or the distribution of sex or study groups at baseline from those who did not attend these examinations. The median (interquartile range) of 2-year follow-up time was 2.1 (2.1–2.2) years in both groups. The median (interquartile range) of 8-year follow-up time was 8.3 (8.1–8.3) for the intervention group and 8.1 (8.0–8.3) for the control group.

Assessment of Arterial Health

cIMT was assessed at 8-year follow-up by 2 trained sonographers using a standardized protocol.[4] Imaging was performed using the Sequoia 512 ultrasound scanner (Acuson, Mountain View, CA) with a 14.0-MHz linear array transducer. An electrocardiographic signal was drawn on the ultrasound image by the ultrasound scanner. A 5-second cine loop, which included the beginning of the left carotid artery bifurcation and the left common carotid artery, was recorded and stored for subsequent off-line analyses. Blood pressure was measured just before and immediately after the carotid ultrasound scanning using an automated Omron M4 sphygmomanometer (Omron Matsusaka Co., Ltd, Kyoto, Japan). After imaging, the digitally stored scan was manually analyzed by the sonographer using the calipers of the ultrasound scanner. For the assessment of cIMT, the best quality end-diastolic frames, incident with the R-wave on a continuously recorded electrocardiogram, were selected from the video clip. Three measurements were taken from the far wall of the left common carotid artery ≈10 mm proximal to the carotid bifurcation to derive the maximal cIMT. The diameter of the common carotid artery was measured twice both at end-diastole and at end-systole. The means of the measurements were used as the end-diastolic and end-systolic diameters. These measurements and analyses were performed at Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital.

At 8-year follow-up, aorto-popliteal arterial PWV was measured after 15-minute supine rest using the Circmon B202 impedance cardiography device (JR Medical Ltd, Saku Vald, Estonia).[20] The participants were asked to rest for 15 minutes in a supine position before the measurement. The CircMon software estimates the foot of the impedance cardiography signal that coincides with pulse transmission in the aortic arch. The distal impedance plethysmogram was recorded from a popliteal artery at knee joint level. Utilizing the measured pulse transit time (Δt) and assessed distance (L) between these 2 sites, the CircMon software calculates PWV using the equation PWV (m/s)=L/Δt.[21]

Calculation of AHA Cardiovascular Health Score

The AHA cardiovascular health score was calculated based on modified AHA health metrics[1] by accounting poor cardiovascular health as 0 points, intermediate cardiovascular health as 1 point, and ideal cardiovascular health as 2 points for each component (Table 2). Smoking metric was modified to 3 categories (current smoker=0 points, previous smoker=1 point, nonsmoker=2 points). The AHA cardiovascular health score was calculated as the sum of each metric point. An average AHA cardiovascular health score over 8 years was calculated as an average of the scores from the baseline, 2-year follow-up, and 8-year follow-up examinations.

Assessment of Tobacco Use

Tobacco use of the participants was assessed at 8-year follow-up using a questionnaire.

Measurement of Body Size and Composition

At baseline, 2-year follow-up, and 8-year follow-up, a research nurse measured body height 3 times using

Table 2. Definitions for Poor, Intermediate, and Ideal Cardiovascular Health in Children and Adolescents

Metric	Poor (0 points)	Intermediate (1 point)	Ideal (2 points)	Modifications to original metric
Smoking status	Tried prior 30 d		Never tried; never smoked whole cigarette	Modified to categories: Current smoker/Previous smoker/nonsmoker
BMI	>95th percentile	85th-95th percentile	<85th percentile	…
Physical activity	None	0–59 min/d MVPA every day	≥60 min/d MVPA every day	…
Healthy diet score	0–1 components	2–3 components	4–5 components	…
Total plasma cholesterol	≥200mg/dL	170–199 mg/dL	<170 mg/dL	…
Blood pressure (systolic and diastolic)	>95th percentile	90–95th percentile	<90th percentile	Either systolic or diastolic at least 95th percentile provides poor result while both systolic and diastolic must be less than 90th percentile to provide ideal result.
Fasting plasma glucose	≥126 mg/dL	100–125 mg/dL	<100 mg/dL	…

The healthy diet score is based on adherence to the following dietary recommendations: fruits and vegetables, ≥4.5 cups per day (≥450 g/d); fish, ≥2 servings of 3.5-oz (99.2 g) per week; sodium, ≤1500 mg/d; sugar-sweetened beverages, ≤450 kcal (36 oz; 1020.6 g) per week; and whole grains, ≥3 servings a day scaled to a 2000 kcal/d diet.[1] BMI indicates body mass index; and MVPA, moderate-to-vigorous physical activity.

a wall-mounted stadiometer to accuracy of 0.1 cm for the children standing in the Frankfurt plane without shoes. The mean of the nearest 2 values was used in the analyses. A research nurse measured body weight twice using the InBody 720 bioelectrical impedance device (Biospace, Seoul, South Korea) to accuracy of 0.1 kg with the children having fasted for 12 hours, having emptied the bladder, and standing in light underwear. The mean of the 2 values were used in the analyses. BMI was calculated by dividing body weight (kg) with body height (m) squared and BMI-SDS using the Finnish reference values.[22] Body fat mass and lean body mass were measured using the Lunar dual-energy X-ray absorptiometry (DXA) device (Lunar Prodigy Advance; GE Medical Systems, Madison, WI) with the participants being at a nonfasting state, having emptied the bladder, and lying in light clothing with all metal objects removed. These measurements were performed at the Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital.

