

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Risk Factors Identified in Childhood and Decreased Carotid Artery Elasticity in Adulthood: The Cardiovascular Risk in Young Finns Study

Markus Juonala, Mikko J. Jarvisalo, Noora Mäki-Torkko, Mika Kähönen, Jorma S.A. Viikari and Olli T. Raitakari

Circulation 2005;112:1486-1493; originally published online Aug 29, 2005;

DOI: 10.1161/CIRCULATIONAHA.104.502161

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2005 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/cgi/content/full/112/10/1486>

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Risk Factors Identified in Childhood and Decreased Carotid Artery Elasticity in Adulthood

The Cardiovascular Risk in Young Finns Study

Markus Juonala, MD, PhD; Mikko J. Järvisalo, MD, PhD; Noora Mäki-Torkko, BM; Mika Kähönen, MD, PhD; Jorma S.A. Viikari, MD, PhD; Olli T. Raitakari, MD, PhD

Background—Exposure to risk factors in childhood may have long-term influences on vascular function. We examined the relationship between risk factors identified in childhood and arterial elasticity assessed in adulthood.

Methods and Results—Carotid artery compliance (CAC), Young's elastic modulus (YEM), and stiffness index (SI), 3 measures of large-artery elasticity, were assessed with noninvasive ultrasound in 2255 healthy white adults aged 24 to 39 years participating in a population-based cohort study and who had risk factor data available since childhood. In multivariate models, childhood obesity (skinfold thickness) predicted decreased CAC ($P<0.001$), increased YEM ($P<0.01$), and increased SI ($P<0.01$) in adulthood. Childhood blood pressure was inversely associated with CAC ($P<0.001$) and directly associated with YEM ($P<0.001$). The number of risk factors identified in childhood, which included high LDL cholesterol (at or above 80th percentile), elevated blood pressure, skinfold thickness, low HDL cholesterol (at or below 20th percentile), and smoking, was related inversely with CAC ($P<0.001$) and directly with YEM ($P<0.001$). These associations remained highly significant after adjustment for the number of risk factors identified in adulthood ($P=0.005$ for CAC and $P<0.001$ for YEM).

Conclusions—Cardiovascular risk factors identified in childhood and adolescence predict decreased carotid artery elasticity in adulthood. These data suggest that risk factors operating in early life may have sustained deleterious effects on arterial elasticity. (*Circulation*. 2005;112:1486-1493.)

Key Words: risk factors ■ elasticity ■ obesity ■ atherosclerosis ■ epidemiology

Ultrasonographically assessed arterial elasticity is a useful means to study early pathophysiological changes in the arteries relevant to the development of atherosclerosis.¹ Risk factors such as high LDL cholesterol, elevated blood pressure, obesity, and smoking have been associated with decreased arterial elasticity in cross-sectional studies.²⁻⁴ Furthermore, decreased arterial elasticity has been implicated as an independent predictor of cardiovascular events in high-risk individuals.⁵ These observations thus suggest that reduced arterial elasticity may reflect increased atherosclerotic burden.

Although the clinical complications of coronary heart disease mainly occur in middle age or later in life, atherosclerosis has its roots in childhood. Recent observations by us⁶ and others^{7,8} have consistently shown that risk factors identified in childhood predict the occurrence of preclinical carotid atherosclerosis in adulthood. On the other hand, previous observations concerning the relationship between risk factors in childhood/adolescence and arterial elasticity later in life have been controversial. In the Bogalusa Heart

Study,⁹ childhood blood pressure correlated with pulse-wave velocity (PWV) in adulthood, whereas in the Atherosclerosis Risk in Young Adults (ARYA) study,¹⁰ no association between adolescent blood pressure and adult PWV was observed. Therefore, to gain more insight on childhood determinants of adult vascular health, we measured 3 indices of arterial elasticity—carotid artery compliance (CAC), Young's elastic modulus (YEM), and stiffness index (SI)—in 2255 adults aged 24 to 39 years. These individuals were participants of the prospective Cardiovascular Risk in Young Finns Study for whom risk factor data were available since their childhood.

Methods

Subjects

The Cardiovascular Risk in Young Finns Study is an ongoing, multicenter, follow-up study of atherosclerosis risk factors of Finnish children and young adults. A cross-sectional survey was conducted in 1980 for 3596 subjects aged 3, 6, 9, 12, 15, and 18 years.¹¹ In 2001, we reexamined these individuals, then aged 24 to 39 years. The loss to follow-up was approximately 34%. In the present study,

Received August 23, 2004; revision received May 2, 2005; accepted May 25, 2005.

From the Research Centre of Applied and Preventive Cardiovascular Medicine (M.J., M.J.J., N.M.-T.) and the Departments of Clinical Physiology (M.J.J., O.T.R.) and Medicine (J.S.A.V.), University of Turku, Turku, Finland; and the Department of Clinical Physiology (M.K.), University of Tampere, Finland.

Correspondence to Dr Olli T. Raitakari, Department of Clinical Physiology, PO Box 52, 20521 Turku, Finland. E-mail olli.raita@utu.fi

© 2005 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.104.502161

we have analyzed the associations of risk factors measured in childhood and adulthood with carotid artery elasticity indices assessed in adulthood. Subjects gave written informed consent, and the study was approved by local ethics committees.

