

Distensibility of the Aorta and Carotid Artery and Left Ventricular Mass From Childhood to Early Adulthood

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Abstract—In adults, arterial distensibility decreases with age and relates to changes in cardiac left ventricular mass. Longitudinal data on changes in arterial distensibility from childhood to adulthood are lacking. Our aim was to study the effect of age and sex, and low-saturated fat dietary counseling on arterial distensibility from childhood to early adulthood. In addition, we assessed the association of arterial distensibility with left ventricular mass. Distensibility of the abdominal aorta and common carotid artery was measured repeatedly at ages 11, 13, 15, 17, and 19 years ($n=395\text{--}472$) in an atherosclerosis prevention trial (Special Turku Coronary Risk Factor Intervention Project [STRIP]). Aortic and carotid distensibility decreased with age (both $P<0.0001$). In boys, distensibility values were generally lower ($P<0.0001$) and showed steeper decrease by age (age and sex interaction: both $P<0.01$). The low-saturated fat dietary counseling given in STRIP was not significantly associated with arterial distensibility. Left ventricular mass increased with age ($P<0.0001$), and it was greater in boys ($P<0.0001$). In conclusion, a marked age-related decrease in vascular distensibility was found already at this young age, and this decrease was more pronounced in boys than girls. The longitudinal progression of aortic and carotid distensibility was related with changes in left ventricular mass.

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Conduit arteries, such as aorta and carotid artery, function as a physiological buffer during cardiac contraction because of their distensible walls.¹ Arterial stiffness increases with advancing age in adults.² Arteries stiffen because mechanical stress causes fatigue and fracture of elastin lamellae in arterial wall, especially at older ages.³ Arterial stiffness may also be caused by atherosclerosis and relates with traditional cardiovascular disease risk factors in adults and associates with elevated cardiovascular disease risk in healthy persons.⁴⁻⁶ Childhood cardiovascular disease risk factors, such as elevated blood pressure, are suggested to predict carotid artery stiffness in adulthood.² In adults, arterial stiffening has also been associated with left ventricular hypertrophy.⁷ Local arterial stiffness, arterial distensibility, can be estimated with ultrasound and is defined as the change in arterial diameter during systole and diastole divided by pulse pressure.⁸

We have previously reported that childhood exposure to tobacco smoke decreases aortic distensibility in healthy children at the age of 11 years.⁹ Recently, we showed a favorable association of fitness and ideal cardiovascular health score

with arterial distensibility in adolescents.^{10,11} Two recent cross-sectional studies in children and adolescents have reported arterial stiffening with age.^{12,13} However, longitudinal data on changes in distensibility from childhood to adulthood are still lacking. Especially, data on aortic distensibility would be of great interest because postmortem analyses indicate that atherosclerotic alterations are first seen in the abdominal aorta.¹⁴

Therefore, this study analyzed longitudinal data on aortic and carotid artery distensibility and cardiac left ventricular mass (LVM) from the Special Turku Coronary Risk Factor Intervention Project for children (STRIP). The study is a longitudinal dietary intervention trial begun in infancy with an aim to prevent atherosclerosis. Distensibility of the abdominal aorta and common carotid artery was measured repeatedly at the age of 11, 13, 15, 17, and 19 years and LVM beginning of age 15 years. Our aim was to study the effect of age and sex, and low-saturated fat dietary counseling on changes in arterial distensibility from childhood to early adulthood. We also studied the association of arterial distensibility with LVM in adolescence.

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Methods

Design and Subjects

The STRIP is a prospective, randomized intervention trial.^{15,16} Briefly, families of 5-month-old infants were recruited to the study at the well-baby clinics in Turku, Finland, between February 1990 and June 1992 (extended methods, please see online-only Data Supplement). This study cohort comprised those children for whom vascular ultrasound data (distensibility) was available at ages of 11, 13, 15, 17, and 19 years. The cohort characteristics are shown in Table S1 in the online-only Data Supplement. The STRIP study was conducted according to the guidelines of the Declaration of Helsinki, and the study protocol was approved by the local ethics committee. Written informed consent was obtained from the parents in the beginning of the study and from the children at the age of 15 years.