Assessment of Physical Activity

At baseline and 2-year follow-up, we assessed physical activity at different intensities using a combined accelerometer and heart rate monitor (Actiheart, CamNtech, Papworth, UK).[23,24] A combined movement and heart rate sensor was attached to the children's chest with standard electrocardiogram electrodes (Bio Protech Inc, Wonju, South Korea). The Actiheart monitor was set to record acceleration and heart rate in 60-second epochs. The participants were asked to wear the monitor continuously for a minimum of 4 days including 2 weekdays and 2 weekend days including sleep. At 8-year follow-up, we assessed physical activity using the Actiheart monitor with wear time of 7 days including sleep. At baseline, the median (range) monitor wear time was 104 hours (52–212 hours), at 2-year follow-up 101 hours (48–171 hours), and at 8-year follow-up 170 hours (65–425 hours). We defined sedentary time as time spent in activity ≤1.5 metabolic equivalent tasks (METs) excluding sleep and light, moderate, and vigorous physical activity as time spent in activity >1.5 and ≤4.0 METs, >4.0 and ≤7.0 METs, and >7.0 METs, respectively, by defining 1 MET as 71.2 J/min per kg. Moderate-to-vigorous physical activity (MVPA) included moderate and vigorous physical activity. These cut-offs have been commonly applied in investigations of physical activity among children and youth.[25,26]

Assessment of Dietary Factors

The consumption of food and drinks was assessed using food records.[27] The food records covered 4 predefined and consecutive days, including 2 weekdays and 2 weekend days (99.5%) or 3 weekdays and 1 weekend day (0.5%). The clinical nutritionists, who were trained based on the protocol of the study, gave the instructions about the food records to the participants at the research site during the study visits. At baseline and 2-year follow-up, a clinical nutritionist instructed the parents to record all food and drinks consumed by their child using household or other measures, such as tablespoons, deciliters, and centimeters. At 8-year follow-up, the adolescents were instructed to record their food and drink consumption by themselves. A clinical nutritionist checked the returned food records together with the children and their parents at baseline and 2-year follow-up and with the adolescents at 8-year follow-up and filled in any missing information. Food consumption and nutrient intake were calculated using the Micro Nutrica dietary analysis software, Version 2.5. The software is based on detailed information about the nutrient content of foods in Finland and other countries.[28] Moreover, a clinical nutritionist updated the software by adding new food items and products with their precise nutrient content based on new data in the Finnish food composition database[29] or received from the producers. The healthy diet score was assessed according to AHA recommendations: fruits and vegetables, ≥4.5 cups per day (estimated as ≥450 g/d[30]); fish, ≥2 servings of 3.5-ounces per week; sodium, ≤1500 mg/d; sugar-sweetened beverages, ≤450 kcal (36 oz) per week; and whole grains, ≥3 servings of 1 ounce a day.[1] The food consumption goals defined by AHA are expressed for a 2000-kcal diet, so we first scaled these goals according to the total energy intake of each participant. Healthy diet score of 2 (ideal) was appointed if at least 4 of the above recommendations were followed, 1 (intermediate) in case 2 to 3 components, and 0 points (poor) in case 1 or fewer components were followed.

Measurement of Glucose and Cholesterol

A research nurse took venous blood samples in the morning after children had fasted overnight for at least 12 hours and having been seated for 10 minutes. Plasma glucose concentration was measured using the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany). The within-day and between-day coefficients of variation for the glucose analyses were 0.7% to 0.9% (5.1–11.9 mmol/L) and 1.5–1.8% (3.4–14.1 mmol/L), respectively. Plasma total cholesterol concentration was measured using a clinical chemistry analyzer (Hitachi High Technology Co, Tokyo, Japan) and a colorimetric enzymatic assay (Roche Diagnostics GmbH, Mannheim, Germany).

