Adolescent Blood Pressure and Blood Pressure Tracking Into Young Adulthood Are Related to Subclinical Atherosclerosis: The Atherosclerosis Risk in Young Adults (ARYA) Study

Lydia E. Vos, Anath Oren, Cuno Uiterwaal, Wim H.M. Gorissen, Diederick E. Grobbee, and Michiel L. Bots

Background: Increased blood pressure (BP) in young adulthood is associated with cardiovascular morbidity and mortality. Longitudinal studies of patients at young ages are, however, limited. Our aim was to study the relationships of adolescent BP and tracking of BP into young adulthood with subclinical atherosclerosis, as assessed by carotid intima-media thickness (CIMT), at the age of 28 years.

Methods: The Atherosclerosis Risk in Young Adults (ARYA) study comprises of a community-based sample of 750 subjects aged 27 to 30 years. In the 352 men and 398 women, at least one BP measurement was recorded at a mean age of 13 years in school health records. Recently, all participants completed a questionnaire on cardiovascular risk factors, had a fasting blood sample drawn, and underwent an ultrasound examination of both common carotid arteries to assess CIMT.

Results: Linear regression showed that adolescent systolic BP was associated with thickening of the intima-media (an increase of 7.5 μm in CIMT per standard deviation increase in systolic BP; 95% CI 4.3 to 10.6). Similar relations were found for pulse pressure and mean arterial pressure. When sex, age, and body mass index at adolescence and young adulthood and adult BP were taken into account, the relations attenuated, but for pulse pressure they remained statistically significant. Furthermore, subjects who tracked in the highest systolic BP and pulse pressure levels from adolescence into young adulthood showed the thickest CIMT.

Conclusion: Our findings strengthen the notion that elevated BP at adolescence and a relative increase in BP from adolescence to adulthood unfavorably affect cardiovascular risk, as indicated by increased CIMT. Am J Hypertens 2003;16:549–555 © 2003 American Journal of Hypertension, Ltd.

Key Words: Systolic blood pressure, pulse pressure, tracking, atherosclerosis, intima-media thickness, adolescence, young adulthood.

Cardiovascular diseases are the main causes of morbidity and mortality in western countries, and the chronic development of atherosclerosis is the responsible underlying mechanism. Although cardiovascular disease becomes manifest only at the age of 45 years or more, its subclinical roots are already found in childhood. The progression of atherosclerosis is congruent with the level and number of cardiovascular risk factors, among which blood pressure (BP) is one of the main modifiable risk factors. It is known that BP at childhood and adolescence is positively associated with BP in early adulthood, and that BP at young adulthood is associated with cardiovascular morbidity and mortality after several decades. However, longitudinal studies on adolescent BP and adverse events are lacking. Only limited studies on adolescent BP and vascular damage in young adulthood are available. In a post mortem study, increased systolic BP and diastolic BP in subjects aged between 2 and 39 years were related to atherosclerosis measured post mortem. Other investigators have found a positive relationship between BP and the carotid intima-media thickness (CIMT), an intermediate measure of vascular damage, that
is common in young adults; however, these relationships disappeared after adjustment for cardiovascular risk factors at adolescence.\(^1^3\)

In this study, we examined the relationships of adolescent BP and tracking of BP into young adulthood with subclinical atherosclerosis, as assessed by CIMT, at the age of 28 years.

**Methods**

The study population of the Atherosclerosis Risk in Young Adults (ARYA) study comprises two cohorts: a cohort from the city of Utrecht, The Netherlands, with 750 participants, as well as a cohort from The Hague with 262 participants. This article is based on the Utrecht data only because CIMT was not measured in participants in The Hague. The ARYA study was approved by the Medical Ethical Committee of the University Medical Center Utrecht. Written informed consent was obtained from all participants.

Eligible participants were born between 1970 and 1973 and attended secondary school in Utrecht between the ages of 11 and 16 years. Of these individuals, the school health records from the Municipal Health Service were screened. In The Netherlands, virtually all children regularly visit the child health facilities of the Municipal Health Service, starting at 4 weeks until leaving secondary school at the age of 16 to 19 years. Information on BP (measured manually with a sphygmomanometer), height, weight, lifestyle, puberty stage, and medical history is routinely collected and written down in health records by nurses or physicians. Health records were selected that contained information on birth weight and at least one BP measurement during attendance at secondary school. Birth weight approximated with the sign ± was excluded. Of 15,592 medical school records, 4208 subjects were invited by letter at the last known address at adolescence by the Municipal Health Service. Of these letters, 2017 (47.9%) were returned: 726 (36.0%) because of unknown addresses, 416 (20.6%) because the subjects had no interest in participation, 36 (1.8%) because the subjects lived too far from our outpatient clinic, and 18 (0.9%) for other reasons. Of the 4208 subjects, 821 (19.5%) were willing to participate. A total of 57 subjects did not enter the study because of lack of time and distance from the outpatient clinic. This left a total of 750 participants in the Utrecht cohort. We compared birth data and adolescent data of responders and nonresponders born in 1970. No significant differences were found.