Ultrasound Measurements of the Abdominal Aorta, Common Carotid Artery, and LVM

Distensibility of the abdominal aorta and common carotid artery was studied with ultrasonography (Acuson Sequoia 512 mainframe; Acuson, Mountain View, CA) at the age of 11, 13, 15, 17, and 19 years. Measures of arterial distensibility were available for 68%, 84%, 94%, 94%, and 93% at these ages. Distensibility of the aorta and common carotid artery was assessed using M-mode ultrasound images and concomitant measurement of blood pressure in the brachial artery. We additionally calculated the distensibilities using estimated central blood pressure values (see below). Diameter of the aorta and common carotid artery was measured with ultrasonic calipers twice at end diastole and twice at end systole. The mean of the end-diastolic and end-systolic diameters, along with blood pressure, was used to calculate the arterial distensibility. Distensibility was defined as $[(D_s - D_d)/D_d]/(BP_s - BP_d) \times 1000$, where D_s indicates the end-systolic and D_d the end-diastolic diameter of the artery. BP_s stands for systolic and BP_d for diastolic blood pressure. Distensibility measures the ability of the arteries to expand as a response to pulse pressure caused by cardiac contraction and relaxation.¹⁷ Lower distensibility signifies increased vascular stiffness.

Guidelines recommend using local pressures for determination of arterial distensibility.⁸ Because of pulse pressure amplification between central and peripheral arteries, the use of brachial pressures as a surrogate for aortic or carotid pressures may over estimate pulse pressure in central arteries.¹⁸ Because of the lack of direct measurement of central aortic blood pressure in this study, we estimated the central pulse pressure values for 17- and 19-year-olds by using the ratio of peripheral to central pulse pressure reported in the Anglo-Cardiff Collaborative Trial¹⁹ that measured both brachial and central pressures in adolescents and young adults. The formula to calculate estimated central pulse pressure for girls was $[(\text{brachial } BP_s - BP_d) \times 25]/41$ and for boys $[(\text{brachial } BP_s - BP_d) - 29]/50$.¹⁹ Using the estimated central pulse pressures, we calculated the modified aortic and carotid distensibility values.

To assess reproducibility of the ultrasound measurements, we have examined 57 individuals (young adults) at 2 time points 3 months apart. The between-visit coefficient of variation was 2.7% for carotid artery diastolic diameter 16.3% for carotid artery distensibility.²

Echocardiography was performed at the age of 15, 17, and 19 years, and successful left ventricular measurements were obtained from 418, 394, and 420 adolescents. Transthoracic 2-dimensional echocardiography was performed with Acuson Sequoia 512 (Acuson, Mountain View, CA) ultrasonography, using 3.5 MHz scanning frequency phased-array transducer. Linear measurements of end-diastolic interventricular septal wall thickness (SWTd), end-diastolic posterior wall thickness (PWTd), and end-diastolic left ventricular internal diameter (LVIDd) were obtained from M-mode tracings. The uncorrected formula to calculate LVM was $1.04 [(LVIDd + PWTd + SWTd)^3 - LVIDd^3]$. LVM correction was made according to the formula recommended by American Society of Echocardiography: $0.8 (1.04 [(LVIDd + PWTd + SWTd)^3 - LVIDd^3] + 0.6 \text{ g})^{20,21}$ LVM was indexed to body surface area (BSA).

Physical Examination

The physical examination consisted of the measurement of height, weight, systolic and diastolic blood pressure and waist circumference, and classification of pubertal stage (extended methods, please see the online-only Data Supplement).

Arterial Pulse Wave Velocity and Stroke Volume

As an additional measure of aortic stiffness, a whole-body impedance cardiography device (CircMon, JR Medical Ltd) was used to determine pulse wave velocity (PWV) and stroke volume at age 19 years (extended methods, please see online-only Data Supplement).

Statistical Methods

Repeated measures ANOVA with time as repeating factor was used to study the association of STRIP study group with arterial distensibility. Because the study group was neither associated with distensibility of the aorta nor carotid artery, the STRIP intervention and control groups were studied combined. Repeated measures ANOVA was also used to study the association of sex and age with arterial distensibility, its components and LVM. In addition, repeated measures ANOVA with pubertal stage as repeating factor was used to study the association of pubertal stage with aortic and carotid distensibility. If a child stayed in a certain puberty stage for several years, the measures within pubertal stage were averaged for the analyses. The shapes of significant interactions were studied with *t* tests for differences between sexes within each age point. Stability within distensibility during time and associations between distensibility of aortic and carotid artery was measured using Pearson correlations. Values for aortic and carotid distensibility were log-transformed before analyses owing to skewed distribution. Results were considered statistically significant at values of $P < 0.05$. Analyses were performed with the SAS 9.3 (SAS Institute, Cary, NC).

