Association of Fitness With Vascular Intima-Media Thickness and Elasticity in Adolescence

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**KEY WORDS**
atherosclerosis, ultrasonography, exercise, children, prevention

**ABBREVIATIONS**
CI—confidence interval
CV—coefficient of variation
CVD—cardiovascular disease
HDL—high-density lipoprotein
HOMA-IR—homeostasis model of assessment—insulin resistance
hs-CRP—high-sensitivity C-reactive protein
IMT—intima-media thickness
LTPA—leisure-time physical activity
MET—metabolic equivalent
OR—odds ratio
STRIP—Special Turku Coronary Risk Factor Intervention Project
YEM—Young’s elastic modulus

**WHAT’S KNOWN ON THIS SUBJECT:** Atherosclerotic cardiovascular diseases are rooted in childhood. Vascular intima-media thickness (IMT) and elasticity are early surrogate markers of atherosclerosis. In adults, cardiorespiratory fitness is associated with enhanced arterial elasticity and decreased IMT.

**WHAT THIS STUDY ADDS:** Fitness was favorably associated with aortic IMT and elasticity in adolescents. The association was independent of several cardiometabolic risk factors. In fit adolescents, the increase in IMT during the preceding 6 years was smaller compared with low-fit peers.

**OBJECTIVES:** Vascular intima-media thickness (IMT) and elasticity are surrogate markers of atherosclerosis. Data on the effect of cardiorespiratory fitness on these measures of vascular health in adolescence are scarce. The aim was to examine the association of fitness with aortic and carotid artery IMT and elasticity in adolescents.

**METHODS:** Aortic (n = 449) and carotid (n = 467) IMT and elasticity were measured ultrasonographically in 17-year-old adolescents participating in a prospective, longitudinal atherosclerosis prevention study (Special Turku Coronary Risk Factor Intervention Project). Distensibility and Young’s elastic modulus (YEM) were used as measures of arterial elasticity. Cardiorespiratory fitness (maximum oxygen uptake, mL/kg/min) was measured with a maximal cycle ergometer test. Data on fitness were available for 341 of adolescents with aortic and 355 with carotid ultrasound measures.

**RESULTS:** Fitness was inversely associated with aortic IMT (β[SE] = −0.0029 [0.0013]; P = .031) and YEM (β[SE] = −0.012[0.0053]; P = .025) after adjusting for gender, physical activity, high-density lipoprotein/total cholesterol, triglycerides, high-sensitivity C-reactive protein, homeostasis model of assessment—insulin resistance, BMI, systolic blood pressure, and smoking. Risk of having low aortic distensibility (≤10th percentile) decreased with increasing fitness (odds ratio = 0.88, 95% confidence interval 0.82–0.98; P = .014). The increase in aortic IMT and YEM between ages 11 and 17 years was smaller in adolescents who were fit at age 17 compared with adolescents who had the lowest fitness level (P for IMT = .015, P for YEM = .0072). Fitness was not associated with carotid IMT or elasticity. Lifestyle counseling given in the Special Turku Coronary Risk Factor Intervention Project was not associated with fitness.

**CONCLUSIONS:** Fitness was favorably associated with aortic IMT and elasticity in adolescents. No association of fitness with the respective carotid indices was found. These data suggest that fitness in part enhances vascular health in healthy adolescents. *Pediatrics* 2013;132:e77–e84
Although cardiovascular diseases (CVDs) typically manifest in middle age or later in life, the initiation of atherosclerotic CVD begins in childhood. The development and progression of atherosclerosis is associated with adverse functional and structural changes of the arteries. Ultrasonography allows noninvasive assessment of these changes, mainly decreased arterial elasticity and thickening of the arterial wall. Decreased arterial elasticity is associated with conventional CVD risk factors, and it is an independent predictor of cardiovascular events. Increased intima-media thickness (IMT) also predicts future cardiovascular events and is associated with higher cardiovascular mortality.

Low cardiorespiratory fitness (later fitness) predicts development of CVD risk factors, and CVD and all-cause mortality. In adults, fitness is associated with enhanced arterial elasticity and decreased IMT. A high fitness level in adulthood is also linked to reduced progression of IMT. Fitness in adolescence predicts decreased carotid IMT in adulthood. Low fitness is interrelated with physical activity but they are not synonyms. Physical activity, for example, needs to be of sufficient intensity to improve fitness. Fitness is also markedly influenced by genetics; similar physical activity levels or exercise training yield different fitness levels individually. As much as half of the interindividual variance may be explained by genetic factors. In children and adolescents, the association between physical activity and fitness is weak to moderate.

