Association of Physical Activity With Vascular Endothelial Function and Intima-Media Thickness
A Longitudinal Study in Adolescents

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Background—Impairment of vascular endothelial function and increased intima-media thickness (IMT) are important early steps in atherogenesis. Longitudinal data on the effect of physical activity on endothelial function and IMT in healthy adolescents are lacking. We investigated prospectively the association of leisure-time physical activity with endothelial function (brachial artery flow-mediated dilatation; FMD) and aortic IMT in adolescents.

Methods and Results—FMD and IMT were measured with ultrasonography at 13 (n=553), 15 (n=531), and 17 (n=494) years of age in adolescents participating in a longitudinal atherosclerosis prevention study (Special Turku Coronary Risk Factor Intervention Project for Children). Mean aortic IMT, maximum FMD, and total FMD response (area under the dilatation curve 40 to 180 seconds after hyperemia) were calculated. Leisure-time physical activity was assessed with a questionnaire, and metabolic equivalent (MET) hours per week of leisure-time physical activity were calculated by multiplying weekly mean exercise intensity, duration, and frequency. Leisure-time physical activity was directly associated with endothelial function (P for maximum FMD=0.0021, P for total FMD response=0.0036) and inversely with IMT (P=0.011) after adjustment for age, sex, body mass index, high-density lipoprotein/total cholesterol, systolic blood pressure, and C-reactive protein and regarding FMD brachial artery diameter. Sedentary adolescents who increased their leisure-time physical activity from <5 to >5 (IMT) or >30 (maximum FMD) MET h/wk between 13 and 17 years of age had an increased maximum FMD (P=0.031) and decreased progression of IMT (P=0.047) compared with adolescents who remained sedentary. IMT progression was attenuated in persistently active adolescents compared with those who became sedentary (P=0.0072).

Conclusions—Physical activity is favorably associated with endothelial function and IMT in adolescents. Importantly, a moderate increase in physical activity is related to decreased progression of IMT. A physically active lifestyle seems to prevent the development of subclinical atherosclerotic vascular changes in healthy adolescents.


Key Words: atherosclerosis ■ children ■ exercise ■ prevention ■ sedentary

The development and progression of subclinical atherosclerosis during adolescence is associated with functional and structural changes of the arteries.1-3 Impairment of endothelial vasodilatory function is associated with coronary atherosclerosis,4 and it predicts cardiovascular events.5 Flow-mediated dilatation (FMD) of the brachial artery, assessed noninvasively by ultrasound, is a widely used marker of systemic arterial endothelial function.6,7 The carotid artery has commonly been the target for the ultrasonic assessment of early structural changes. Autopsy studies, however, have shown that the earliest morphological alterations in the arterial wall emerge in the abdominal aorta.8 Intima-media thickness (IMT) of the abdominal aorta may therefore be a better surrogate marker of atherosclerosis than carotid IMT, especially at young ages. Consistently we have shown that children with increased risk factor load are identified more efficiently by measurement of aortic than carotid IMT.1 In adults, aortic IMT is associated with coronary heart disease.9

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Physical activity enhances endothelial function in adults10,11 and counteracts the loss of vasodilatory function associated with aging.12 Children also benefit from exercise.13-17 Physical activity is associated with decreased progression of carotid IMT in healthy adults18 and in patients with coronary heart disease19 or hypertension.20 Cross-sectional studies, however, have often failed to find an association between physical activity and carotid IMT.21-23 To date, no studies have investigated longitudinally the association of physical activity with IMT of the aorta, where the structural changes are suggested to appear first.
We have shown that physical activity has a favorable effect on endothelial function in healthy adolescent boys.24 Data on the effect of physical activity on vascular function and structure in adolescents are still scarce, and longitudinal studies are lacking. Therefore, we investigated the association of physical activity with vascular function (FMD) and structure (aortic IMT) in nearly 500 adolescents studied repeatedly at 13, 15, and 17 years of age.