Results

Distensibility of Abdominal Aorta

Aortic distensibility decreased with age and was lower in boys than girls (both $P < 0.0001$; Figure 1A). Age and sex interaction was significant indicating that the effect of age on aortic distensibility was different by sex ($P < 0.0001$). At the age of 11 years, aortic distensibility was similar in boys and girls ($P = 0.53$), whereas at the age of 13 years, the difference between boys and girls was borderline significant ($P = 0.055$) and thereafter boys had significantly lower distensibility than girls (Figure 1A; $P < 0.0001$). The sex difference remained statistically highly significant when the modified aortic distensibility calculated at ages 17 and 19 years using estimated central pulse pressure was compared (see methods; girls: age-adjusted mean \pm SE $5.46 \pm 0.089\%/10 \text{ mm Hg}$, boys: $4.34 \pm 0.090\%/10 \text{ mm Hg}$; $P < 0.0001$).

The components of aortic distensibility, pulse pressure and aortic diameter, were studied to gain more insight on the sex difference in distensibility (Figure 1B). First we adjusted the model including age and sex with pulse pressure and second with arterial diameter. When pulse pressure was added in the model, the sex difference in aortic distensibility disappeared ($P = 0.14$). When adjustment was made for arterial diameter, the sex difference persisted (systolic and diastolic diameter: P for sex < 0.0001 , P for sex = 0.020). The effect of age on pulse pressure differed in boys and girls (age by sex interaction; $P < 0.0001$; Figure 1B). In girls, pulse pressure increased 5.8 mm Hg between age 11 and 19 years, whereas in boys the increase was 17.5 mm Hg.