Measurement of Blood Pressure

At baseline, 2-year follow-up, and 8-year follow-up, a research nurse measured systolic and diastolic blood pressure from the right arm using the Heine Gamma G7 aneroid sphygmomanometer (Heine Optotechnik, Herrsching, Germany) with auscultatory method to an accuracy of 2 mm Hg. The first and last Korotkoff sounds were used for systolic and diastolic pressure accordingly. The measurement protocol included a rest of 5 minutes and thereafter 3 measurements in the sitting position at 2-minute intervals. The mean of all 3 values was used as the systolic and diastolic blood pressure. Blood pressure percentiles were calculated with the R package pedbp[31] by age, sex, and height according to Lo et al.[32]

Assessment of Cardiorespiratory Fitness

Peak oxygen uptake ($\dot{V}O_{2peak}$, mL×min^{-1}) was assessed during an incremental exercise test to volitional fatigue on an electromagnetically braked cycle ergometer by the Oxycon Pro (Jaeger, Hoechberg, Germany) respiratory gas analyzer at 8-year follow-up. The exercise test protocol included a 2.5-minute anticipatory period with the child sitting on the ergometer; a 3-minute warm-up period with a workload of 5 watts; a 1-minute steady-state period with a workload of 20 watts; and an exercise period with

Table 3. Missing Values at Baseline, 2-Year Follow-up, and 8-Year Follow-up

	Baseline		2-year follow-up		8-year follow-up	
	Girls N=243	Boys N=261	Girls N=214	Boys N=223	Girls N=126	Boys N=151
Height	0	0	0	0	1	0
Carotid intima–media thickness	NA	NA	NA	NA	1	11
Pulse wave velocity	NA	NA	NA	NA	22	34
AHA cardiovascular health score	55	75	58	60	80	89
Smoking	NA	NA	NA	NA	10	17
Body mass index	0	0	0	0	0	1
Physical activity	18	35	27	36	71	61
Healthy diet score	37	44	29	20	11	36
Plasma total cholesterol	6	5	8	5	9	5
Blood pressure	1	1	1	1	2	0
Fasting plasma glucose	7	5	8	5	8	5
Pubertal stage	1	1	1	16	12	24
Lean and fat mass	4	7	6	14	1	11
VO_2peak/lean mass	NA	NA	44	44	32	30

AHA indicates American Association; NA, not available; and VO_2peak oxygen consumption.

Table 4. Characteristics of Participants

	Baseline			2-year follow-up			8-year follow-up		
	Girls N=243	Boys N=261	*P* value	Girls N=214	Boys N=223	*P* value	Girls N=126	Boys N=151	*P* value
General characteristics									
Age, y	7.6±0.4	7.7±0.4	0.2	9.7±0.4	9.8±0.4	0.2	15.8±0.4	15.8±0.5	0.064
Height, cm	127.8±5.6	129.7±5.6	<0.001	139.7±6.5	141.2±6.0	0.014	165.7±5.8	176.6±7.4	<0.001
Weight, kg	26.5±5.1	27.3±5.0	0.10	33.6±7.2	35.0±7.3	0.051	57.9±9.1	65.8±15.1	<0.001
Arterial health indicators									
Carotid IMT, mm							0.4±0.1	0.5 0.1)	0.002
Pulse wave velocity, m/s							5.9±0.6	5.8±0.6	0.7
AHA cardiovascular health score	9.3±1.5	9.6±1.2	0.015	9.2±1.4	9.1±1.3	0.5	11.3±1.4	11.0±1.5	0.2
Smoking status									0.5
Nonsmoker							106 (91.4%)	116 (86.6%)	
Previous smoker							6 (5.2%)	12 (9.0%)	
Current smoker							4 (3.4%)	6 (4.5%)	
BMI-SDS	−0.2±1.1	−0.2±1.1	0.8	-0.2±1.0	−0.1±1.1	0.7	0.1±0.9	−0.1±1.1	0.12
Moderate-to-vigorous physical activity, min/d	95.7±54.4	134.3±67.6	<0.001	79.9±38.6	119.1±56.2	<0.001	41.7±20.2	47.9±29.5	0.047
Healthy diet score	1.5±1.0	1.3±1.0	0.11	1.4±0.9	1.3±0.9	0.2	1.7±1.0	1.3±0.9	0.002
Plasma total cholesterol, mmol/L	4.3±0.6	4.2±0.6	0.10	4.3±0.7	4.3±0.6	0.5	4.0±0.7	3.7±0.6	<0.001
Systolic blood pressure, mm Hg	99.9±7.5	100.5±7.1	0.4	100.5±7.6	100.4±7.7	0.9	110.4±9.1	115.7±10.9	<0.001
Diastolic blood pressure, mm Hg	61.3±7.2	61.6±7.1	0.6	61.4±7.9	61.3±7.8	>0.9	66.7±9.9	68.0±9.5	0.3
Fasting plasma glucose, mmol/L	4.8±0.4	4.9±0.4	<0.001	4.9±0.4	5.1±0.4	<0.001	5.1±0.3	5.3±0.4	<0.001
Pubertal stage by Tanner			0.060			<0.001			0.001
1	233 (96.3%)	257 (98.8%)		142 (66.7%)	180 (87.0%)				
2	9 (3.7%)	3 (1.2%)		71 (33.3%)	27 (13.0%)				
3							4 (3.5%)	17 (13.4%)	
4							61 (53.5%)	78 (61.4%)	
5							49 (43.0%)	32 (25.2%)	
Fat mass, kg	6.4±3.5	5.2±3.5	<0.001	9.1±5.0	8.3±5.4	0.12	17.1±6.9	12.2±9.7	<0.001
Lean mass, kg	19.5±2.1	21.7±2.2	<0.001	23.5±2.9	25.9±2.9	<0.001	38.2±4.0	51.5±6.9	<0.001
VO_2 peak/lean body mass, mL/min per kg				65.9±6.0	69.0±6.3	<0.001	61.0±5.6	62.4±6.7	0.13