Methods

Study Design and Subjects

This study is a part of the ongoing prospective randomized Special Turku Coronary Risk Factor Intervention Project for Children (STRIP).25 In brief, between February 1990 and June 1992, families of 6-month-old infants were recruited to the study at well-baby clinics in Turku, Finland. At 7 months of age, 1062 infants (56.5% of the eligible age cohort) were randomly allocated to a dietary intervention (n = 522) group. The intervention group received individual-ized dietary and subsequently antismoking counseling at least biannu-

| Table 1. Characteristics of the Study Cohort (Adolescents With Maximum Flow-Mediated Dilatation Data) |
|----------------|----------------|----------------|
| BMI, kg/m²     | Boys           | Girls          |
| 13 y of Age    | 15 y of Age    | 17 y of Age    | 13 y of Age    | 15 y of Age    | 17 y of Age    | 13 y of Age    | 15 y of Age    | 17 y of Age    |
| 19.5±3.3 (229) | 20.7±3.2 (232) | 21.6±3.4 (231) | 19.1±3.0 (255) | 20.3±3.2 (256) | 21.5±3.2 (238) |
| LTPA, MET h/wk | 23.9±20.8 (229) | 25.3±21.1 (204) | 25.5±19.1 (225) | 31.2±23.0 (254) | 31.9±24.2 (225) | 29.3±25.7 (227) |
| Sedentary, %   | 33.6 (77)      | 24.0 (49)      | 31.0 (52)       | 20.1 (51)       | 18.2 (41)       | 26.0 (59)       |
| Moderately active, % | 48.5 (111) | 52.9 (108) | 53.3 (120) | 48.8 (124) | 42.7 (98) | 42.3 (96) |
| Active, %     | 17.9 (41)      | 23.1 (47)      | 23.6 (53)       | 31.1 (79)       | 39.1 (88)       | 31.7 (72)       |
| Regular smoker, % | 0.46 (1/216)  | 3.0 (7/230)    | 6.6 (15/228)    | 0 (0)           | 1.6 (4/254)     | 8.1 (19/236)    |
| Systolic blood pressure, mm Hg | 105.6±8.2 (227) | 108.4±7.7 (231) | 110.0±8.6 (230) | 108.3±8.0 (248) | 117.7±9.0 (252) | 121.3±9.9 (238) |
| Diastolic blood pressure, mm Hg | 61.5±4.5 (221) | 61.5±4.9 (231) | 63.3±5.5 (230) | 61.9±5.1 (248) | 62.7±5.2 (252) | 64.6±5.9 (238) |
| Total cholesterol, mmol/L | 4.27±0.73 (229) | 4.16±0.76 (233) | 4.34±0.76 (229) | 4.15±0.72 (255) | 3.76±0.72 (253) | 3.79±0.63 (237) |
| HDL cholesterol, mmol/L | 1.21±0.23 (229) | 1.23±0.23 (232) | 1.33±0.27 (229) | 1.20±0.25 (255) | 1.08±0.23 (253) | 1.06±0.21 (235) |
| LDL cholesterol, mmol/L | 2.66±0.65 (229) | 2.52±0.64 (232) | 2.56±0.64 (229) | 2.59±0.61 (255) | 2.28±0.64 (253) | 2.30±0.57 (235) |
| Triglycerides, mmol/L | 0.75 (0.39) (229) | 0.75 (0.39) (233) | 0.90 (0.59) (229) | 0.66 (0.49) (255) | 0.75 (0.49) (253) | 0.85 (0.39) (237) |
| hs-CRP, mg/L | 0.21 (0.32) (220) | 0.31 (0.43) (230) | 0.60 (1.13) (221) | 0.27 (0.41) (253) | 0.29 (0.42) (251) | 0.43 (0.74) (234) |
| FMDmax, % | 9.8±4.3 (231) | 10.6±4.4 (233) | 11.2±4.8 (231) | 9.5±4.3 (256) | 9.7±4.9 (256) | 9.2±4.2 (238) |
| FMDauc, %×s | 705.4±497.0 (230) | 786.2±531.5 (230) | 815.5±570.4 (223) | 731.2±568.0 (255) | 777.6±615.8 (250) | 659.2±516.0 (232) |
| Arterial diameter, mm | 2.78±0.28 (231) | 2.75±0.28 (233) | 2.74±0.28 (231) | 3.03±0.31 (256) | 3.16±0.31 (256) | 3.31±0.33 (238) |
| IMT (aorta, mm) | 0.53 (0.12) (227) | 0.53 (0.09) (218) | 0.52 (0.11) (219) | 0.52 (0.12) (253) | 0.53 (0.085) (238) | 0.55 (0.11) (225) |

BMI indicates body mass index; LTPA, leisure-time physical activity; MET, metabolic equivalent; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; FMDmax, maximum flow-mediated dilatation; FMDauc, flow-mediated dilatation area under dilatation response versus time curve; and IMT, intima-media thickness. Data are given as mean±SD (n), median (interquartile range) [n] for triglyceride and hs-C-reactive protein concentrations, or % (n) for LTPA group and smoking status.