Clinical Characteristics

Height and weight were measured, and body mass index (BMI) was calculated. Skinfold thicknesses (in childhood) were measured by Harpenden calipers (Holtain and Bull-British Indicators instruments) to 0.2-mm readings in 1980. The combined thickness of 3 skinfold measurements (subscapular, triceps, and biceps) was used in the analysis. Blood pressure was measured from the brachial artery with a standard mercury sphygmomanometer in 1980. In 3-year-olds, blood pressure was measured with an ultrasound device. The mean of 3 measurements was used in the analysis. In 2001, brachial blood pressure was measured during the ultrasound study with an automated sphygmomanometer (Omron M4, Omron Matsusaka Co). The mean of 2 measurements was used in the analysis. Smoking habits were ascertained with a questionnaire in subjects aged 12 years or older. Smoking was modeled as a dichotomous variable (smoking/nonsmoking). Smoking was defined as regular cigarette smoking on a weekly basis or more often in adolescents, and in adults, it was defined as smoking on a weekly basis or regular smoking in the past.

Biochemical Analyses

For the determination of serum lipid levels, venous blood samples were drawn after an overnight fast. All lipid determinations were done in duplicate in the same laboratory. Standard enzymatic methods were used for serum total cholesterol, triglycerides, and HDL cholesterol. LDL cholesterol concentration was calculated by the Friedewald formula. Fasting plasma high-sensitivity C-reactive protein (CRP) concentrations were analyzed by latex turbidimetric immunoassay (Wako Chemicals GmbH). The lower detection limit reported for the assay was 0.06 mg/L. Glucose concentrations were analyzed enzymatically (glucose dehydrogenase, Olympus Diagnostica GmbH). In 1980, serum insulin was measured with a modification of the immunoassay method of Herbert et al.¹² In 2001, serum insulin was measured by microparticle enzyme immunoassay kit (Abbott Laboratories, Diagnostic Division, Dainabot). Details of these methods have been described previously.¹³

Carotid Artery Studies

Ultrasound studies were performed with Sequoia 512 ultrasound mainframes (Acuson) with 13.0-MHz linear-array transducers between September 2001 and January 2002. The left carotid artery was scanned according to a standardized protocol. Several moving-image clips of the beginning of the carotid bifurcation and the common carotid artery with a duration of 5 seconds were acquired and stored in digital format for subsequent offline analysis. The digitally stored scans were analyzed by one reader blinded to subjects' details (M.J.). Carotid artery intima-media thickness was measured as described previously.^{6,14}

To assess carotid artery elasticity indices, the best-quality cardiac cycle was selected from the 5-second image clips. The common carotid diameter 10 mm from carotid bifurcation was measured from the B-mode images with ultrasonic calipers at least twice in end diastole and end systole, respectively. The means of the measurements were used as the end-diastolic and end-systolic diameters. Ultrasound and concomitant brachial blood pressure measurements were used to calculate the following indices of arterial elasticity: $CAC = (D_s - D_d)/D_d / (P_s - P_d)$, $YEM = (P_s - P_d \times D_d) / [(D_s - D_d) / IMT]$, and $SI = \ln(P_s/P_d) / [(D_s - D_d)/D_d]$, where D_d is the diastolic diameter, D_s is the systolic diameter, P_s is systolic blood pressure, P_d is diastolic blood pressure, and IMT is carotid artery intima-media thickness.

CAC measures the ability of the arteries to expand as a response to pulse pressure caused by cardiac contraction and relaxation, whereas YEM gives an estimate of arterial stiffness that is independent of wall (intima-media) thickness.¹⁵ SI has been developed to reduce the impact of the curvilinear pressure-stiffness relationship on

arterial stiffness and is therefore considered to be relatively independent of blood pressure.¹⁶ These indices correlated highly significantly (P always <0.001) with each other, with Pearson's correlation coefficients of $r = -0.71$ between CAC and YEM, $r = -0.73$ between CAC and SI, and $r = 0.88$ between YEM and SI. Carotid artery wall thickness correlated weakly with CAC in men ($r = -0.06$, $P = 0.051$) but not in women ($r = -0.01$, $P = 0.64$). Wall thickness was not related to SI either in men ($r = 0.03$, $P = 0.28$) or in women ($r = -0.03$, $P = 0.20$).

To assess reproducibility of ultrasound measurements, we reexamined 57 subjects 3 months after the initial visit (2.5% random sample). The between-visit coefficient of variation was 2.7% for carotid artery diastolic diameter, 16.3% for CAC, 19.5% for YEM, and 16.6% for SI.

Statistical Methods

The comparisons between men and women and between study dropouts and participants were performed with t tests. The bivariate relationships between risk factors and carotid artery elasticity were examined by Pearson's correlation analysis. To examine the effect of multiple risk factors on arterial elasticity, we calculated a risk score, defined as the number of risk factors. Risk factors were defined as values at or above the age- and sex-specific 80th percentile for LDL cholesterol, systolic blood pressure, skinfold thickness (childhood), and BMI (current); at or below the 20th percentile for HDL cholesterol; and smoking. The mean number of risk factors was 0.9 (range 0 to 5) in childhood and 1.3 (range 0 to 5) in adulthood. Because smoking was only evaluated in children aged 12 years or older, we repeated all analysis using a risk score that did not include smoking as a risk variable and obtained essentially similar results.