The values are numbers (percentages) for categorical variables and mean±SD for continuous variables. *P* values are from the Fisher exact test for continuous variables with normal distributions, the Mann–Whitney *U* test for continuous variables with skewed distributions, and the Pearson χ^2 test for categorical variables for the comparison of boys and girls.

AHA indicates American Heart Association; IMT, intima–media thickness; BMI-SDS, body mass index SD score; and VO_2 peak, peak oxygen consumption.

an increase in the workload of 1 watt per 6 seconds until exhaustion according to the guidelines.[33] The children were verbally encouraged to exercise until voluntary exhaustion. The exercise test was considered maximal if objective and subjective criteria (heart rate >85% of predicted, sweating, flushing, inability to continue exercise test regardless of strong verbal encouragement) indicated maximal effort and maximal cardiovascular capacity.[34] There was no association between lean body mass and VO_{2peak} in the present study population (r=0.02, P=0.75), and thus allometric scaling was not deemed necessary and VO_{2peak} relative to lean body mass was used.

Assessment of Pubertal Status

A research physician assessed pubertal status according to breast development for girls (scored M 1–5) and according to testicular volume measured by an orchidometer for boys (scored G 1–5) using the stages described by Tanner.[35,36]

Statistical Analysis

Statistical analyses were performed using R software, Version 4.1.2.[37] Descriptive statistics are expressed as mean±SD for continuous variables and the numbers of cases with percentages (%) for categorical variables.