*Less than 5 MET h/wk (<10 min/d of moderate-intensity LTPA).
†Five to 50 MET h/wk.
‡More than 50 MET h/wk (>1.5 h/d moderate-intensity LTPA).
§Smoking at least once a day.

Vascular Endothelial Function and IMT

Endothelial function of the left brachial artery was studied with ultrasonography (Acuson Sequoia 512 mainframe; Acuson, Mountain View, CA) with a 13.0-MHz linear-array transducer.26 The method is based on the measurement of the arterial diameter at baseline and after increased blood flow. At first, luminal diameter of the artery was measured at rest at a fixed position at end diastole, incident with the R wave on ECG (3 measurements; the mean was used in the analyses). The artery was then occluded by inflating a blood pressure cuff placed around the forearm to a pressure of 250 mm Hg. After 4.5 minutes, the cuff was deflated, causing increased blood flow, reactive hyperemia. A continuous scan was recorded for 30 to 180 seconds after cuff release, and dilatation of the artery from baseline was measured offline at end diastole, incident with the R wave, at 10-second intervals. From these data, FMDmax (%) was measured. The total dilatation response, defined as the area under the dilatation response versus time curve 40 to 180 seconds after hyperemia (FMDauc; %×s), was also assessed. The interobserver variation (coefficient of variation) of FMD measurements was 8.6%, and the between-visits coefficient of variation was 9.0% in our laboratory.27

For the aortic IMT measurements, the most distal 15 mm of the abdominal aorta was scanned with a linear-array transducer with a 1 adolescent reported regular smoking, whereas the number of regular smokers was 11 at 15 years of age and 34 at 17 years of age. Although approximately half of the initially recruited families had discontinued participation during the 17 years of follow-up, serum total cholesterol concentration and saturated fat intake were similar in the children who remained in the study and those who discontinued participation.26 In addition, the mean body mass index (BMI) of the children who remained in the study at 13 years of age was similar to the mean BMI of those who had discontinued participation at the beginning of the study and at 13 months and 2, 5, and 10 years of age. This suggests that discontinuance caused no or marginal bias to this study examining the association of physical activity and vascular health.
scanning frequency of at least 10 MHz. The image was focused on the far wall (dorsal arterial wall), and image quality was optimized with gain settings. Images 15 mm in width were magnified with resolution box. All images were taken at end diastole, incident with the R wave. An image of the most distal 15 mm aortic far wall was captured and stored for subsequent offline analysis. Four measurements of IMT covering the entire far wall segment were taken with ultrasonic calipers, and the average of these measurements was utilized. The interobserver coefficient of variation for aortic IMT measurements was 3.9%, and the between-visits coefficient of variation was 4.9%.1

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

Physical Activity
LTPA was assessed at 13, 15, and 17 years of age with a self-administered questionnaire in which the frequency, duration, and intensity of habitual LTPA were reported in multiple-choice questions.28 For the habitual LTPA intensity, the choices were as follows: never sweating and becoming breathless, some sweating and becoming breathless, and heavy sweating and becoming breathless. For the frequency of the LTPA, the choices were less than once a month, once a month, once a week, 2 to 4 times a week, and once a day. For the average duration of an LTPA bout, 4 choices were given: <20, 20 to 40, 40 to 60, and >60 minutes. LTPA was calculated as a multiple of the resting metabolic rate (metabolic equivalent [MET] h/wk) by multiplying the frequency, mean duration, and mean intensity of weekly LTPA.29 For intensity (METs) of LTPA, coefficient values of 4, 6, and 10 corresponding to light, moderate, and vigorous physical activity30 were used in the calculation. LTPA comprised recreational and organized physical activity/sports outside school hours. The questionnaire has been widely used in studies involving children, adolescents, and adults.29,31,32 It correlates relatively well with objective physical activity data derived from accelerometers (r=0.26–0.40) and pedometers (r=0.30–0.39)33 in young adults and with directly assessed maximal exercise capacity (V\text{O}_2 max) (r=0.49–0.53).34 We have previously shown among these adolescents that low LTPA is associated with decreased FMD at 13 years of age.24 Therefore, the effect of an increase in LTPA between 13 and 17 years of age on FMD and IMT compared with remaining sedentary participants was studied. Adolescents with persistently low LTPA were defined as those who exercised <5 MET h/wk at 13 and 17 years of age (n=53). A moderate LTPA increase was defined as an LTPA increase from <5 to >5 MET h/wk (n=74). Those with an LTPA increase from <5 to >30 MET h/wk (n=28) made up the group with an extensive LTPA increase. The level of 5 MET h/wk corresponds to ~1 hour of moderate intensity physical activity weekly and indicates a very low exercise level. The cutoff point of 30 MET h/wk corresponds to ~1 hour of moderate-intensity exercise daily, recommended as the minimum amount of physical activity for adolescents.35