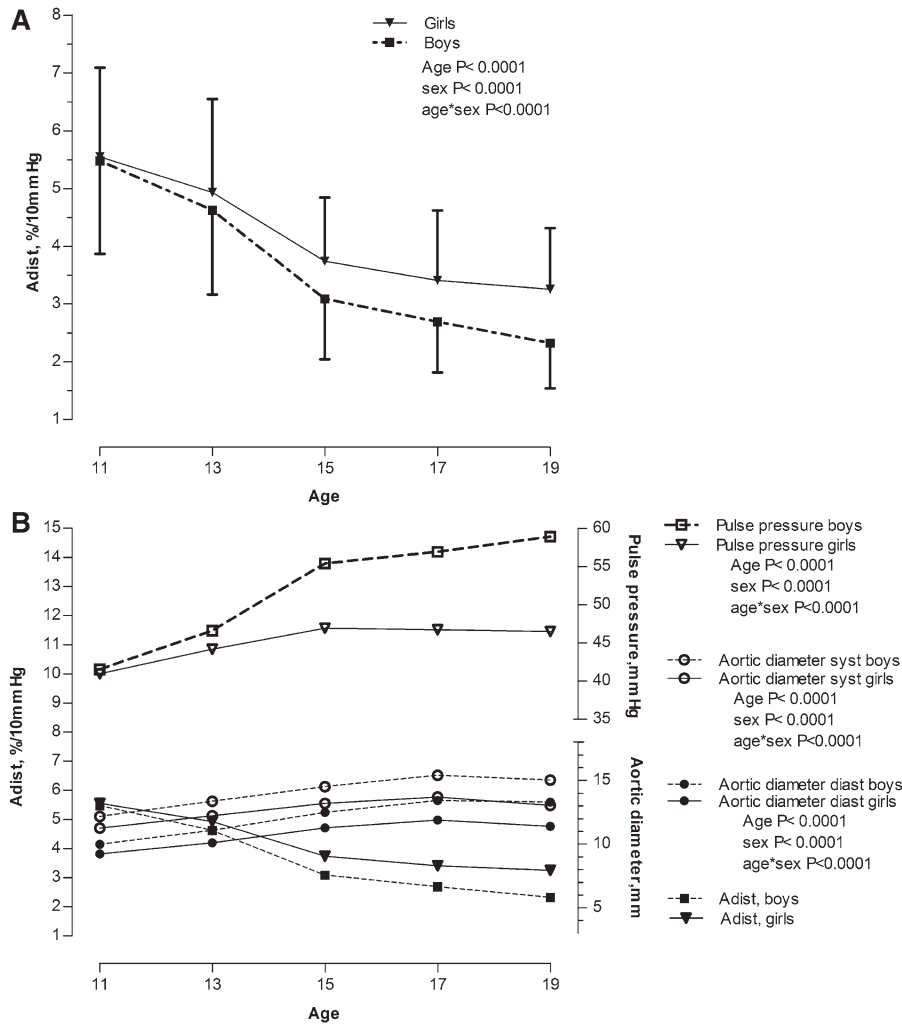


Figure 1. A, Mean±SD aortic distensibility (Adist) in adolescents between age 11 and 19 years. **B,** Components of the Adist.

There was parallel increase by age in pulse pressure and body size, and these relationships were more pronounced in boys (Table S1). Therefore, we examined if the sex differences in pulse pressure and distensibility were driven by larger changes in body size in boys than girls. We additionally analyzed, using cross-sectional data at age 19 years, whether differences in stroke volume would explain the sex difference in distensibility. In these analyses, we found no evidence that the sex difference in distensibility would be explained by body size or stroke volume (extended results, please see online-only Data Supplement).

Aortic distensibility decreased with increasing pubertal stage ($P=0.047$; adjusted for age and sex; Figure S1). Pubertal stage by sex interaction was significant ($P<0.0001$); in sex-stratified analysis, the effect of pubertal stage was no longer significant in boys ($P=0.15$) or in girls ($P=0.24$).

The dietary counseling given in the STRIP study was not associated with aortic distensibility ($P=0.24$, age- and sex-adjusted mean [SE]; intervention: 1.28 [0.014], control: 1.26 [0.013]; log-transformed values).

To study the stability of aortic distensibility, we examined correlations between the distensibility measurements. Aortic distensibility measured at the age of 11 years correlated with subsequent measurements at age 13, 15, 17, and 19 years (Figure S2, all $P<0.05$).

Distensibility of Common Carotid Artery

Similar to aortic distensibility, carotid distensibility decreased with age and was lower in boys than girls (both $P<0.0001$; Figure 2A). To compare our findings with a previous population data, we have shown the distensibility values previously reported in the Young Finns Study² in Figure 2A. Age and sex interaction was significant, indicating that the effect of sex was different by age ($P=0.0026$). The difference between boys and girls in carotid distensibility was evident already at the age of 11 years ($P=0.002$) and became even more pronounced with increasing age (13 years: $P=0.0005$; 15–19 years: $P<0.0001$). The sex difference remained statistically highly significant when the modified carotid distensibility calculated at ages 17 and 19 years using estimated central pulse pressure was compared (see methods; girls: age-adjusted mean±SE 5.88±0.069%/10 mmHg, boys 5.32±0.068%/10 mmHg; $P<0.0001$).

The components of carotid distensibility were also studied in more detail (Figure 2B). First, we adjusted the model including age and sex with pulse pressure and second with arterial diameter. When pulse pressure was added in the model, the sex difference became borderline nonsignificant ($P=0.075$). The sex difference persisted when adjustment was made for arterial diameter (systolic and diastolic diameter: both P for sex <0.0001).