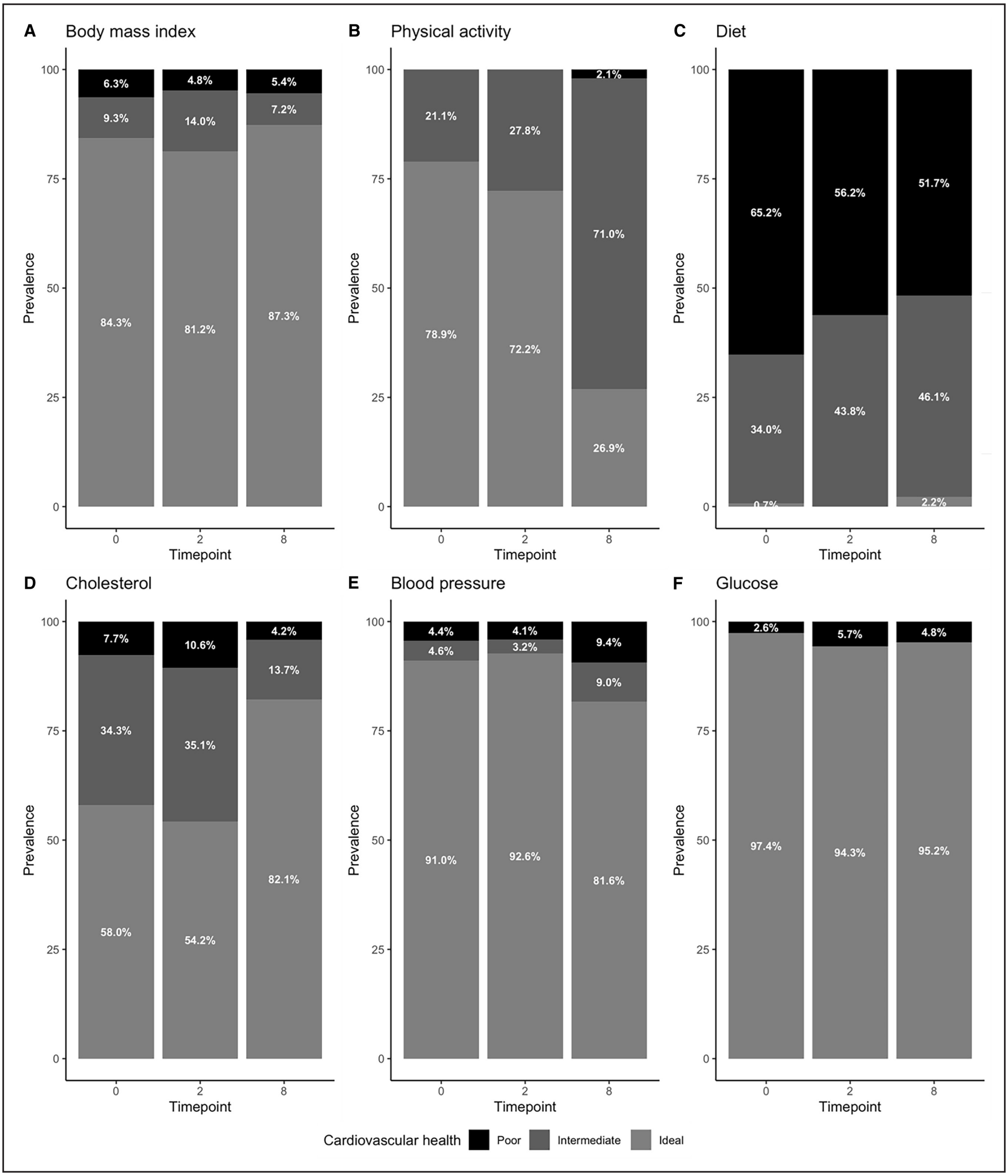

Figure 2. AHA cardiovascular health metrics at baseline, 2-year follow-up, and 8-year follow-up.
(A) through **(F)** correspond to body mass index, physical activity, diet, cholesterol, blood pressure, and glucose prevalence of ideal, intermediate, and poor category at different timepoints. AHA indicates American Heart Association.

Differences in baseline characteristics between sexes were tested using the Fisher exact test for variables with normal distributions and the Mann–Whitney *U* test for variables with skewed distributions. The Pearson χ^2 test was used for comparison of categorical variables.

The associations of the AHA cardiovascular health score at baseline and at 8-year follow-up and their average, the AHA cardiovascular health metrics at 8-year follow-up (smoking status, BMI-SDS, MVPA, healthy diet score, plasma total cholesterol, diastolic and systolic blood pressure percentiles, fasting plasma glucose), and cardiorespiratory fitness, lean mass, and fat percentage at 8-year follow-up with cIMT and PWV at 8-year follow-up were investigated using multivariable linear regression analyses. The magnitudes of the associations were expressed as standardized regression coefficients and their 95% CIs. These associations were adjusted for age, sex, height, and pubertal status at 8-year follow-up. The associations dealing with PWV were additionally adjusted for systolic blood pressure at 8-year follow-up as it has been shown to be associated with PWV.[38,39] The associations regarding cardiorespiratory fitness, lean mass, and fat mass were additionally adjusted for the AHA cardiovascular health score at 8-year follow-up to study whether the results were independent of this score. Statistical analyses revealed that there were no confounding effects of the intervention to our variables of interest, and adding the intervention variable into the analysis did not improve the models in any ways and therefore was not used in this article (Table 1). Complete data on all variables were used for each regression model. The numbers of missing values for each variable are shown in Table 3. Differences and associations with *P* values <0.05 were considered statistically significant.

RESULTS

Characteristics of Participants

All 504 children participating in the PANIC study were included in the present analyses. Of these children, 243 were girls and 261 were boys, and the average age of the girls was 7.6 years and that of the boys was 7.7 years. Almost all participants were prepubertal at baseline, and all of them were pubertal or postpubertal at 8-year follow-up (Table 4). Height, weight, the AHA cardiovascular health score, MVPA, fasting plasma glucose, and lean mass were higher and fat mass was lower in boys than in girls at baseline. Height, weight, cIMT, percentage of current smokers, MVPA, blood pressure, fasting plasma glucose, and lean mass were higher and the healthy diet score, plasma total cholesterol, and fat mass were lower in boys than in girls at 8-year follow-up.

Levels of Cardiovascular Health Metrics Over 8 Years

The prevalence of ideal cardiovascular health throughout the 8-year follow-up was dependent on the specific metric (Figure 2). The proportion of participants with ideal MVPA and blood pressure decreased over 8 years, while no such trend was seen for BMI or fasting plasma glucose levels. The proportion of participants with ideal diet quality and fasting plasma total cholesterol increased over 8 years. Most of the ideal cardiovascular health metrics at 8-year follow-up were higher than the corresponding estimates presented in the AHA strategic impact goal paper[1] based on the results of the NHANES 2005–2006 study (Table 5). The only exceptions were physical activity (27% in PANIC, 44% in NHANES) and blood pressure (82% in PANIC, 82% in NHANES).

Associations of AHA Cardiovascular Health Score With Arterial Health Indicators

The AHA cardiovascular health score improved throughout the 8-year follow-up period with >75% of the participants achieving at least 10 points by the 8-year follow-up (Figure 3). A higher AHA cardiovascular health score at baseline was associated with lower PWV at 8-year follow-up (Table 6). The inverse association between the average AHA cardiovascular health score over 8 years and PWV at 8-year follow-up was even stronger but did not reach statistical significance.

Associations of AHA Cardiovascular Health Metrics With Arterial Health Indicators in Adolescence

Higher BMI-SDS at 8-year follow-up was associated with higher cIMT and PWV at 8-year follow-up (Table 7). Higher MVPA at 8-year follow-up was associated with higher cIMT and lower PWV at 8-year follow-up. A higher systolic blood pressure percentile at 8-year follow-up was associated with higher cIMT and PWV at 8-year follow-up.