As a secondary analysis, the effect of decrease in LTPA to the level of <5 MET h/wk compared with being persistently active was studied. For the analyses, the adolescents were divided into groups with LTPA >5 MET h/wk at 13 and 17 years of age (n=270) and LTPA decrease from >5 to <5 MET h/wk (n=66). Furthermore, the effect of an extensive decrease in LTPA from >30 to <5 MET h/wk (n=37) compared with having LTPA persistently >30 MET h/wk (n=160) was studied.

Physical Examination and Smoking
Height was measured by a Harpenden stadiometer (Holtain, Crymych, Great Britain) and weight with an electronic scale (Soehnle S10; Soehnle Murrhardt, Germany). BMI was calculated as weight in kilograms divided by height in meters squared. Adolescents were classified overweight/obese if their BMI exceeded the international age- and sex-specific criteria.36 Blood pressure was measured 3 times from the right arm with an automated sphygmomanometer during the ultrasonography study (Omrion M4; Omron Matsusaka, Matsuaka, Japan). The mean of the 3 measurements was used. Mean arterial blood pressure was calculated as follows: diastolic blood pressure + [(systolic−diastolic blood pressure)/3]. Smoking habits were assessed with a questionnaire. Adolescents who reported smoking at least once a day were regarded as regular smokers.

Laboratory Measures
A fasting venous blood sample was drawn, and after clotting at room temperature for 30 to 60 minutes and centrifugation at 3400 g for 12 minutes, serum was separated and stored at −25°C. Serum total cholesterol concentration was determined with a fully enzymatic cholesterol oxidase-p-aminophenazone method (CHOD-PAP, Merck, Darmstadt, Germany). Serum high-density lipoprotein (HDL) cholesterol concentration was analyzed after precipitation of low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol with dextran sulfate 500 000. Serum triglyceride concentration was analyzed with the colorimetric GPO-PAP method (Merck). High-sensitivity C-reactive protein (hs-CRP) was assayed by a turbidimetric immunoassay (Wako Chemicals GmbH, Neuss, Germany) with a sensitivity of 0.06 mg/L.

Statistical Analyses
Girls and boys were analyzed together because there was no interaction between sex and LTPA when FMD (estimated \( \beta = -0.017 \); 95% confidence interval [CI] = -0.038 to 0.0052; \( P = 0.14 \)) or IMT (estimated \( \beta = -0.00030 \); 95% CI = -0.0086 to 0.00026; \( P = 0.29 \)) was the explanatory variable. Exposure of the adolescent to the dietary counseling and smoking prevention in the STRIP study was not associated with LTPA at 13 years of age (LTPA mean: intervention group, 28.9 MET h/wk [95% CI, 26.2–31.6]; control group, 25.9 MET h/wk [95% CI, 23.3–28.5]; \( P = 0.18 \)), 15 years of age (LTPA mean: intervention group, 29.2 MET h/wk [95% CI, 26.0–32.4]; control group, 27.7 [95% CI, 24.9–30.5]; \( P = 0.49 \)), or 17 years of age (LTPA mean: intervention group, 29.2 MET h/wk [95% CI, 25.9–32.5]; control group, 25.2 MET h/wk [95% CI, 22.7–27.8]; \( P = 0.11 \); Cochrane–Mantel–Haenszel statistics). The adolescents in the STRIP intervention or control group were therefore combined for analysis.