From October 1999 to December 2000, all Utrecht participants had a physical examination during two visits at the outpatient clinic of the Julius Center by two trained research nurses and two medical doctors. All were similarly instructed and blinded for data in the medical school health records, including previous BP. After a 5-min rest in sitting position, BP was measured using a Dynamap (Critkon Inc., Tampa, FL) at the left upper arm. The measurement was repeated after 5 to 15 min of rest. The same procedure was followed at the second visit after a mean interval of 20.4 days (SD 10.7). The average of four readings was used in the analyses. Body weight was measured with indoor clothes (without shoes) to the nearest 0.5 kg. To compensate for the weight of clothes we subtracted 0.5 kg. Body height was measured in standing position (without shoes) to the nearest 0.1 cm.

During the first visit at our outpatient clinic the common CIMT of the right and left carotid artery was measured. In the design phase of the study we decided to assess common carotid intima-media thickness only. This decision was based on the observations in several population-based studies that the common CIMT predicts cardiovascular disease as well as CIMT from bifurcation of the internal carotid artery, and that in this study the common CIMT is regarded as a marker for generalized atherosclerosis and cardiovascular risk. Ultrasound examination was performed by six trained sonographers using a 7.5-MHz linear array transducer (Acuson Aspen, Mountain View, CA). The common CIMT was measured at eight different angles (right carotid artery: 180, 150, 120, and 90 degrees; left carotid artery: 180, 210, 240, and 270 degrees) using Meijer’s arc (Fig. 1). When an optimal two-dimensional image of the distal part of the common carotid artery was obtained it was frozen on the top of the R-wave of the electrocardiogram and recorded on tape. Two readers measured the common CIMT off-line with an automated edge detection program over a length of 10 mm, starting at the beginning of the dilatation of the bifurcation.\(^1^4\) Of the 16 common CIMT measurements per participant (near and far walls, four angles, and right and left carotid arteries), the average intima-media thickness was calculated and used in all analyses. The reproducibility was assessed by scanning 21 participants a second time.
at the next visit by another sonographer. The absolute mean (\pm standard error) difference was 0.012 \pm 0.004 mm, and the intraclass correlation coefficient was 0.84. All sonographers and readers were blinded to the data in the medical health records and measurement results.

Further information on risk factors was obtained by a written questionnaire. Participants were asked to contact one of their parents, when appropriate. The questions regarded ethnicity, smoking (yes/no), alcohol consumption (yes/no), use of oral contraception (yes/no), and any cardiovascular risk factors and diseases in the family (did the first degree family members experience myocardial infarction or stroke, or diabetes, hypertension, or hypercholesterolemia: yes/no). Socioeconomic status at adolescence was estimated by the highest education level of father, and at young adulthood by the highest education level of the participant (low/middle/high).

**Data Analysis**

First, we estimated the relation of adolescent systolic BP per standard deviation (as the independent variable) with common CIMT (as the dependent variable) using linear regression models. Similar models were used for the independent variables diastolic BP, pulse pressure (systolic BP – diastolic BP), and mean arterial pressure (diastolic BP + 1/3 pulse pressure) per standard deviation. Because adolescent BP was significantly related to sex, adolescent age, and adolescent body mass index, the models were also adjusted for these factors.

Second, a linear regression model was used to estimate the association of adult BP per standard deviation with common CIMT, also adjusted for sex, adult age, and adult body mass index.

Third, we estimated the individual adolescent BPs independent of sex, adolescent age, and adolescent body mass index, the individual BP per standard deviation by adjustment for these factors in a linear regression model, and the individual outcome was called the adolescent BP residual. The adult BP residuals were similarly calculated by adjusting the adult BP for sex, adult age, and adult body mass index. Using linear regression analysis we studied the relationship between the adolescent BP residuals and the common CIMT, and this relation was subsequently adjusted for adult BP residuals.