Table 5. Prevalence of Ideal Cardiovascular Health Metrics Based on NHANES 2005 to 2006 Cohort, AHA Strategic Impact Goals Through 2020 and Beyond, and PANIC 8-Year Follow-up Results

	NHANES 2005–2006 (%)*	AHA 2020 goal (%)*	PANIC 8-year follow-up (%)
Smoking	83.0	99.6	88.8
Body mass index	69.0	82.8	87.3
Physical activity	44.0	52.8	26.9
Healthy diet score	0.5	0.6	2.2
Plasma total cholesterol	67.0	80.4	82.1
Blood pressure	82.0	98.4	81.6
Fasting plasma glucose	81.0	97.2	95.2

AHA indicates American Heart Association; NHANES, National Health and Nutrition Examination Survey; and PANIC, Physical Activity and Nutrition in Children.

*Data presented in the AHA Strategic Impact Goals Through 2020 and Beyond[1] for the prevalence (NHANES 2005–2006) as well as future goals (AHA 2020 goal).

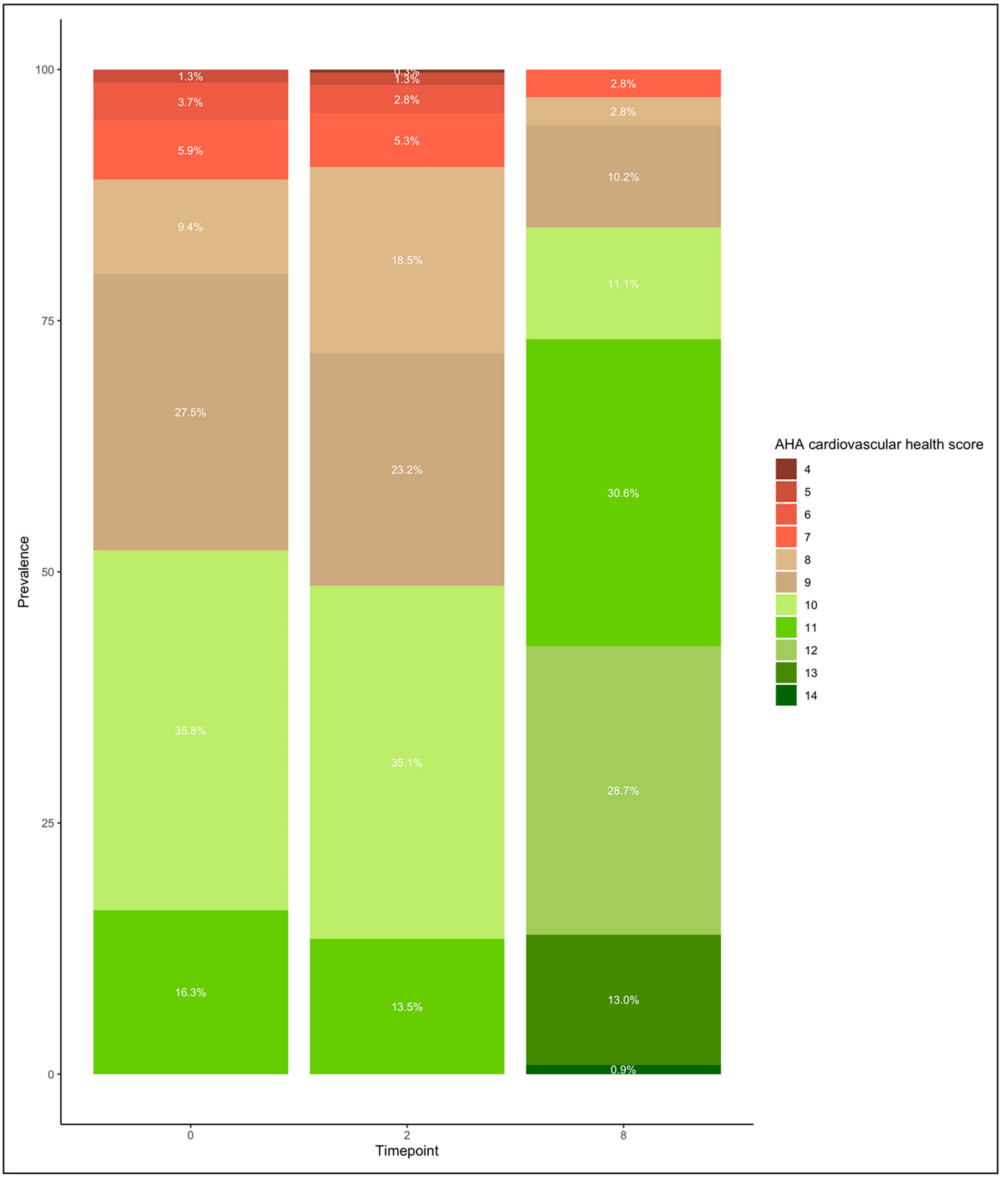

Figure 3. American Heart Association (AHA) cardiovascular health score at baseline, 2-year follow-up, and 8-year follow-up.