The association of LTPA with FMD and IMT between 13 and 17 years of age was studied with a linear mixed-effects model using compound symmetry covariance structure. In the model, LTPA was used as a continuous variable. The analyses were adjusted for potentially confounding variables. For FMD, adjustment was made for age, sex, and brachial artery diameter (Figure 1) and further adjusted for BMI, HDL/total cholesterol, systolic or mean arterial blood pressure, and hs-CRP (Table 2). Except for arterial diameter, the adjusted variables were similar for IMT (Figure 2 and Table 3). hs-CRP was logarithmically transformed. In addition, adjustment was made for smoking status.

To illustrate the associations between the continuous LTPA and IMT variables (Figures 1 and 2), we calculated the adjusted means (SE) for FMD/IMT by physical activity levels using cutoff points of <5, 5 to 50, and >50 MET h/wk, indicating low, moderate to high, and very high levels of physical activity. The \( t \) test was used to analyze the difference in IMT progression (IMT at 17 years of age minus IMT at 13 years of age) and FMD change (FMDmax at 17 years of age minus FMDmax at 13 years of age) in adolescents who were persistently sedentary compared with adolescents who had increased LTPA. Similarly, the \( t \) test was used to compare IMT and FMD change in persistently active adolescents with those in whom LTPA decreased. In the analyses, adjustment was made for sex, IMT or FMD at 13 years of age, BMI, HDL/total cholesterol, systolic or mean arterial blood pressure, and hs-CRP at 17 years of age; for the FMD analyses, adjustment was also made for brachial artery diameter.

The association of LTPA with brachial artery diameter was studied with a linear mixed-effects model using compound symmetry covariance structure (adjusted for age and sex). The \( t \) test was used to compare arterial diameter at 17 years of age in persistently active adolescents with that in adolescents whose LTPA increased extensively. Values of \( P < 0.05 \) were considered significant. SAS release 9.2 (SAS Institute, Cary, NC) was used for the analyses.
Results
Physical Activity, Endothelial Function, and IMT Between 13 and 17 Years of Age
Markers of vascular endothelial function, ie, FMDmax and FMDauc, were directly associated with LTPA in analyses adjusted for age, sex, and brachial artery diameter (Figure 1). FMDmax and FMDauc were closely correlated ($r_{\text{Pearson}} = 0.87–0.90$). IMT of the abdominal aorta decreased with increasing LTPA (adjusted for age and sex; Figure 2). For both FMD and IMT, interaction of sex and LTPA ($P$ for FMDmax $= 0.14$, $P$ for IMT = 0.29) and for age and LTPA ($P$ for FMDmax $= 0.69$, $P$ for IMT = 0.26) was nonsignificant, indicating that the effect of LTPA on FMD and IMT was similar in girls and boys at different ages.

Table 2. Multivariable Correlates of Maximum Flow-Mediated Dilatation and Flow-Mediated Dilatation Area Under Dilatation Versus Time Curve

<table>
<thead>
<tr>
<th></th>
<th>FMDmax, %</th>
<th>FMDauc, %×s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leisure-time physical activity, MET h/wk</td>
<td>$0.017 \pm 0.0054$, 0.0021</td>
<td>$1.97 \pm 0.67$, 0.0036</td>
</tr>
<tr>
<td>Age, y†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>$-0.69 \pm 0.28$, 0.050</td>
<td>$-48.78 \pm 35.70$, 0.24</td>
</tr>
<tr>
<td>15</td>
<td>$-0.36 \pm 0.25$, 0.050</td>
<td>$4.86 \pm 32.32$, 0.24</td>
</tr>
<tr>
<td>Sex, boys vs girls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs girls</td>
<td>$-1.49 \pm 0.34$, &lt;0.0001</td>
<td>$-239.26 \pm 41.04$, &lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>$0.26 \pm 0.046$, &lt;0.0001</td>
<td>$26.94 \pm 5.57$, &lt;0.0001</td>
</tr>
<tr>
<td>HDL/total cholesterol</td>
<td>$0.54 \pm 2.10$, 0.80</td>
<td>$-168.74 \pm 253.85$, &lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>$0.012 \pm 0.014$, 0.42</td>
<td>$0.34 \pm 1.78$, 0.85</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>$-0.036 \pm 0.045$, 0.42</td>
<td>$-4.06 \pm 5.62$, 0.47</td>
</tr>
<tr>
<td>Brachial artery diameter, mm</td>
<td>$-6.47 \pm 0.43$, &lt;0.0001</td>
<td>$-714.50 \pm 52.79$, &lt;0.0001</td>
</tr>
</tbody>
</table>

FMDmax indicates maximum flow-mediated dilatation; FMDauc, flow-mediated dilatation area under dilatation response versus time curve; MET, metabolic equivalent; BMI, body mass index; HDL, high-density lipoprotein; and hs-CRP, high-sensitivity C-reactive protein.