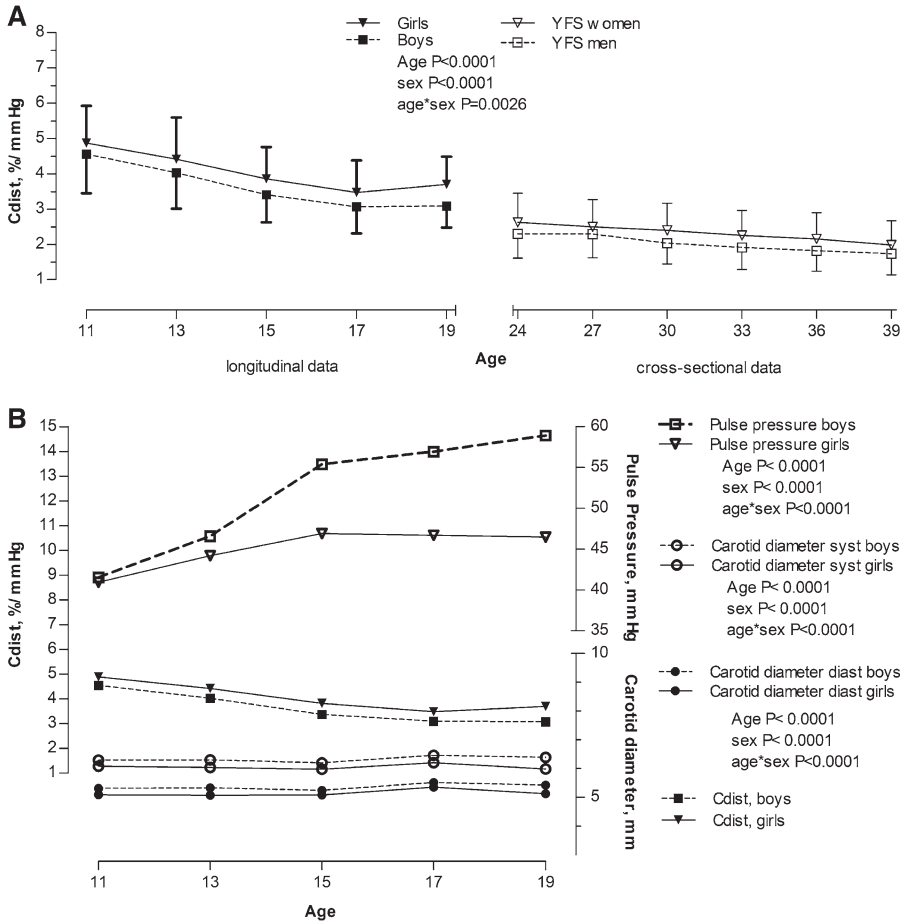


Figure 2. A, Mean±SD carotid distensibility (Cdist) in adolescents between age 11 and 19 years and carotid distensibility in women and men in the Young Finns Study (YFS).² **B**, Components of the Cdist.

Pubertal stage was not independently associated with carotid distensibility ($P=0.16$; adjusted for age and sex; Figure S1). Pubertal stage by sex interaction was not significant ($P=0.090$).

The dietary counseling given in the STRIP study was not associated with carotid distensibility ($P=0.84$, age- and sex-adjusted mean [SE]; intervention: 1.31 [0.010], control: 1.31 [0.010]; log-transformed values).

To study the stability of carotid distensibility, we examined correlations between the distensibility measurements. Correlations of carotid distensibility measured at the age of 11 years with subsequent measurements until the age of 19 years are shown in Figure S2 (all $P < 0.02$).

We also examined correlations between distensibility of the aorta and carotid artery. The correlations between aortic and carotid distensibility ranged from $r=0.25$ to $r=0.38$ during the follow-up (Table S3, all $P < 0.0001$).

Pulse Wave Velocity

At age 19 years, boys had higher PWV than girls (median [interquartile range]; girls: 6.30 [4.50] m/s, boys: 6.50 [5.80] m/s; $P < 0.0001$ for log-transformed PWV). Participation in STRIP intervention had no association with PWV ($P=0.32$; STRIP study group by sex interaction; $P=0.56$).

Association Between Arterial Distensibility and LVM

In girls, LVM increased 3.2 g between the age of 15 and 19 years (106.4–109.6 g), whereas in boys the increase was 13.9

g (131.3–145.2 g). Boys had greater LVM/BSA than girls ($P < 0.0001$; Figure 3). Age and sex interaction was not significant, indicating that the effect of age on LVM/BSA was similar in girls and boys ($P=0.79$). Participation in STRIP intervention had no association with LVM/BSA ($P=0.92$; STRIP study group by sex interaction $P=0.19$).