We have previously reported a favorable association of physical activity with vascular endothelial function and aortic IMT in adolescents. Data on the effect of fitness on arterial structure and elasticity in adolescence are still scarce. We therefore investigated the association of fitness with IMT and elasticity of aortic and carotid arteries in ~350 17-year-old adolescents.

### METHODS

#### Study Design and Subjects

This study is a part of the prospective, randomized Special Turku Coronary Risk Factor Intervention Project (STRIP). Briefly, between February 1990 and June 1992, families of 6-month-old infants were recruited. At age 7 months, 1062 infants (56.5% of eligible age-cohort) were randomly allocated to a dietary intervention (n = 540) or control (n = 522) group. The intervention group received individualized dietary and subsequently antismoking counseling at least biannually. The study was approved by the Joint Commission on Ethics of the Turku University and Turku University Central Hospital. Written informed consent was obtained from the parents in the beginning of the study and from children at age 15.

This study comprised adolescents for whom measures of arterial IMT and elasticity, and fitness were available at age 17. Aortic and carotid ultrasound measures were provided for 449 and 467 adolescents, respectively. Data on fitness were available for 341 (76%) of the adolescents with aortic and 355 (76%) of those with carotid ultrasound measures. Aortic and carotid IMT was similar in adolescents with fitness data to those who lacked measurement of fitness (P for aortic IMT = .94, P for carotid IMT = .17).

#### Vascular IMT and Elasticity

IMT and elasticity of abdominal aorta and common carotid artery were studied with ultrasonography (Acuson Sequoia 512 mainframe; Acuson, Mountain View, CA) biyearly from the age of 11, when aortic and carotid ultrasound measures were available for 435 and 442 children, respectively. For aortic IMT measurements, the most distal 15 mm of abdominal aorta was scanned with a ≥10 MHz linear-array transducer. The image was focused on the dorsal wall, captured, and stored for subsequent offline analysis. Four measurements of IMT covering the far wall were taken and the average was used. In our laboratory, interobserver coefficient of variation (CV) was 3.9% (n = 88) and between-visits CV was 4.9% (n = 21).

To assess carotid IMT, the far wall of the distal common carotid arteries on both sides 1 to 2 cm from the bulb were scanned from anterior oblique and lateral angles using a 13-MHz linear-array transducer. Two end-diastolic frames from both interrogation angles on both sides were analyzed. Four measures were obtained in each image; the mean indicated average carotid IMT. In our laboratory, interobserver variation was 3.0% (n = 88), and between-visit CV was 3.9% (n = 21).

Elasticity of aortic and carotid arteries was assessed using M-mode images and concomitant measurement of blood pressure in the brachial artery. Arterial diameter was measured twice at end diastole and twice at end systole. Mean of the end-diastolic and end-systolic diameters, along with blood pressure and IMT, were used to calculate arterial elasticity indices: distensibility and Young’s elastic modulus (YEM). Higher distensibility and lower YEM value indicate greater arterial elasticity. Aortic and carotid elasticity indices, respectively, were closely correlated (aortic distensibility and YEM: r = −0.88, P < .0001; carotid distensibility and YEM: r = −0.80, P < .0001).

Ultrasonography studies were performed in silence in a temperature-controlled clinical research laboratory. On measurement day, adolescents were advised to refrain from smoking, caffeinated drinks, juice, high-fat meals, and vitamin supplementation.

#### Fitness

Fitness (maximum oxygen uptake [VO2max], mL/kg/min) was measured
with maximal cycle ergometer exercise test (Ergoselect 100 K; Ergoline, Bitz, Germany). The test began at a workload of 50 W, which was increased by 30 W (boys)/25 W (girls) every 2 minutes until exhaustion. Mean workload during the last 4 minutes of work was calculated and VO2max was estimated as recommended by the American College of Sports Medicine. Adolescents who failed to reach a heart rate of 177 beats per minute ((205–0.5 × age) × 0.9) were excluded. Mean maximum heart rate was 194 beats per minute. Genderwise tertile cutoff points for fitness were calculated to indicate low-, moderate-, and high-fit adolescents.

**Physical Activity**

Leisure-time physical activity (LTPA) was assessed with a self-administered questionnaire, and calculated by multiplying mean frequency, duration, and intensity (multiple of resting metabolic rate; metabolic equivalent [MET]) of weekly LTPA (MET h/wk). LTPA comprised recreational and organized physical activity/sports outside school hours. The questionnaire correlates moderately well with objective physical activity measures. Because of previously reported association between LTPA and aortic IMT, the combined effect of fitness and LTPA on aortic IMT was studied. According to LTPA, groups of adolescents with low (<10 MET h/wk) and high (>30 MET h/wk) LTPA were formed. LTPA of 30 MET h/wk corresponds to ∼1 hour of moderate-intensity physical activity daily, recommended as the minimum amount of physical activity for adolescents; 10 MET h/wk corresponds to ∼2 hours of moderate intensity physical activity weekly and indicates a low LTPA level in adolescents. To form the combined fit- ness and LTPA groups, adolescents with fitness below genderwise-assessed 50th percentile and (1) low LTPA (n = 73) or (2) high LTPA (n = 42) were determined.