*Estimated regression coefficients±SE for a 1-unit change in the covariate.
†Compared with 17 years of age.

Figure 1. Association of maximum flow-mediated dilatation (FMDmax) and FMD area under the dilatation vs time curve (FMDauc) with leisure-time physical activity (LTPA). $P$ values shown are from a linear mixed-effects model with LTPA as a continuous variable. Adjustment was made for age, sex, and brachial artery diameter. To depict the data in each age group, adjusted mean values are shown for adolescents exercising <5, 5 to 50, and >50 metabolic equivalent (MET) h/wk (adjusted for sex and brachial artery diameter).

Figure 2. Association of intima-media thickness (IMT) of the abdominal aorta with leisure-time physical activity (LTPA). $P$ values shown are from a linear mixed-effects model with LTPA as a continuous variable. Adjustment was made for age and sex. To depict the data in each age group, adjusted mean values are shown in adolescents exercising <5, 5 to 50, and >50 metabolic equivalent (MET) h/wk (adjusted for sex).
The direct association of LTPA with FMDmax and FMDauc remained significant after further adjustment for BMI, HDL/total cholesterol, systolic blood pressure, and hs-CRP (Table 2). The results were similar when mean arterial blood pressure was used instead of systolic blood pressure (data not shown). In addition to LTPA, brachial artery diameter was inversely and BMI was directly associated with FMD measures. Girls had higher FMD compared with boys. Inclusion of smoking status in the analyses did not change the results (data not shown).

Similar to endothelial function, the favorable effect of LTPA on IMT remained significant after further adjustment for BMI, HDL/total cholesterol, systolic blood pressure, and hs-CRP (Table 3). Adjustment for mean arterial blood pressure instead of systolic blood pressure did not change the results (data not shown). BMI was directly associated with IMT. Between 13 and 17 years of age, age and sex were not associated with IMT. The results were similar after smoking status was included in the analysis (data not shown). The effect of LTPA on IMT was similar at different BMI values (P for interaction of LTPA and BMI = 0.79) and in adolescents with normal body weight or who were overweight (P for interaction of LTPA and normal weight/overweight = 0.19).

Relation Between LTPA Change and IMT
A moderate increase in LTPA from <5 to >5 MET h/wk between 13 and 17 years of age was associated with decreased progression of IMT compared with adolescents who remained sedentary (<5 MET h/wk; P = 0.047, adjusted for sex, BMI, HDL/total cholesterol, systolic blood pressure, and hs-CRP at 17 years of age and IMT at 13 years of age; Figure 3). In line with this result, adolescents who became sedentary (<5 MET h/wk) by 17 years of age had an increased progression of IMT compared with adolescents who remained at least moderately active (>5 MET h/wk; P = 0.0072, adjusted for sex, BMI, HDL/total cholesterol, systolic blood pressure, and hs-CRP at 17 years of age and IMT at 13 years of age; Figure 3). In these analyses, the results were similar when mean arterial blood pressure was used instead of systolic blood pressure (data not shown). An extensive increase in LTPA from <5 to >30 MET h/wk was not associated with further decreased IMT progression (IMT change, 0.004 mm). Adolescents whose LTPA was persistently >30 MET h/wk had an IMT progression similar to that of adolescents whose LTPA was persistently >5 MET h/wk (IMT change, 0.004 versus 0.007 mm).

Relation Between LTPA Change and FMD
In sedentary adolescents, an extensive increase in LTPA to >30 MET h/wk was associated with a significant increase in FMDmax compared with the persistently sedentary adolescents (P = 0.031, adjusted for sex, brachial artery diameter, BMI, HDL/total cholesterol, systolic blood pressure, and hs-CRP at 17 years of age and FMD at 13 years of age; Figure 4). A moderate increase in LTPA was not associated with changes in FMDmax (data not shown). FMDmax change was similar in persistently active (>30 MET h/wk) adolescents and those whose LTPA decreased extensively (from >30 to <5 MET h/wk; Figure 4). Adjustment for mean arterial blood pressure instead of systolic blood pressure did not change the results (data not shown).