To evaluate which childhood risk variables were independently associated with carotid elasticity indices, we used multivariate regression analysis. Similarly, multivariate modeling was used to examine which current risk variables were independent correlates for elasticity indices. Variables in initial stepwise multivariate models included age, sex, and childhood and current LDL cholesterol, HDL cholesterol, triglycerides, BMI (in childhood models, skinfold thickness), systolic blood pressure, insulin, and smoking. In current models, CRP and glucose were also analyzed.

Next, we examined whether each of those childhood risk variables that turned out to be significantly related to adult elasticity indices had an independent effect after the effect of the current risk variable in question was taken into account. To accomplish this, we calculated the change in regression coefficient between childhood risk variable and elasticity index after introducing the current risk variable into the same model. All analysis were performed with the Statistical Analysis System, SAS (version 8.1), and statistical significance was inferred at a 2-tailed probability value <0.05 . When performing multiple bivariate correlations between elasticity indices and risk variables, we applied the Bonferroni correction by adjusting the probability values (the probability value of each bivariate correlation analysis was multiplied by the number of correlations being tested). Values for triglycerides, insulin, and CRP were log-transformed before analyses owing to skewed distributions.

Results

The representativeness of the present study cohort was tested by comparing its baseline (1980) characteristics with the dropouts. There were more males than females among dropouts, and the dropouts were younger than participants in both genders. Otherwise, when dropouts and participants were compared with age-adjusted analysis, there were no statistically significant differences in total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, blood pressure, or BMI (Table 1). Table 2 summarizes the mean values of carotid artery elasticity indices in men and women. Men had lower CAC and higher YEM, SI, and carotid diameters than

TABLE 1. Baseline Characteristics (in 1980) of Participants and Dropouts in the Follow-Up (in 2001)

	Men		Women	
	Participants (n=1012)	Dropouts (n=752)	Participants (n=1243)	Dropouts (n=589)
Age in 1980*	10.7†	9.9	10.7*	10.1
Total cholesterol, mmol/L‡	5.02	5.05	5.19	5.12
HDL cholesterol, mmol/L‡	3.2	3.22	3.33	3.29
LDL cholesterol, mmol/L‡	1.48	1.5	1.5	1.47
Triglycerides, mmol/L‡	0.75	0.74	0.79	0.79
Systolic blood pressure, mm Hg‡	114	112	112	112
Diastolic blood pressure, mm Hg‡	69	69	69	69
BMI, kg/m ² ‡	17.9	17.7	17.8	17.9
Smoking prevalence, %§	21.7	27.0	16.3	18.8

* $P<0.05$, † $P<0.001$, ‡ tests applied between participants and dropouts to examine differences in age.

‡Differences between participants and dropouts were examined with regression analysis adjusted with age (P always >0.05).

§Smoking prevalences in 15- to 18-year-old subjects; differences between participants and dropouts were examined with χ^2 test (P always >0.05).

women. Elasticity indices correlated strongly with age in both sexes (Figure 1).

Childhood Risk Factors and Carotid Artery Elasticity

Correlation coefficients between risk factors and CAC are shown in Table 3. Childhood systolic blood pressure, BMI, insulin, and skinfold thickness correlated inversely with CAC both in men and in women (Table 3). When the CAC variable was substituted with YEM, we found significant direct correlations between YEM and childhood triglycerides ($P<0.001$), blood pressure ($P<0.001$), skinfold thickness ($P<0.001$), insulin ($P<0.001$), and BMI ($P<0.001$). SI correlated directly with childhood triglycerides ($P<0.001$), blood pressure ($P<0.001$), skinfold thickness ($P<0.001$), insulin ($P<0.001$), and BMI ($P<0.001$).

In multivariate models, childhood skinfold thickness and systolic blood pressure predicted decreased CAC and increased YEM in adulthood. Childhood skinfold thickness was also directly related to adult SI (Table 4). Childhood BMI was directly associated with YEM ($P=0.002$) when included in the multivariate model instead of skinfold thickness.

A decreasing trend in CAC ($P<0.001$) and an increasing trend in YEM ($P<0.001$) was observed across the groups

TABLE 2. Mean Values of Ultrasound Measurements (n=2255)

	Men (n=1012)	Women (n=1243)
Age, y	31.7±5.0	31.7±5.0
Carotid artery diastolic diameter, mm	6.02±0.51	5.50±0.45
CAC, %/10 mm Hg	2.00±0.66	2.31±0.78
YEM, mm Hg-mm	334±152	280±153
SI	5.60±1.95	5.30±2.50

Plus-minus values are mean±SD.

All comparisons (t tests) between men and women $P<0.001$, except for age.

with an increasing number of childhood risk factors (Figure 2). The association between the number of childhood risk factors and SI was of borderline significance ($P=0.07$).

Current Risk Factors and Carotid Artery Elasticity

In univariate analysis, current LDL cholesterol, triglycerides, blood pressure, BMI, and insulin correlated inversely with CAC in both sexes. In men, CRP was also inversely correlated with CAC (Table 3). LDL cholesterol ($P<0.001$), triglycerides ($P<0.001$), blood pressure ($P<0.001$), BMI ($P<0.001$), insulin ($P<0.001$), and glucose ($P<0.001$) were directly related to YEM in both sexes. In men, CRP ($P<0.001$) was inversely associated with YEM. LDL cholesterol ($P<0.001$), triglycerides ($P<0.001$), BMI ($P<0.001$), and insulin ($P<0.001$) correlated directly with SI in both sexes. In addition, in men, blood pressure ($P<0.001$) and CRP ($P<0.001$) were directly related to SI. In multivariate models, current LDL cholesterol, systolic blood pressure, and insulin were inversely related to CAC and directly related to YEM and SI. BMI correlated directly with YEM (Table 5).