Finally, we used Spearman’s rank correlation coefficients to obtain correlation and tracking coefficients. To study both tracking and detracking from adolescence to young adulthood in one model, we defined four groups of subjects: 1) a group with tracking of BP residuals below the median from adolescence to young adulthood (LL); 2) a group with detracking of BP residuals from below the median to above the median (LH); 3) a group of subjects with BP detracking from above the median to below the median (HL); and 4) a group with BP tracking above the median (HH). A linear regression model was used to relate tracking and detracking with common CIMT, using dummy variables with LL as the reference group.

All analyses were carried out with the statistical analysis software SPSS 9.0 (SPSS, Chicago, IL). Statistical significance was set at \( P < .05 \).

**Results**

Table 1 shows the general characteristics of the ARYA study cohort for men and women separately. The mean (\pm SD) interval between the adolescent BP measurement and common CIMT measurement at young adulthood was 14.9
Our third question concerned the impact of adult BP, weight, height, waist-hip ratio, percentage of smokers, and common CIMT were higher in men. Table 2 shows that systolic BP, pulse pressure, and mean arterial pressure at the age of 13 years are positively related to common CIMT at young adulthood. The relations attenuated after adjustment for sex, adolescent age, and adolescent body mass index, but the associations with adolescent systolic BP residuals and common CIMT remained statistically significant. Further adjustment for other factors did not affect the findings.

At the age of 28 years, systolic BP and pulse pressure were related to common CIMT after adjustment for sex, adult age, and adult body mass index (4.3 μm/SD systolic BP mm Hg (95% confidence interval [CI] 1.0 to 7.7) and 5.0 μm/SD pulse pressure mm Hg (95% CI 1.7 to 8.4). The relationship with adult diastolic BP and mean arterial pressure was less strong and not significant (1.0 μm/SD diastolic BP mm Hg (95% CI −2.0 to 4.0) and 2.5 μm/SD mean arterial pressure mm Hg (95% CI −0.6 to 5.7), respectively).

Our third question concerned the impact of adult BP, which was measured by adjusting the relationship between adolescent BP and common CIMT for adult BP. Because BP tracks from adolescence to young adulthood, an apparent association with adolescent BP might appear, although the true relation exists between adult BP and common carotid intima-media thickness. Therefore, we adjusted the relation between adolescent systolic BP residuals and common CIMT for adult systolic BP residuals. The relations between adolescent systolic BP residuals and common CIMT attenuated slightly and became statistically nonsignificant. A similar finding was found for pulse pressure, which remained statistically significant (Table 3).

Blood pressure showed a moderate degree of tracking from adolescence into young adulthood in our population. Overall, the unadjusted correlation (r) was 0.22 for systolic BP (P < .01), r = 0.09 for diastolic BP (P < .05), r = 0.14 for pulse pressure (P < .01), and r = 0.14 for mean arterial pressure (P < .01). The correlation of the BP residuals was r = 0.19 for systolic BP (P < .01), r = 0.08 for diastolic BP (P < .05), r = 0.12 for pulse pressure (P < .01), and r = 0.13 for mean arterial pressure (P < .01). Of the 750 adolescents, 212 (28.3%) showed tracking of the systolic BP residuals above the median (HH). The tracking groups HL, LH, and LL consisted of 162, 160, and 207 subjects, respectively. A similar number of subjects was observed in the tracking groups for diastolic BP, pulse pressure, and mean arterial pressure. Fig. 2 shows that subjects tracking above the median of systolic BP and
pulse pressure (i.e., the HH group) had significantly larger common CIMT than subjects tracking in the LL group. The subjects detracking between below and above the median (the LH and HL groups) had a comparable common CIMT in between that of subjects tracking in either below or above the median. Pulse pressure showed similar results.

**Discussion**

We found that adolescent systolic BP and pulse pressure levels are positively related to the thickening of the carotid arterial walls in healthy young adults. Furthermore, a high BP at adolescence tracking into young adulthood was associated with the largest common CIMT.

To appreciate the results of this study, some issues need to be addressed. First, a single and routine BP examination by school doctors does not provide a standardized BP level of an adolescent due to intraindividual and interobserver variability. Therefore, we believe that our results reflect an underestimation of the true relationships of adolescent BP and BP tracking with common CIMT. Second, although common CIMT is regarded as a valid indicator of generalized atherosclerosis and cardiovascular risk in middle-aged and elderly individuals, it has been argued that at lower degrees of common CIMT, and thus at younger age, the thickening may reflect a nonatherosclerotic adaptive response to changes in shear and tensile stress. However, post mortem observational studies have shown that raised fatty streaks are present in subjects as early as 15 through 34 years of age. These are regarded as the intermediate lesion between the juvenile (flat) fatty streak and the raised lesion of atherosclerosis. The raised lesions are related to cardiovascular risk factors. Also, cross-sectional studies have shown that BP and lipid levels in healthy young adults are associated with increased common CIMT and other measurements of vascular damage such as coronary artery calcification. These observations indicate that an increased common CIMT at young adulthood most likely reflects exposure to cardiovascular risk factors and, as such, confers risk of cardiovascular morbidity and mortality later in life.