To further examine the markedly enhanced FMDmax in the adolescents who had extensively increased their LTPA, we studied the association of LTPA with brachial artery diameter, an important determinant of FMD (Table 2; inverse association). In the entire cohort, LTPA was directly associated with arterial diameter (estimated β ± SE = 0.0099 ± 0.00035; P = 0.0090, adjusted for age and sex). Mean ± SD diameter of the brachial artery, however, was smaller at the 17 years of age in adolescents who had extensively increased their LTPA level compared with those who were persistently active (2.96 ± 0.41 versus 3.14 ± 0.44 mm). Because an increase in LTPA and a smaller arterial diameter were associated with a greater FMDmax (Table 2), the markedly enhanced FMDmax in adolescents who became...
physically active may be explained in part by the combination of increased LTPA and a relatively small arterial diameter.

**Discussion**

This prospective, longitudinal study showed for the first time in healthy adolescents that a physically active lifestyle is associated with a decreased progression of aortic IMT. Importantly, the beneficial effect was seen with only a moderate LTPA increase in the sedentary adolescents. Our findings are in line with long-term exercise intervention studies in obese children and adolescents showing a beneficial effect of physical activity on progression of carotid IMT.15,37 In these studies, exercise training was able to induce regression in IMT, as also observed in our study. In adults, exercise training for 3 months was unable to improve carotid IMT,38 whereas longer-term lifestyle intervention, including physical activity, decreased carotid IMT progression.39

Consistently, longitudinal regression analyses showed a favorable effect of LTPA on aortic IMT. Importantly, LTPA affected IMT beneficially regardless of whether the adolescent was overweight or had a normal body weight. There are no previous studies on physical activity and aortic IMT. In children and adults, cross-sectional studies have often shown a lack of association between physical activity and carotid IMT,21–23 whereas in recent longitudinal studies, physical activity was reported to retard the age-associated thickening of the carotid arterial wall.18–20 Moreover, we have shown that low physical activity in childhood predicts increased progression of carotid IMT in adulthood.40

Little is known about the mechanisms that produce the physical activity–associated improvements in IMT.41 Physical activity is suggested to affect carotid IMT through having a favorable impact on cardiovascular risk factors, eg, adiposity, serum lipoproteins, and inflammation.21,41 In this study, the beneficial effect of LTPA increase on aortic IMT was evident independently of BMI, HDL/total cholesterol, systolic blood pressure, and hs-CRP at the end of the follow-up, as well as baseline IMT and sex. In line with these findings, LTPA was inversely associated with aortic IMT in longitudinal regression analysis after adjustment for these risk factors plus smoking. These data suggest that the beneficial effect of LTPA on IMT progression was not entirely mediated through a more favorable risk factor profile, at least regarding the risk factors considered here.

Endothelial function was also favorably affected by LTPA increase. Adolescents who increased their LTPA from <5 to >30 MET h/wk had a substantially enhanced FMDmax. One explanation for this marked improvement in endothelial function may relate to the diameter of the artery. Small brachial arteries show greater ability to dilate in response to hyperemia than large arteries.52 Physical activity for one is associated with the increased arterial diameter43 observed also in this cohort. However, in adolescents who extensively increased their LTPA, the diameter of the brachial artery was still smaller than in the persistently active adolescents at 17 years of age. An explanation for the marked improvement in endothelial function in those who increased their LTPA may thus be that an increase in physical activity influences vasodilatation capacity before adaptations in the vessel diameter occur that normalize shear stress and subsequently endothelial function, as suggested previously.41,43 The beneficial effect of LTPA increase on FMDmax was evident only when the sedentary adolescents increased their LTPA extensively, ie, to >30 MET h/wk, corresponding to, eg, playing soccer 5 h/wk. This suggests that a relatively large increase in LTPA is needed to enhance endothelial function. The amount and intensity of physical activity required to improve endothelial function are unknown, with recent data suggesting the need for vigorous-intensity exercise.17

The beneficial effect of physical activity is suggested to be mediated by exercise-induced enhancement of blood flow, leading to augmented shear stress, which further stimulates nitric oxide production and bioavailability, followed by arterial structural adaptations that increase the diameter of the vessel lumen.43 Previous exercise intervention studies in obese children and adolescents suggest that the favorable effect of physical activity on endothelial function is attenuated after training cessation.14,15 In healthy adolescents, data on the effect of decreased physical activity on endothelial function are lacking. In this study, change in FMDmax between 13 and 17 years of age was similar in adolescents who decreased their LTPA compared with adolescents who remained active. This finding suggests that in healthy adolescents with preserved endothelial function, some favorable effects of previous LTPA may be still be evident.