Associations of Cardiorespiratory Fitness, Lean Mass, and Fat Percentage With Arterial Health Indicators in Adolescence

Better cardiorespiratory fitness and higher lean mass at 8-year follow-up were associated with higher cIMT at 8-year follow-up independent of the AHA cardiovascular health score at 8-year follow-up (Table 8). No other statistically significant associations were present.

DISCUSSION

The main goal of the current analysis was to investigate the associations of cardiovascular health metrics with

Table 6. Associations of AHA Cardiovascular Health Score at Baseline and at 8-Year Follow-up and Average AHA Cardiovascular Health Score Over 8 Years With Arterial Health Indicators at 8-Year Follow-up

Variable	N	β	95% CI	*P* value
Carotid intima media thickness				
Baseline AHA cardiovascular health score	187	−0.15	−0.31 to 0.00	0.053
8-y follow-up AHA cardiovascular health score	95	0.04	−0.19 to 0.28	0.711
Average AHA cardiovascular health score	67	−0.06	−0.19 to 0.08	0.432
Arterial pulse wave velocity				
Baseline AHA cardiovascular health score	160*	−0.19*	−0.34 to −0.05*	0.011*
8-y follow-up AHA cardiovascular health score	105	−0.15	−0.38 – 0.07	0.187
Average AHA cardiovascular health score	58	−0.28	−0.59 – 0.04	0.084

The values are standardized regression coefficients β and their 95% CIs and *P* values from linear regression models adjusted for age, sex, height, and pubertal status, and in the case of pulse wave velocity additionally adjusted for systolic blood pressure. AHA indicates American Heart Association.

*Values for statistically significant associations.

arterial measures in a general population of children followed up until adolescence. Our results showed that a higher mid-childhood AHA cardiovascular health score predicted lower adolescence PWV, indicating lower arterial stiffness. Higher adolescence BMI-SDS and systolic blood pressure were associated with higher adolescence cIMT and PWV. From body composition measures, the association between cIMT was present with lean mass, but not with fat percentage. Higher adolescence MVPA was associated with higher adolescence cIMT but with lower adolescence PWV. Better cardiorespiratory fitness was also associated with higher cIMT independent of the AHA cardiovascular health score in adolescence.

Pahkala and co-workers showed in the STRIP (Finnish Special Turku Coronary Risk Factor Intervention

Table 7. Associations of AHA Cardiovascular Health Metrics at 8-Year Follow-up With Arterial Health Indicators at 8-Year Follow-up

Variable	N	β	95% CI	*P* value
Carotid intima media thickness				
Previous smoking	240	0.01	−0.77 to 0.79	0.984
Current smoking	240	0.26	−0.37 to 0.90	0.414
Body mass index SD score	241*	0.18*	0.05 to 0.31*	0.009*
Moderate to vigorous physical activity	130*	0.25*	0.07 to 0.43*	0.008*
Healthy diet score	210	0.10	−0.04 to 0.24	0.158
Plasma total cholesterol	229	−0.06	−0.19 to 0.08	0.398
Systolic blood pressure percentile	240*	0.13*	0.00 to 0.25*	0.049*
Diastolic blood pressure percentile	234	0.04	−0.09 to 0.17	0.515
Fasting plasma glucose	230	0.11	−0.03 to 0.24	0.111
Arterial pulse wave velocity				
Previous smoking	210	−0.23	−1.10 to 0.64	0.610
Current smoking	210	−0.09	−0.83 to 0.64	0.806
Body mass index SD score	211*	0.20*	0.07 to −0.34*	0.003*
Moderate-to-vigorous physical activity	117*	−0.25*	−0.44 to −0.06*	0.010*
Healthy diet score	186	−0.01	−0.14 to 0.13	0.924
Plasma total cholesterol	200	0.02	−0.11 to 0.15	0.729
Systolic blood pressure percentile	211*	0.13*	0.00 to 0.26*	0.049*
Diastolic blood pressure percentile	205	0.12	−0.01 to 0.25	0.071
Fasting plasma glucose	201	0.03	−0.09 to 0.16	0.599

The values are standardized regression coefficients β and their 95% CIs and *P* values from linear regression models adjusted for age, sex, height, and pubertal status, and in the case of pulse wave velocity additionally adjusted for systolic blood pressure (except for systolic blood pressure analyses). AHA indicates American Heart Association.

*Values for statistically significant associations.