Longitudinal data about the relationship between cardiovascular risk factors and atherosclerosis in young adulthood are limited. In contrast to our findings, in the Muscatine study, neither adolescent systolic or diastolic BP were related to common CIMT in healthy young adults after adjustment for adolescent total cholesterol in boys, and adolescent body mass index and total cholesterol in girls. Only when a time-weighted average of all (±6) diastolic BP measurements were used in the multivariate analyses, a positive relationship was found, albeit in men only. The latter finding underlines the issue that variability in BP measurements may attenuate such associations. In the Bogalusa Heart Study, systolic BP and diastolic BP showed a positive relationship with atherosclerosis measured post mortem in subjects until 39 years of age, but other risk factors were not taken into account. Our findings are in agreement with data in middle-aged and elderly subjects, showing that BP is related to common CIMT measured after 19 months until 15 years of follow-up. In general, systolic BP was found to be more strongly related to common CIMT than diastolic BP, and this may relate from the consistent finding that the diastolic BP measurements are more variable than systolic BP. In the ARYA study, the correlation for systolic BP was 0.7 and for diastolic BP 0.6 between the first and second visits in young adulthood.

The ARYA study findings expand the available evidence by indicating that adolescent pulse pressure is related to a thicker common CIMT at the age of 28 years than is adolescent systolic BP. Studies on pulse pressure in adolescents and young adults are lacking; however, longitudinal studies in middle-aged and elderly subjects reported on pulse pressure, and similarly showed that the relationship between common CIMT and pulse pressure was stronger than systolic BP. The rise in pulse
pressure in older age is caused by a fall in diastolic BP due to increased arterial stiffness of the large arterial vessels, and pulse pressure seems to be the best predictor of cardiovascular morbidity and mortality. In contrast, at young age both systolic BP and diastolic BP appear to be better predictors of cardiovascular morbidity and mortality than is pulse pressure. Yet, it is difficult to investigate whether pulse pressure is independently associated with cardiovascular risk, or whether this association is due to a strong correlation with systolic BP. In our study, pulse pressure is strongly correlated with systolic BP (0.8) and not with diastolic BP (0.1). The difference in impact of these two BP indices on the common CIMT remains to be elucidated by further research.

The relevance of our findings may be expressed by relating the magnitude of the observed associations to an estimated progression rate of CIMT and to an estimated risk of coronary heart disease. A progression rate of CIMT is approximately 14.7 μm per year, based on a pooling of estimates from placebo groups in randomized controlled trials. Our observation of a change of 7.5 μm in CIMT per standard deviation in systolic BP would relate to an increased vascular aging of 6 months that is already present at adolescence. In the Rotterdam Study among 55-year-old subjects, an increase of 163 at adolescence. In the Rotterdam Study among 55-year-old subjects, an increase of 163 m per year, based on a pooling of estimates from placebo groups in randomized controlled trials. Our observation of a change of 7.5 μm in CIMT per standard deviation in systolic BP would relate to an increased vascular aging of 6 months that is already present at adolescence. In the Rotterdam Study among 55-year-old subjects, an increase of 163 μm correlated with a relative increase in CHD risk of 41%. This may be extrapolated to a 7.5-μm increased CIMT as equivalent to a relative increase of 1.9% risk of CHD.

In conclusion, the results of the ARYA study provide evidence that routinely measured high systolic BP and pulse pressure in adolescence are related to an increased common CIMT at the age of 28 years. This increase was found to be independent of other variables at adolescence and young adulthood, including age, sex, body mass index, and adult BP. Our results strengthen the notion that the process of increasing cardiovascular risk is already initiated at adolescence.

Acknowledgments
We thank all participants in the ARYA study for giving their time and enthusiasm. We thank Dr. Annette Bak for her logistic support, and Marjon van de Meer and Janneke van de Brink for inviting participants and collecting data. We acknowledge Rudy Meijer for training in CIMT measurements and the sonographers Marjan de Boer, Gea Boschkker, Binnur Gürsoy, and Lilian HAVEKES. We thank INGEBORG van der TWEEN for her statistical advice.

References