Second, adolescents with fitness above genderwise-assessed 50th percentile and (1) low LTPA (n = 23) or (2) high LTPA (n = 129) were determined.

**Physical Examination and Smoking**

Height and weight were measured, and BMI calculated as weight/height² (kg/m²). Blood pressure was measured 3 times (mean used) from the right arm with an automated sphygmomanometer during the ultrasonography study (Omron M4; Omron Matsusaka, Matsusaka, Japan). Smoking habits were assessed with a questionnaire in which the adolescents reported to have smoked 0, 1, 2 to 50, or >50 cigarettes during their lives.

**Laboratory Measures**

A fasting venous blood sample was drawn and concentrations of serum total and high-density lipoprotein (HDL)-cholesterol, triglyceride, and insulin and glucose were determined. Low-density lipoprotein-cholesterol concentration was calculated by using the Friedewald formula. HOMA-IR (homeostasis model of assessment-insulin resistance) was calculated as fasting insulin (µU/mL) × fasting glucose (mmol/L)/22.5. High-sensitivity C-reactive protein (hs-CRP) was assayed by a turbidimetric immunoassay with sensitivity of 0.06 mg/L. Values >10 mg/L were excluded.

**Statistical Analyses**

Interaction between fitness and gender was assessed for the variables included in Table 1 by using multivariate linear regression analysis. Because no fitness-by-gender interactions were found (ie, the association of fitness with, eg, aortic IMT, was similar in girls and boys), the genders were analyzed combined. Exposure of the adolescent to the STRIP study intervention was not associated with fitness (mean [SD] VO2max: intervention group 41.1 [7.3], control group 39.9 [7.1] mL/kg/min; P = .10 [t test], study group-by-gender interaction P = .22). Therefore, the STRIP study groups also were analyzed combined. For ultrasound measures that were borderline significantly associated with fitness (P = .05–10; Table 1) gender-specific, categorical risk variables were formed by using 10th/90th percentile cutoff points indicating high-risk adolescents (aortic distensibility: ≤10th percentile, carotid IMT: ≥90th percentile). Aortic and carotid YEM, triglycerides, hs-CRP, and insulin were logarithmically transformed. Fitness was used as continuous variable (Tables 1, 2, and 3) or as a categorical variable (gender-specific tertile/median cutoff points) (Figs 1, 2, and 3). Multivariate linear regression analysis was used to study association of fitness with ultrasound measures and cardiometabolic risk factors (Table 1), and correlates of aortic and carotid IMT and YEM (Tables 2 and 3). In Tables 2 and 3, cardiometabolic risk factors associated with fitness, and systolic blood pressure and LTPA were entered into the model. To avoid multicollinearity, HDL/total cholesterol and HOMA-IR were used. To further ensure that multicollinearity did not confound the results, variance inflation was assessed. It was <3 in all multivariate models, indicating that the variables could be included in the analyses simultaneously.

Association of fitness with categorical high-risk aortic distensibility and carotid IMT was studied with logistic regression analysis with covariates. Analysis of covariance was used to study the change in aortic and carotid IMT and YEM between ages 11 and 17, and differences in aortic IMT at age 11, in low-, moderate-, and high-fit adolescents (Figs 1 and 2). Tukey-Kramer adjustment was applied for pairwise comparisons. In adolescents with fitness below genderwise-determined 50th percentile, t test was used to compare aortic IMT among those with low or high LTPA. Similar analysis was performed in adolescents with fitness.
above the genderwise-determined 50th percentile. Values of 2-tailed $P < .05$ were considered significant; SAS release 9.3 (SAS Institute, Cary, NC) was used.

**RESULTS**

**Fitness and Vascular IMT**

Fitness was inversely associated with aortic IMT (Table 1). The favorable association of fitness with aortic IMT remained after adjustment for cardiometabolic risk factors and LTPA (Table 2). The progression of aortic IMT between ages 11 and 17 years was smaller in adolescents who were fit at age 17 compared with adolescents who had the lowest fitness level (Fig 1). Fit 17-year-old adolescents had a smaller aortic IMT compared with low-fit adolescents already at age 11 ($P = .017$).