Independent Effect of Childhood Risk Factors

Childhood systolic blood pressure, skinfold thickness, and risk score were significantly associated with carotid elasticity in adulthood. Each of these childhood risk variables also correlated significantly with the correspondent current risk factor variable, with correlation coefficients ranging between $r=0.2$ and $r=0.3$ (P always <0.001). To examine how the associations between childhood risk and adult carotid elasticity changed when the effect of adult risk was taken into account, we calculated the associations of these variables with elasticity indices before and after adjustment for current risk factors. Figure 3 shows the unadjusted and adjusted regression coefficients and their 90% CIs for CAC. Overall, the effect of childhood risk factors on adult CAC was

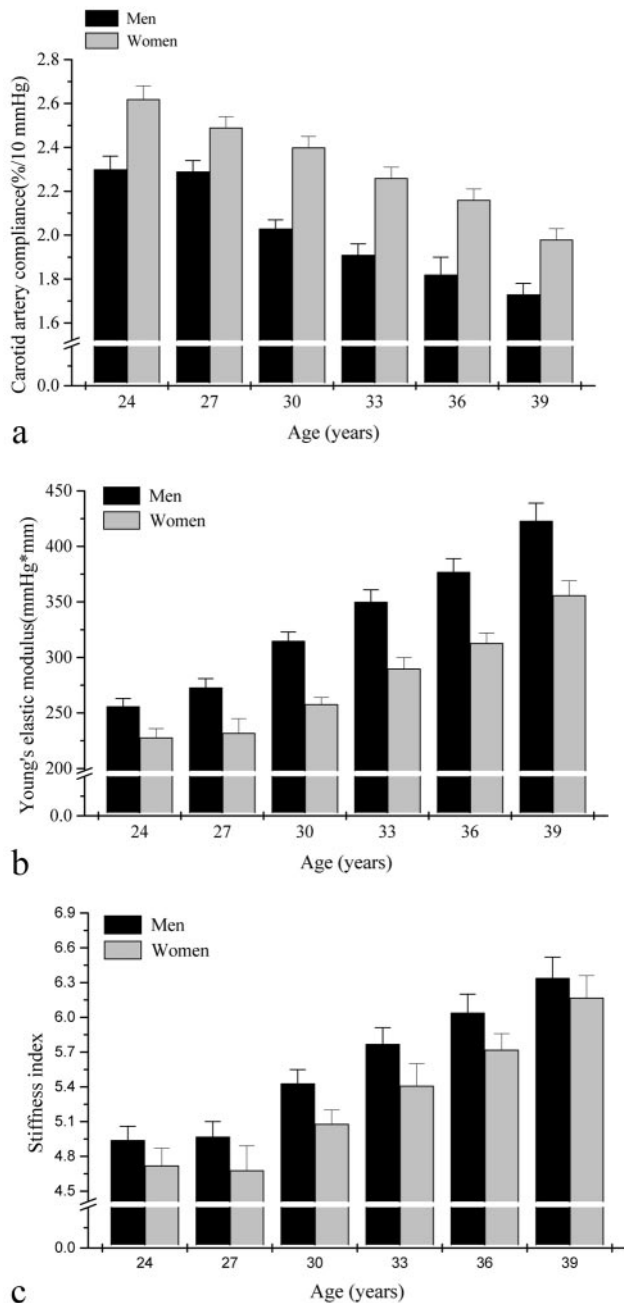


Figure 1. CAC (A), YEM (B), and SI (C; mean±SEM) in men and women aged 24 to 39 years. *P* for trend <0.001 (correlation with age) in all variables in both genders.

attenuated ≈50% when the effects of current risk factors were taken into account. The effect of childhood risk score remained highly significant when the current risk score was introduced into the same regression model (*P*=0.005). The effect of childhood systolic blood pressure remained of borderline significance (*P*=0.08) when the current blood pressure was introduced.

The association between childhood risk score and YEM (*P*<0.001) also remained significant after adjustment with the current risk score. Furthermore, the effect of childhood blood pressure on YEM (*P*=0.003) remained significant when adjusted with current blood pressure.

TABLE 3. Relationships Between Risk Factors and CAC

	Childhood (1980)		Adult (2001)	
	n	r	n	r
Males				
LDL cholesterol	1003	-0.09	981	-0.14*
HDL cholesterol	1003	0.06	1004	0.06
Triglycerides	1003	-0.10	1006	-0.16*
Systolic blood pressure	994	-0.30*	1007	-0.38*
BMI	1001	-0.26*	1009	-0.26*
Insulin	994	-0.21*	1006	-0.15*
Skinfold thickness	995	-0.14*		
Glucose			1007	-0.07
CRP			1007	-0.16*
Smoking	517	0.04	1011	0.05
Females				
LDL cholesterol	1228	-0.01	1235	-0.17*
HDL cholesterol	1228	0.03	1237	0.002
Triglycerides	1230	-0.09	1237	-0.16*
Systolic blood pressure	1235	-0.23*	1228	-0.34*
BMI	1235	-0.23*	1231	-0.22*
Insulin	1224	-0.17*	1237	-0.20*
Skinfold thickness	1224	-0.22*		
Glucose			1238	-0.09
CRP			1238	-0.07
Smoking	644	-0.01	1243	0.02

r values are Pearson's correlation coefficients.