Similar to IMT, a beneficial impact of LTPA on endothelial function was found in the longitudinal regression analyses adjusted for a variety of potentially confounding factors. These results agree with results from previous cross-sectional studies reported by us24 and others23 in healthy children and adolescents and with exercise intervention studies in adoles-
cents with obesity or type 1 diabetes mellitus. Interestingly, although in some studies obesity was associated with endothelial dysfunction in children and adolescents, BMI was directly associated with FMD in this study. We have also previously found this unexpected association between BMI and endothelial function in this cohort and in adults. In adults, we showed that the association of BMI with FMD may be curvilinear rather than linear, and an upward slope of this relation was observed. An increase in body size within the nonobese range in a healthy population may thus be associated with physiological changes that lead to enhanced FMD responses. In this study, only a minority of the adolescents were obese. Therefore, the negative influence of obesity on endothelial function is difficult to assess in this cohort.

The major strength of this study was its longitudinal design with repeated data assessment, unique in studies concerning physical activity and vascular function and structure in healthy adolescents. Furthermore, ultrasonic, laboratory, and physical examination data were assessed with well-established methods in a large number of adolescents. With a continuous 2.5-minute FMD assessment, we were able to assess the actual FMDmax. A limitation is that we used a subjective method to assess physical activity and LTPA in contrast to studying total physical activity. Assessment of physical activity only during leisure-time excluding, eg, physical education at school may cause bias in our study in that the adolescents reporting low physical activity during leisure time may be physically active in other times of the day. The amount of LTPA, however, is the important discriminating factor regarding physical activity because physical education at school is compulsory for adolescents of this age group. We used 2-year intervals in LTPA data collections, whereas a more frequent data series would potentially have provided more accurate estimates of the effects on vascular biology. Further limitations with regard to assessment of FMD are the lack of data on shear rate, the girls’ menstrual cycle phase, or the adolescents’ last bout of exercise at the time of the ultrasonography. We were also unable to measure smooth muscle–dependent vasodilatation of the brachial artery.

Conclusions

LTPA had a favorable effect on vascular function and structure in adolescents. Importantly, the avoidance of a sedentary lifestyle was associated with a decreased progression of IMT. Concerning FMD, some beneficial effect of previous LTPA may be preserved in healthy adolescents. The results emphasize the need to promote physical activity, especially in sedentary adolescents, to support cardiovascular health.

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Disclosures

None.

References


### CLINICAL PERSPECTIVE

The development and progression of subclinical atherosclerosis in adolescence are associated with functional and structural changes of the arteries, including impairment of the arterial vasodilatory function and thickening of the arterial wall. Flow-mediated dilatation of the brachial artery, assessed noninvasively by ultrasound, is a widely used marker of systemic arterial endothelial function. Although the carotid artery has commonly been the target for ultrasonic assessment of early structural changes, the earliest morphological alterations emerge in the abdominal aorta. Intima-media thickness of the abdominal aorta may therefore be a better surrogate marker of atherosclerosis than carotid intima-media thickness especially at young age. Physical activity has a beneficial effect on vascular function and structure by enhancing endothelial function and decreasing the progression of carotid intima-media thickness. To date, data on the effect of physical activity on vascular function and structure in adolescents are scarce and longitudinal studies are lacking. Our study shows the favorable effect of leisure-time physical activity on flow-mediated dilatation and intima-media thickness in nearly 500 adolescents studied repeatedly at 13, 15, and 17 years of age. Importantly, even a moderate increase in physical activity among those who were sedentary was related to a decreased progression of intima-media thickness. These results emphasize the potential of promoting physical activity, especially in inactive adolescents, to support cardiovascular health. Clinicians should encourage physical activity among adolescents, and enjoyable ways to increase physical activity should be paid attention to, especially for those who are sedentary.
Association of Physical Activity With Vascular Endothelial Function and Intima-Media Thickness
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