Fitness was not associated with IMT of the carotid artery (Table 1). Adjustment for cardiometabolic risk factors and LTPA did not change the result (Table 3). Fitness was also not associated with the risk of having high carotid IMT (odds ratio [OR] = 1.01, 95% confidence interval [CI] = 0.96–1.07; $P = .76$), adjusted for gender) or to the change in carotid IMT between ages 11 and 17 years ($\beta$[SE] = −0.0019 [0.0039], $P = .63$).

**Fitness and Vascular Elasticity**

Fitness was associated with improved arterial elasticity determined by YEM (Table 1). Adjustment for cardiometabolic risk factors and LTPA did not change the result (Table 2). Aortic YEM increased less between ages 11 and 17 years in adolescents who were fit at age 17 compared with adolescents who had the lowest fitness level (Fig 2). Fitness was associated with a decreased risk of having a low aortic distensibility (OR = 0.94, 95% CI = 0.89–0.99).
Fitness (VO2max), mL/kg/min  
-0.0030 (0.00066) .64  
0.0044 (0.0030) .14
Gender (girls versus boys)  
-0.026 (0.087) .0029  
-0.080 (0.039) .041
BMI, kg/m²  
0.0030 (0.0012)  
0.010  
0.013 (0.0053) .011
HDL/total cholesterol  
-0.0053 (0.052) .92  
0.084 (0.23) .72
Triglycerides, mmol/L  
-0.0063 (0.0090) .48  
-0.026 (0.041) .53
hs-CRP, mg/L  
0.00050 (0.0029)  
0.06  
0.0089 (0.013) .50
Systolic BP, mm Hg  
0.00042 (0.0035) .23  
0.0086 (0.0016) <.0001
HOMA-IR  
-0.0043 (0.0067) .92  
-0.0034 (0.030) .91
Smoking  
0.0081 (0.0028) .0038  
0.0022 (0.013) .86
Leisure-time physical activity, MET h/wk  
0.00013 (0.00016) .39  
-0.00097 (0.00070) .17

BP, blood pressure.  
* Logarithmically transformed.  
* Regression coefficient ($\beta$) and SE for a 1-unit change in the explanatory variable.  
P, 1, 2–50, or >50 cigarettes smoked during life.

**TABLE 3** Multivariable Correlates of Carotid IMT and Elasticity (YEM*)

**FIGURE 1**
Mean (SE) aortic IMT in adolescents with low, moderate, or high fitness at age 17. P value: association of the variable with change in aortic IMT. Change in aortic IMT in high- versus low-fit adolescents: $P = .015$ (Tukey-Kramer adjusted pairwise comparison, gender included in the model). Other pairwise comparisons were nonsignificant.

$P = .028$, adjusted for gender. Mean (SD) fitness (VO2max) was 38.2 (8.0) mL/kg/min in adolescents with a low aortic distensibility and 40.6 (7.2) mL/kg/min in adolescents with aortic distensibility >10th percentile. The favorable association of fitness with decreased risk for low aortic distensibility persisted after further adjustment for BMI, Hdl/total cholesterol, triglycerides, hs-CRP, HOMA-IR, LTPA, systolic blood pressure, and smoking (OR = 0.89, 95% CI = 0.82–0.98; $P = .014$). When aortic distensibility was treated as a continuous variable, there was no association between fitness and distensibility (Table 1).

Contrary to elasticity indices of the aorta, fitness was not associated with the carotid artery elasticity (Table 1). Adjustment for cardiometabolic risk factors and LTPA did not change the result (YEM; Table 3) nor was fitness associated with the change in carotid elasticity (YEM) between ages 11 and 17 years ($\beta$[SE] = -1.13[2.89], $P = .69$).

**DISCUSSION**
This study shows that fitness is favorably associated with aortic IMT and elasticity in adolescents. The association was not diluted after adjustment for LTPA and a variety of cardiometabolic risk factors. In the adolescents who were fit at age 17, the increase in aortic IMT and YEM during the preceding 6 years was smaller compared with those who had the lowest fitness level.