**P*<0.001 (after Bonferroni correction).

Discussion

Risk factors that operate in early life may have long-term effects on arterial physiology. We found that skinfold thickness and blood pressure measured in childhood and adolescence predicted decreased carotid artery elasticity in adulthood. Moreover, we demonstrated that the number of risk factors identified in childhood correlated inversely with carotid artery elasticity in adulthood. Our observations thus suggest that childhood risk factors predict decreased carotid artery elasticity in adulthood. We assessed 3 indices (CAC, YEM, and SI) that may reflect different aspects of arterial elasticity^{16,17} with consistent results concerning the associations between risk variables and elasticity parameters.

Obesity in children and young adults has been associated with decreased arterial elasticity.^{4,18} Nevertheless, to the best of our knowledge, this is the first study indicating that childhood obesity has predictive value for decreased arterial elasticity in adulthood. There are different potential mechanisms to explain the association between childhood obesity and decreased arterial elasticity in adults. Obesity-associated hyperinsulinemia has been shown to decrease arterial elasticity.¹⁵ Consistently, we observed that insulin levels measured in adulthood were associated independently with carotid artery elasticity. Second, obesity might decrease arterial elasticity through inflammation. Overweight has been related with low-grade inflammation,¹⁹ and recently, Yasmin et al²⁰ showed that CRP correlates directly with arterial stiffness. In

TABLE 4. Multivariate Models of the Relationships Between Risk Variables Measured in Childhood at Ages 3 to 18 Years and Carotid Artery Elasticity Indices, Including Compliance (CAC), YEM, and SI Measured 21 Years Later in 2187 Adults at Ages 24 to 39 Years

	Mean±SD	CAC, β ±SE	YEM, β ±SE	SI, β ±SE
Age y	10.7±5.0	-0.025±0.004§	6.8±0.8§	0.093±0.010§
Male sex, %	44.9	-0.333±0.031§	56.8±6.6§	0.378±0.101‡
Skinfold thickness, mm	26.1±11.4	-0.065±0.016§	10.1±3.5†	0.139±0.053†
Systolic blood pressure, mm Hg	112±12	-0.106±0.017§	23.7±3.7§	
Model R^2		14%	15%	6%

β -Values are regression coefficients for a 1-unit change in age and a 1-SD change in continuous variables.

Initial stepwise regression models included age, sex, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, skinfold thickness, insulin, and smoking as independent variables. The nonsignificant predictors did not act as confounders, because the significant relations shown were not affected by inclusion or exclusion of these variables.

* $P<0.05$, † $P<0.01$, ‡ $P<0.001$, § $P<0.0001$.

the present study, CRP correlated inversely with arterial elasticity in a univariate model in men. However, because of a strong correlation with BMI, this relationship did not remain significant in multivariate models. Finally, elevation in leptin levels, a hormone that plays a key role in the regulation of appetite and body weight, has been related to impaired arterial distensibility in children.²¹

In addition to obesity, elevated systolic blood pressure measured in childhood was an independent predictor of arterial elasticity in young adults. Elevated blood pressure accelerates atherosclerosis, collagen synthesis, and arterial smooth muscle hyperplasia and hypertrophy, which contributes to decreased arterial elasticity.¹⁹ Our findings suggest that high blood pressure levels operating in childhood may induce adverse vascular effects. In an analysis from the Bogalusa Heart Study,⁹ high childhood blood pressure was an independent predictor of increased ankle-brachial PWV in young adults. Their study group consisted of 835 black and white adults aged 24 to 44 years with an average follow-up of 26.5 years. Conversely, in the ARYA study,¹⁰ blood pressure measured at the mean age of 13.5 years did not predict carotid-femoral PWV in 527 white adults aged 27 to 30 years. The present results among a substantially larger cohort of 2255 white young adults in the 21-year follow-up are in line with the observations from the Bogalusa Heart Study. We assessed carotid artery elasticity indices ultrasonically. PWV used in the 2 above-mentioned studies measured the speed of transmission of pulse pressure wave between 2 arteries to determine an index of the average elastic state of the vessel pathway. These 2 methods have been shown to correlate with each other, which supports the concept that they measure similar arterial properties.²² Therefore, the discrepancy with the results from the ARYA study is probably not due to methodological issues. Instead, it may be explained by differences in blood pressure measurements. We measured blood pressure using a standardized protocol in the entire cohort, whereas values in the ARYA study were obtained from school health records.