Table 8. Associations of Cardiorespiratory Fitness, Lean Mass, and Fat Percentage at 8-Year Follow-up With Arterial Health Indicators at 8-Year Follow-up

Variable	N	B	95% CI	P value
Carotid intima–media thickness				
VO_2peak/lean mass	98*	0.29*	0.08 to 0.51*	0.008*
Lean mass	105*	0.51*	0.03 to 0.98*	0.036*
Fat percentage	105	0.07	−0.18 to 0.33	0.579
Pulse wave velocity				
VO_2peak/lean mass	89	0.02	−0.18 to 0.21	0.870
Lean mass	95	0.32	−0.11 to 0.75	0.141
Fat percentage	95	0.07	−0.15 to 0.28	0.534

The values are standardized regression coefficients β and their 95% CIs and *P* values from linear regression models adjusted for age, sex, height, pubertal status, and the AHA cardiovascular health score and in the case of PWV additionally adjusted for systolic blood pressure. AHA indicates American Heart Association; PWV, pulse wave velocity; and VO_2peak, peak oxygen consumption.

*The values for statistically significant associations.

Project) study that physical activity decreased, serum total cholesterol increased, and smoking became more common but other components of the AHA cardiovascular health score remained stable from the age of 15 to 19 years.[40] We also found that MVPA decreased while BMI and fasting plasma glucose levels remained stable over 8 years. Moreover, diet quality improved, blood pressure increased, and plasma total cholesterol decreased over 8 years in the PANIC study, whereas no such changes were found in the STRIP study. Together the results of these 2 studies as well as other research[41,42] show that physical activity tends to decrease from childhood to adolescence and further to adulthood and emphasize that the trends of physical activity in youth require attention and finding ways for improvement is important. Nevertheless, for a comprehensive prediction of the development of CVD in later life, there is a need for a better estimation of cardiovascular health in addition to evaluating single risk factors.

A large prospective i3C cohort study[3] and a nationwide epidemiological database analysis in Japan[43] showed that childhood risk factors predicted an increased risk of cardiovascular events in adulthood. We found that a higher AHA cardiovascular health score in childhood predicted lower PWV in adolescence, but we observed no cross-sectional association between the AHA cardiovascular health score and PWV in adolescence. Our results suggest that a longer exposure to cardiovascular risk factors in childhood and adolescence may be needed to increase arterial stiffness in later life.

Raitakari and co-workers have shown that higher levels of cardiovascular risk factors in childhood predict higher cIMT in adulthood.[4] The AHA cardiovascular health score was associated with PWV but not cIMT in our longitudinal study in a general population of children followed up until adolescence. This finding suggests that PWV is a more sensitive indicator for cardiovascular health in childhood and adolescence than cIMT.

The ALSPAC (Avon Longitudinal Study of Parents and Children) study has shown that higher lean mass relates to higher cIMT in adolescents aged 17 years.[44] Cardiorespiratory fitness and exercise training load were also directly associated with cIMT in another study among adolescents aged 14 years.[28] Moreover, physical activity and exercise training have been found to lead to functional and structural adaptation of the arterial wall, making it more elastic but also more thick, thereby increasing cIMT.[45] We observed that higher MVPA and lean mass in childhood predicted lower PWV in adolescence, suggesting that higher MVPA and skeletal muscle mass protect against arterial stiffening and may thus counteract the adverse effects of risk factors for arterial stiffening in youth. However, we found associations of higher MVPA, lean mass, and cardiorespiratory fitness with higher cIMT in adolescents. These observations suggest that childhood cIMT may not serve as an indicator of arterial health in childhood and adolescence and that PWV may be a better measure for this purpose.

The strengths of our study include the longitudinal study design and the availability of measures for not only the cardiovascular health metrics but also those for arterial structure and function to have a more comprehensive overview of correlates and predictors for arterial health in childhood and adolescence. We slightly adjusted the criteria used to compute the cardiovascular health metrics and the AHA cardiovascular health score to the availability and the methods used to measure these metrics that make it more difficult to compare our findings with those of other studies. A limitation of our study is that there were missing values in the cardiovascular health metrics that could have weakened statistical power to observe their true associations with cIMT and PWV in childhood and adolescence. It is also important to note that although oscillometric devices validated in children should be used for BP screening according to current guidelines,[46] this study used aneroid sphygmomanometers. Finally, we had data on cIMT and PWV only from adolescence and therefore were unable to assess the associations of cardiovascular risk factors with changes in these measures of arterial health from childhood to adolescence. Our study sample included apparently healthy White adolescents, and therefore our findings may not be directly generalizable to other populations.

CONCLUSIONS

In conclusion, the findings of this study demonstrate the complexity of relationships between cardiovascular health metrics and arterial health indicators in childhood and adolescence. We found different associations of cardiovascular health metrics with cIMT and PWV in childhood and adolescence, calling for caution when interpreting the results of various cardiovascular risk factors with measures of arterial health, particularly in youth. It is important to note that cIMT does not purely reflect arterial health but also functional adaptation to regular MVPA, better cardiorespiratory fitness, and higher lean mass. These results underscore the importance of early intervention strategies aimed at promoting cardiovascular health in youth.

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