Aortic and carotid distensibility were inversely associated with LVM (aorta: $\beta=-4.28$; SE, 1.75; $P=0.015$; carotid: $\beta=-5.81$; SE, 2.59; $P=0.025$, adjusted for sex and age). Aortic and carotid distensibility were not associated with LVM/BSA (aorta: $\beta=-1.12$; SE, 0.90; $P=0.21$; carotid: $\beta=-1.60$; SE,

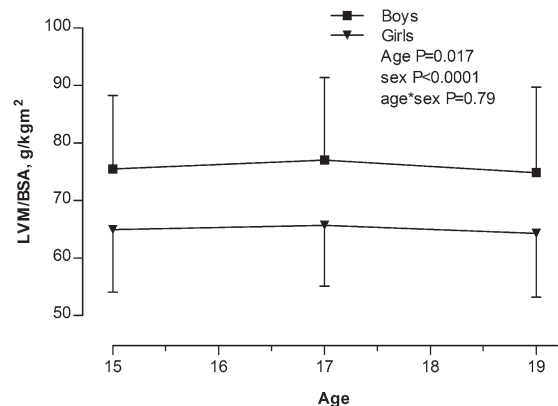


Figure 3. Mean±SD left ventricular mass indexed to body surface area (LVM/BSA) in adolescents.

1.32; $P=0.23$, adjusted for sex and age). Sex-adjusted correlations of aortic and carotid distensibility with LVM/BSA are shown in Table S3.

Discussion

To best of our knowledge, this is the first study showing the longitudinal progression of repeatedly measured aortic and carotid distensibility from childhood to early adulthood. Already at this young age, a marked age-related decrease in vascular distensibility was found and it was more pronounced in boys. Regarding carotid distensibility, the sex difference was evident already at the age of 11 years, reflecting that boys may have stiffer arteries even earlier in childhood. Detailed analysis of the components of distensibility suggested that the effect of sex on arterial distensibility is driven by the difference in pulse pressure.

These longitudinal data demonstrate that arterial distensibility decreases by age between ages 11 and 19 years. Our results are in line with data from the Young Finns Study (Figure 2A), together indicating that the process continues steadily until middle age.² In a recent cross-sectional study examining 2- to 18-year-old children, a systematic decrease in aortic distensibility was seen beginning from the age of 2 years.¹² In contrast, a previous cross-sectional study demonstrated that effect of age on aortic distensibility is not linear; distensibility increased from birth and was greatest at about the age of 10 years, thereafter decreasing with advancing age, and distensibility equal to that present at birth was usually seen in the age of 18 years.²² Regarding carotid artery, decrease in distensibility has been reported to begin from the age of 6 years.^{13,23}

This study also showed that the boys had stiffer arteries than the girls. In line, a previous cross-sectional study in young adults, aged 18 years and older, demonstrated lower brachial artery distensibility in men than women.²⁴ Regarding aortic distensibility, we observed a significant sex difference beginning at the age of 15 years. In line, it has been demonstrated cross sectionally that aortic distensibility was similar in both sexes from birth to 14 to 15 years of age and thereafter boys had lower distensibility holding it into late forties.²² In our study, carotid distensibility was lower in boys already at the age of 11 years and the sex difference became more pronounced with increasing age. These results are in line with a previous cross-sectional study in 6 to 18-year-old subjects showing a sex difference in carotid distensibility starting from the age of 15 years.¹³ In detailed analysis of the components of arterial distensibility, the sex difference disappeared when pulse pressure was included in the analyses possibly indicating that effect of sex on distensibility is driven by the difference in pulse pressure, not by the difference in arterial diameter.

The distensibility of conduit arteries results from the elastin to collagen ratio in their walls.^{25,26} Increased arterial stiffness with age is considered as a physiological change, related to the loss of elastic fibers in the vessel wall caused by continuous cycles of expansion and contractions leading to elastic fiber degeneration and higher ratio of stiffer collagen fibers in arterial wall especially at older ages.^{3,27} However, it has been estimated that it takes 30 years until elastin breakdown becomes relevant.²⁸ Therefore, other mechanisms related to growth may play a role in the age-related changes seen in the present

study. As demonstrated by the data from this study and the cross-sectional Young Finns Study (Figure 2A), the decline in carotid distensibility seems rather linear between ages 11 and 39 years.