The number of risk factors identified in childhood was significantly associated with decreased CAC and increased YEM. Risk factors included in the model were high LDL cholesterol, low HDL cholesterol, obesity, elevated blood pressure, and smoking. The present results are in line with earlier observations that showed that the presence of multiple risk factors may lead to acceleration of atherosclerosis in young people.^{6,23} This finding may have implications in the prevention of cardiovascular disease, because these risk factors (apart from smoking) are mainly metabolically linked,

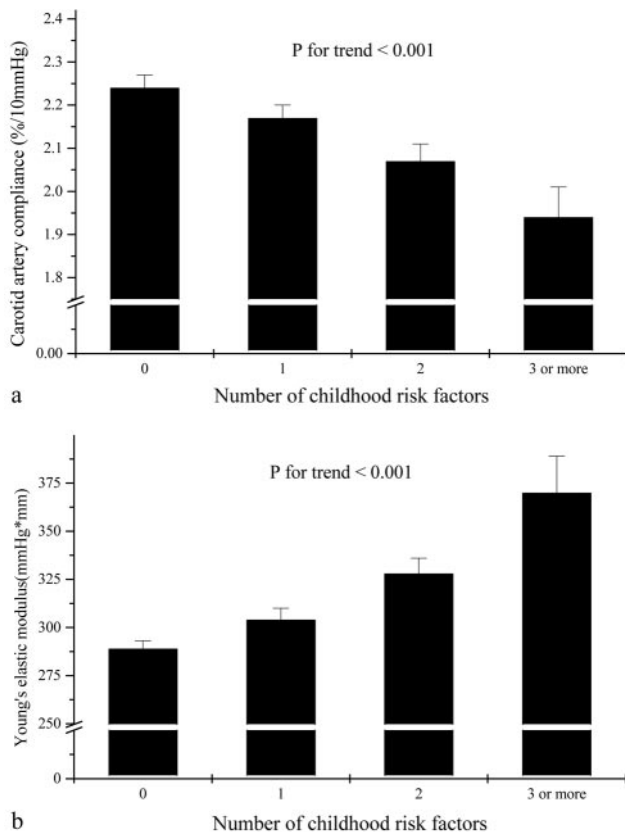


Figure 2. CAC (A) and YEM (B; mean±SEM) in 24- to 39-year-old adults by number of childhood risk factors (risk score). Risk factors, including LDL cholesterol, systolic blood pressure, and skinfold thickness at or above 80th percentile, HDL cholesterol at or below 20th percentile, and smoking (assessed in subjects 12 years old and older), were measured at ages 3 to 18 years. Probability values shown are adjusted for age.

TABLE 5. Multivariate Models of the Relationships Between Current Risk Variables and Carotid Artery Elasticity Indices, Including Compliance (CAC), YEM, and SI in 2191 Adults Aged 24 to 39 Years

Risk Variable	Mean±SD	CAC, β ±SE	YEM, β ±SE	SI, β ±SE
Age, y	31.7±5.0	-0.036±0.003‡	8.7±0.6‡	0.096±0.010‡
Male sex, %	44.4	-0.135±0.030‡	21.7±6.4†	
LDL cholesterol, mmol/L	3.28±0.84	-0.047±0.015*	8.9±3.1*	0.146±0.049*
Systolic blood pressure, mm Hg	116±13	-0.228±0.015‡	36.9±3.3‡	0.153±0.049*
Insulin, μ U/mL	7.7±5.6	-0.079±0.015‡	10.0±3.5*	0.218±0.050‡
BMI, kg/m ²	25.0±4.4		15.7±3.7‡	
Model R ²		24%	23%	7%

β -Values are regression coefficients for a 1-unit change in age and a 1-SD change in continuous variables.

Initial stepwise regression models included age, sex, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, skinfold thickness, insulin, CRP, glucose, and smoking as independent variables. The nonsignificant predictors did not act as confounders, because the significant relations shown were not affected by inclusion or exclusion of these variables.

* P <0.01, † P <0.001, ‡ P <0.0001.

and previous reports have suggested that they tend to cluster in childhood.²⁴

Current risk factors showed a stronger relation to elasticity indices than childhood risk factors. For example, \approx 14% of the variance in CAC was explained by risk variables measured in childhood, whereas 24% of the variance in CAC was explained by current risk variables. Risk factors show significant tracking, and therefore, the relationship between childhood risk and later reduced arterial elasticity could be explained in part by tracking of risk factor values from

childhood to adulthood. However, the fact that childhood risk factors continued to be significant predictors of CAC and YEM even after adjustment for adult risk factors suggests a direct relation between childhood risk factors and arterial elasticity.

We have previously shown that childhood risk factors correlate with carotid artery intima-media thickness, a structural marker of subclinical atherosclerosis, rather independently of current risk factors.⁶ In the present study, adjustment for current risk factors attenuated the effect of childhood risk factors on adult arterial elasticity approximately by half. This may suggest that structural changes in the arterial wall represent lifetime exposure to risk factors, whereas a functional change in arterial elasticity may be dynamic and more dependent on current risk factor status. In line with this assumption, intervention studies have shown that arterial elastic properties are rapidly influenced with nitrates, calcium channel blockers, and ACE inhibitors and possibly with statins.^{1,25–27}

An important limitation of the present study is the blood pressure measurement method. The pulse pressure used in the equations to calculate elasticity indices was measured from the brachial artery. It would be ideal to study the pulse pressure from the artery in question, because the use of brachial pressures may overestimate pulse pressure in central arteries.²⁸ This increase is a consequence of pulse-wave reflection from the periphery, which augments the peak of the pressure wave in peripheral arteries close to the reflection sites. PWV is closely related to age. Therefore, the difference between central and peripheral pulse pressure is likely to be similar between study subjects within a narrow age range, as in the present study. Moreover, Borow and Newburger²⁹ have shown an excellent correlation of $r=0.98$ between systolic blood pressures and $r=0.97$ between diastolic pressures measured invasively from ascending aorta and noninvasively from brachial artery. The close positive relationship between brachial pulse pressure and the relative diameter increase of carotid artery during systole, as shown by Reneman et al,³⁰ also supports the assumption that brachial pulse pressure can