To our knowledge, there are no previous studies investigating the association of fitness with aortic IMT. Regarding carotid IMT, an inverse association between fitness and IMT has been reported in adults.9,10 In obese children, exercise training was associated with smaller increase in IMT during follow-up,24 and children with high IMT tended to be less fit.25 In longitudinal studies, fitness measured in adolescence was inversely associated with carotid IMT as an adult.12 and during adulthood, high fitness may reduce the progression of carotid IMT.11 In line with these studies, we found that with increasing fitness level, aortic IMT was reduced, but in contrast, no association between fitness and carotid IMT was observed. Autopsy studies have shown that the earliest morphologic alterations in the arterial wall emerge in the abdominal aorta, before the carotid artery. Aortic IMT may therefore be a better surrogate marker for atherosclerosis at young age. Consistently, we have reported that children with increased risk factor load...
are more efficiently identified by measuring aortic than carotid IMT. The lack of association between fitness and carotid IMT may be because the effect of fitness on carotid IMT emerges only at later age and is not evident in adolescence. Indeed, a high fitness level was shown to associate with reduced carotid IMT in subjects older than 60 years, but not in younger subjects. It may also be that the effect of fitness on IMT is site specific, more evident in muscular (e.g., femoral) but not in elastic (e.g., carotid) arteries.

In addition to aortic IMT, a favorable association between fitness and aortic elasticity was found. Previous studies in adults have reported enhanced carotid artery elasticity with a higher fitness level. Similar to IMT, we found no association between fitness and carotid elasticity among the adolescents. We suspect that the reasons for this resemble those of carotid IMT. The effect of fitness on arterial elasticity may differ by age; in middle-aged and older men (≥37 years), fitness was associated with enhanced carotid artery elasticity, whereas no association was observed in younger adults (18–37 years). The effect of fitness on elasticity may also differ between arteries. Fitness in adolescence did not predict carotid elasticity in adulthood, whereas a higher adolescent fitness level was associated with enhanced elasticity of the adult femoral artery.

Interestingly, fitness at age 17 was associated with the increase in aortic IMT and YEM between ages 11 and 17 years. In adolescents who were fit, the 6-year increase in these indices was smaller compared with those who had the lowest fitness level. The difference in aortic IMT between the most and least fit 17-year-olds was evident already at age 11. The association between current fitness and previous progression of aortic IMT and YEM may be due to the stability of fitness; those 17-year-old adolescents who were fit may have been the fit ones also at age 11. Unfortunately, we do not have fitness data on the 11-year-olds to verify this. Other studies have reported a marked tracking of fitness from childhood to adolescence, supporting our suggestion. We have previously reported a favorable association between LTPA and aortic IMT. In this study, when LTPA along with fitness was included in the analysis investigating the determinants of aortic IMT, LTPA showed no association with IMT. With regard to arterial elasticity, it has been suggested that fitness is more strongly related to arterial stiffness than physical activity. In general, the relationship between physical activity and health outcomes is weaker than that of fitness. The lack of association...
between LTPA and aortic IMT, when fitness was taken into account, could in this study be because of the difference in precision of the methodologies used to assess physical activity and fitness. An objective method was used to study fitness, whereas LTPA data were collected by using a questionnaire, prone to several limitations. The larger measurement error in the assessment of physical activity may thus have decreased the probability of detecting a significant association. To gain more insight, we investigated the effect of a high or low LTPA level in adolescents who were either above or below the fitness median. In both fitness groups, low LTPA was associated with increased aortic IMT compared with having a high LTPA level, suggesting that both fitness and physical activity favorably associate with aortic wall thickness. Nevertheless, it is obvious that physical activity remains the only means to improve fitness, making it the relevant target for health improvement.

Data on the mechanisms linking fitness to arterial IMT and elasticity in adolescents are scarce. Arterial IMT and elasticity are associated with cardiometabolic risk factors, and it is suggested that the favorable effect of fitness on these vascular indices is mediated through the risk characteristics. In this study, higher fitness level was indeed associated with lower levels of several cardiometabolic risk factors. However, the association of fitness with aortic IMT and elasticity remained after taking these risk factors into account, suggesting that the association was not completely mediated via the risk factors considered.

A limitation of the study is that in the calculation of the elasticity indices, pulse pressure measured from the brachial artery, and not from the arteries in question, was used. However, an excellent correlation between systolic and diastolic blood pressures measured invasively from the ascending aorta and noninvasively from the brachial artery has been shown. Because carotid IMT increases the closer to the bulb the measurement has been performed, scanning of the arteries 1 to 2 cm from the bulb may have caused heterogeneity to the carotid IMT measurements in this study. Of note, no association between STRIP intervention and fitness was found, which likely relates to that physical activity was not a structured, continuous part of the intervention.

CONCLUSIONS

Fitness was favorably associated with aortic IMT and elasticity in adolescents. No association of fitness with carotid IMT and elasticity was found, which may be because this association emerges only at a later age and differs between arteries. These data suggest that fitness may enhance vascular health in healthy adolescents. To improve fitness, physical activity in adolescents should be supported.

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This trial has been registered at www.clinicaltrials.gov (identifier STRIP19902010, NCT00223600).

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