We have previously shown that a component of arterial distensibility, blood pressure, is beneficially affected by the STRIP dietary intervention.²⁹ Furthermore, we recently reported that the dietary counseling associated with better ideal cardiovascular health score, a cluster of health metrics defined by American Heart Association, which for one was favorably associated with aortic distensibility.¹¹ In this analysis, however, the effect of dietary counseling was not reflected on arterial distensibility. The dietary counseling was targeted to reduce the development of atherosclerosis mainly by mechanisms related to lipid lowering, and such an intervention in the early stages of atherosclerosis may not correlate with arteriosclerosis which is typically seen as a consequence of advanced atherosclerosis. This may partly explain the lack of association between the counseling and distensibility. Nevertheless, childhood risk factors have been shown to predict carotid stiffness in adulthood, therefore lifestyle intervention early in life should not be dismissed as a means to promote cardiovascular health.²

In addition to vascular measures, this study shows longitudinally the increase of LVM during the age of 15 to 19 years. Boys had greater LVM than girls throughout the follow-up. In adults, it is hypothesized that there are causative links between pulse pressure, arterial stiffness, and LVM. By advancing age, pulse pressure increases because of arterial stiffening. Elevated pulse pressure increases left ventricular afterload and myocardial oxygen demand and reduces coronary perfusion.³⁰ These changes may lead to left ventricular hypertrophy.⁷ Our data show that changes in arterial distensibility during childhood are associated with changes in LVM. However, when LVM was indexed to BSA, there was no relationship to distensibility. Therefore, it is unclear whether the relationship between arterial distensibility and LVM is causative in this age group or confounded by body size.

A major limitation of this study is that the pulse pressure used to derive distensibility was measured from the brachial artery, not from the artery in question. The use of brachial pressures may overestimate pulse pressure in central arteries. Previous studies have shown an excellent correlation between invasively measured blood pressures from ascending aorta and noninvasively measured blood pressures from brachial artery; however, the differences can be substantial and vary between sexes, females having lower pulse pressure amplification.^{19,31} Thus, guidelines recommend using local pressures in determination of arterial distensibility.⁸ Therefore, to compensate lack of central blood pressure measurement, we calculated modified aortic and carotid distensibility variables using estimated central pulse pressures that were estimated by the data published by the Anglo-Cardiff Collaborative Trial.^{19,32} The sex difference in distensibility remained when the modified variables were used, suggesting that the lower distensibility observed in boys was not because of use of brachial blood pressure. It is important to note, however, that this approach does not indicate central blood pressure values at individual level. In addition, we measured aortic stiffness with an alternative

method. In 19-year-olds, the aortic PWV was measured using a whole-body impedance cardiography device. In line with the lower distensibility measures, we observed significantly higher PWV values in boys compared with girls, thus indicating increased stiffness in males. Correlations between repeated distensibility measures were relatively weak, as reported also previously.³³ This may be linked to physiological fluctuation in the constitutive factors, especially blood pressure, instead of measurement error.

Perspectives

In conclusion, this study shows for the first time the longitudinal progression of both aortic and carotid distensibility from childhood to early adulthood. Arterial distensibility decreased during age, and boys had markedly stiffer arteries than girls. Our findings suggest that the effect of sex on distensibility is driven by the difference in pulse pressure. In this study, the effect of dietary counseling was not reflected on arterial distensibility. Risk factors operating in early life and lifetime risk factor levels affecting distensibility should be further studied to define what characterizes those with the least or highest decrease in distensibility. As a public health implication, this would give insight to which factors should be targeted to prevent atherosclerosis effectively since childhood.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This study shows for the first time the longitudinal progression of both aortic and carotid distensibility from childhood to early adulthood.
- The study reveals effect of age and sex, and low-saturated fat dietary counseling on changes in arterial distensibility and left ventricular mass.

What Is Relevant?

- Already at this young age, a marked age-related decrease in arterial distensibility was found and it was more pronounced in boys.
- Our findings suggest that the effect of sex on distensibility is driven by the difference in pulse pressure.

Summary

Arterial distensibility decreased with age, and boys had markedly stiffer arteries than girls. Our findings suggest that the effect of sex on distensibility is driven by the difference in pulse pressure. Lower aortic and carotid distensibility was related to greater left ventricular mass, suggesting that changes in arterial distensibility during childhood may influence cardiac adaptation.