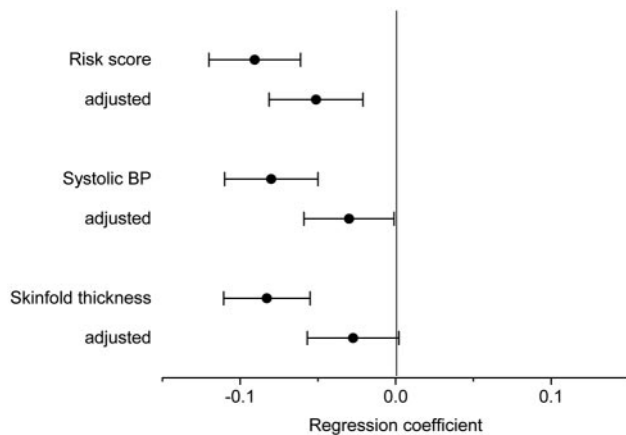


Figure 3. Regression coefficients (adjusted for age and sex) and their 90% CIs for associations of childhood risk score (P <0.001), systolic blood pressure (P <0.001), and skinfold thickness (P <0.001) with CAC (upper lines). Lower lines show the same associations after adjustment for current risk score, blood pressure, and BMI, respectively. After these adjustments, the association between childhood risk score and CAC remained significant ($P=0.005$), whereas the effect of childhood blood pressure became borderline significant ($P=0.08$). Childhood skinfold thickness was not associated with CAC ($P=0.16$) when adjusted for adult BMI. When risk scores were calculated, risk factors were defined as values at or above the age- and sex-specific 80th percentile for LDL cholesterol, systolic blood pressure, skinfold thickness (childhood), and BMI (current), values at or below the 20th percentile for HDL cholesterol, and smoking.

be used to derive CAC. Accordingly, techniques similar to those in the present study are commonly used in cardiovascular research.^{2,4,15,22} The between-visit variations for arterial elasticity indices was rather high (between 15% and 20%), as also observed in previous reports.^{31,32} This is, in part, due to the fact that several variables, including arterial diameter and blood pressure measurements, are used to derive these indices. We observed small variation in the carotid artery diameter measurements (2.7%), however, which suggests that much of the long-term variation in elasticity indices is due to physiological fluctuation and not to measurement error. The reproducibility of elasticity measurements is improved by the use of computerized edge-detection analysis of sequential image frames. With this method, Selzer et al³³ reported very low coefficients of variation of 1.2% in carotid diameter measurements. Because of the large variability in blood pressure measurements (coefficient of variation 6% to 9%), coefficients of variation for elasticity indices ranged between 11% and 15%. The large variation in elasticity indices is a limitation, and the results must be interpreted with caution. The noise in the data is likely to weaken the observed relationships. Therefore, the associations observed between risk factors and arterial elasticity may be underestimated. Another potential limitation is the nonparticipation in the follow-up study. However, baseline risk factors (in 1980) were similar among participants and dropouts in the 21-year follow-up. Thus, the present study cohort appears to be representative of the original study population.

In conclusion, childhood risk factors predict decreased carotid artery elasticity 21 years later in adulthood. Therefore, risk factors operating early in life may have sustained deleterious effects on vasculature.

Acknowledgments

This study was financially supported by the Academy of Finland (grant No. 53392 and 34316), the Social Insurance Institution of Finland, the Turku University Foundation, Special Federal Grants for the Turku University Hospital, the Juho Vainio Foundation, the Finnish Foundation of Cardiovascular Research, the Lydia Maria Julin Foundation, Research Foundation of Instrumentarium, Research Foundation of Orion Corporation, the Maud Kuistila Foundation, the Emil Aaltonen Foundation, the Finnish Medical Foundation, and the Finnish Cultural Foundation.

References

- Oliver JJ, Webb DJ. Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. *Arterioscler Thromb Vasc Biol.* 2003;23:554–566.
- Aggoun Y, Bonnet D, Sidi D, Girardet JP, Brucker E, Polak M, Safar ME, Levy BI. Arterial mechanical changes in children with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol.* 2000;20:2070–2075.
- Liang YL, Shiel LM, Teede H, Kotsopoulos D, McNeil J, Cameron JD, McGrath BP. Effects of blood pressure, smoking, and their interaction on carotid artery structure and function. *Hypertension.* 2001;37:6–11.
- Tounian P, Aggoun Y, Dubern B, Varille V, Guy-Grand B, Sidi D, Girardet JP, Bonnet D. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet.* 2001;358:1400–1404.
- Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end stage renal disease. *Hypertension.* 1998;32:570–574.
- Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäkitorkko N, Järvisalo MJ, Uhari M, Jokinen E, Rönnemaa T, Åkerblom HK, Viikari JSA. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA.* 2003;290:2277–2283.
- Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. *Circulation.* 2001;104:2815–2819.
- Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA.* 2003;290:2271–2276.
- Li S, Chen W, Srinivasan SR, Berenson GS. Childhood blood pressure as a predictor of arterial stiffness in young adults: the Bogalusa Heart Study. *Hypertension.* 2004;43:541–546.
- Oren A, Vos LE, Uiterwaal CS, Gorissen WH, Grobbee DE, Bots ML. Adolescent blood pressure does not predict aortic stiffness in healthy young adults: the Atherosclerosis Risk in Young Adults (ARYA) study. *J Hypertens.* 2003;21:321–326.
- Åkerblom HK, Viikari J, Uhari M, Räsänen L, Byckling T, Louhivuori K, Pesonen E, Suoninen P, Pietikäinen M, Lähde PL, Dahl M, Aromaa A, Sarna S, Pyörälä K. Atherosclerosis precursors in Finnish children and adolescents, I: general description of the cross-sectional study of 1980, and an account of the children's and families' state of health. *Acta Paediatr Scand.* 1985;318(suppl):49–63.
- Herbert V, Lau KS, Gottlieb CW, Bleicher SJ. Coated charcoal immunoassay of insulin. *J Clin Endocrinol Metab.* 1965;25:1375–1384.
- Juonala M, Viikari JSA, Hutri-Kähönen N, Pietikäinen M, Jokinen E, Taittonen L, Marniemi J, Rönnemaa T, Raitakari OT. The 21-year follow-up of the Cardiovascular Risk in Young Finns Study: risk factor levels, secular trends and east-west difference. *J Intern Med.* 2004;255:457–468.
- Juonala M, Viikari JSA, Laitinen T, Marniemi J, Helenius H, Rönnemaa T, Raitakari OT. Interrelations between brachial endothelial function and carotid intima-media thickness in young adults: the Cardiovascular Risk in Young Finns Study. *Circulation.* 2004;110:2918–2923.
- Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes: the ARIC Study: Atherosclerosis Risk in Communities Study. *Circulation.* 1995;91:1432–1443.
- Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction: a noninvasive method to predict severity of coronary atherosclerosis. *Circulation.* 1989;80:78–86.
- Riley WA, Barnes RW, Evans GW, Burke GL. Ultrasonic measurements of the elastic modulus of the common carotid artery: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke.* 1992;23:952–956.
- Wildman RP, Mackey RH, Bostom A, Thompson T, Sutton-Tyrrell K. Measures of obesity are associated with vascular stiffness in young and older adults. *Hypertension.* 2003;42:468–473.
- Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol.* 1999;19:972–978.
- Yasmin, McEniery CM, Wallace S, Mackenzie IS, Cockcroft JR, Wilkinson IB. C-reactive protein is associated with arterial stiffness in apparently healthy individuals. *Arterioscler Thromb Vasc Biol.* 2004;24:969–974.
- Singhal A, Farooqi IS, Cole TJ, O'Rahilly S, Fewtrell M, Kattenhorn M, Lucas A, Deanfield J. Influence of leptin on arterial distensibility: a novel link between obesity and cardiovascular disease? *Circulation.* 2002;106:1919–1924.
- Nagai Y, Fleg JL, Kemper MK, Rywik TM, Earley CJ, Metter EJ. Carotid arterial stiffness as a surrogate for aortic stiffness: relationship between carotid artery pressure-strain elastic modulus and aortic pulse wave velocity. *Ultrasound Med Biol.* 1999;25:181–188.
- Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults: the Bogalusa Heart Study. *N Engl J Med.* 1998;338:1650–1656.
- Raitakari OT, Porkka KV, Räsänen L, Rönnemaa T, Viikari JS. Clustering and six year cluster-tracking of serum total cholesterol, HDL-cholesterol and diastolic blood pressure in children and young adults: the Cardiovascular Risk in Young Finns Study. *J Clin Epidemiol.* 1994;47:1085–1093.
- Fitchett DH, Simkus GJ, Beaudry JP, Marpole DG. Reflected pressure waves in the ascending aorta: effect of glyceryl trinitrate. *Cardiovasc Res.* 1988;22:494–500.

26. London GM, Marchais SJ, Guerin AP, Metivier F, Safar ME, Fabiani F, Froment L. Salt and water retention and calcium blockade in uremia. *Circulation*. 1990;82:105–113.
27. Asmar RG, Pannier B, Santoni JP, Laurent S, London GM, Levy BI, Safar ME. Reversion of cardiac hypertrophy and reduced arterial compliance after converting enzyme inhibition in essential hypertension. *Circulation*. 1988;78:941–950.
28. Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J*. 1993;14:160–167.
29. Borow KM, Newburger JW. Noninvasive estimation of central aortic pressure using the oscillometric method for analyzing systemic artery pulsatile blood flow: comparative study of indirect systolic, diastolic, and mean brachial artery pressure with simultaneous direct ascending aortic pressure measurements. *Am Heart J*. 1982;103:879–886.
30. Reneman RS, van Merode T, Hick P, Muytjens AM, Hoeks AP. Age-related changes in carotid artery wall properties in men. *Ultrasound Med Biol*. 1986;12:465–471.
31. Jensen-Urstad K, Rosfors S. A methodological study of arterial wall function using ultrasound technique. *Clin Physiol*. 1997;17:557–567.
32. Arnett DK, Chambless LE, Kim H, Evans GW, Riley W. Variability in ultrasonic measurements of arterial stiffness in the Atherosclerosis Risk in Communities study. *Ultrasound Med Biol*. 1999;25:175–180.
33. Selzer RH, Mack WJ, Lee PL, Kwong-Fu H, Hodis HN. Improved common carotid elasticity and intima-media thickness measurements from computer analysis of sequential ultrasound frames. *Atherosclerosis*. 2001;154:185–193.