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Arterial Distensibility in Adolescents

The Influence of Adiposity, the Metabolic Syndrome, and Classic Risk Factors

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Background—Atherosclerosis develops from childhood, but the determinants of this preclinical stage remain uncertain. We examined the relations of classic coronary risk factors, adiposity and its associated metabolic disturbances, to arterial distensibility (a marker of early arterial disease) in 13- to 15-year-olds, some of whom had previously been studied at ages 9 to 11 years.

Methods and Results—Brachial artery distensibility was measured by a noninvasive ultrasound technique in 471 British children in whom measures of adiposity, blood pressure, fasting blood lipids, and insulin had been made. All adiposity measures showed strong graded inverse relationships with distensibility. Inverse associations with distensibility were also observed for insulin resistance (homeostasis model assessment), diastolic pressure, C-reactive protein, and the number of metabolic syndrome components present, which had a graded relation to distensibility. Total and LDL cholesterol levels were also inversely related to distensibility, but less strongly than adiposity; homocysteine had no relation to distensibility. Although the relations of total and LDL cholesterol and diastolic pressure to distensibility had been present at 9 to 11 years of age, those of adiposity and insulin resistance were only apparent at 13 to 15 years.

Conclusions—Adiposity and its metabolic consequences are associated with adverse changes in the arterial wall by the teenage years. The graded relation with increasing adiposity was stronger than that for cholesterol and was seen at body mass index levels well below those considered to represent "obesity." This emphasizes the importance of population-based strategies to control adiposity and its metabolic consequences in the young. (***Circulation*. 2005;112:1789-1797.)**

Key Words: epidemiology ■ lipids ■ obesity ■ physiology ■ atherosclerosis

Atherosclerosis begins in childhood, long before its clinical consequences emerge. Although the roles of "classic" risk factors (high blood cholesterol, high blood pressure, and cigarette smoking) in determining risk of coronary atherosclerosis were originally shown in middle age,[1] earlier exposure to these factors (from the first decade of life onward) has been shown to cause endothelial dysfunction and autopsy-documented atherosclerosis.[2,3]

In childhood, levels of classic risk factors associated with markedly increased risks of atherosclerotic disease in adult life are uncommon. However, levels of adiposity and obesity (marked degrees of adiposity) have been increasing rapidly in childhood. In many Western populations, obesity is reaching epidemic proportions,[4] with the most dramatic proportional increases seen in children and young adults.[5] Obesity in adults is associated with clustering of abnormalities generally termed the "metabolic syndrome"[6,7] and is a well-established risk factor for coronary heart disease.[8] It is increasingly recognized that adiposity in childhood is associated with a similar adverse metabolic profile.[9,10] It is therefore important to establish the relative importance of adiposity, its associated metabolic disturbances, and classic risk factors in the development of arterial disease in contemporary children and adolescents. However, this issue has so far been little studied.

Noninvasive ultrasound methods now enable early abnormalities of arterial structure and function to be examined. Arterial distensibility, which reflects the structural arrangement of the artery (particularly its elastic components), provides a marker of coronary heart disease risk in humans,[11,12] and animal studies suggest that reduced arterial elasticity is an early sign of atherosclerotic change.[13] Severe obesity in teenagers has been shown to produce endothelial dysfunction and reduced arterial distensibility.[14,15] We have previously shown that higher levels of total and LDL cholesterol may diminish arterial distensibility in prepubertal children[16] and that higher levels of leptin may do the same during puberty.[17]

We have now examined the relations of adiposity and its associated metabolic disturbances to vascular function and

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compared these with the associations of classic and novel cardiovascular risk factors (including C-reactive protein [CRP] and homocysteine) in a large cohort of well-characterized 13- to 15-year-olds. Comparison of these associations in teenagers with those at 9 to 11 years of age in a subgroup of study participants measured 4 years previously has allowed us to examine the emergence of the adverse vascular correlates of adiposity during the critical period of development around puberty.

Methods

We studied children in 4 towns in the United Kingdom, 2 with high adult cardiovascular mortality rates (Rochdale and Rhondda) and 2 with low adult cardiovascular mortality rates (Bath and Tunbridge Wells). We invited 681 children who had recently taken part in a detailed cardiovascular risk factor measurement survey (February to July 1999) for vascular function measurements, which were performed between October 1999 and April 2000.

Cardiovascular Risk Factor Measurements

Children were examined while they were dressed in light clothing without shoes. Weight was measured with a precalibrated digital weighing scale (Soehnle Ltd) and height with a portable stadiometer (CMS Ltd). Triceps, biceps, and subscapular and suprailiac skinfolds were each measured once by standardized techniques; the sum of the 4 skinfold measurements[18] was used in analysis. Bioimpedance was measured from the left arm and left leg with the Bodystat 500 (Bodystat, Ltd).[19] Percentage body fat was determined from resistance with the equations of Deurenberg et al,[20] validated in children of a similar age. Waist circumference was measured at the end of normal expiration at the midpoint between the iliac crest and the lower edge of the ribs in the midaxillary line and hip circumference at the point of maximum circumference over the buttocks. Pubertal status was recorded by participants in private using a self-assessment questionnaire based on the 5 Tanner stages of pubic hair growth (both sexes), breast development (girls), and penis development (boys).[21]

Blood pressure was measured twice in the right arm with a Dinamap 1846SX oscillometric blood pressure recorder (Critikon Inc)[22] with an appropriate cuff size. The older half of participating children provided a blood sample, which was collected in the morning after an overnight fast, frozen within 6 hours of collection (−20°C), and transferred to a central laboratory for analysis. Total serum cholesterol and HDL cholesterol were measured with a Hitachi 747 automated analyser (Roche Diagnostics); LDL cholesterol concentration was determined with the Friedewald equation. Plasma homocysteine was determined with a modified automated assay, based on precolumn derivatization with monobromobimane, followed by reverse phase HPLC with fluorescence detection.[23] Plasma glucose was measured in a fluoride-oxalate sample with a Falcor 600 automated analyser and serum insulin with an ELISA assay that does not cross-react with proinsulin.[24] CRP was measured with a high-sensitivity, double-antibody sandwich ELISA with rabbit anti-human CRP and peroxide conjugated rabbit anti-human CRP.[25] Cotinine was measured in saliva by an HPLC method.[26] Social class was assessed from parents' occupation, coded in accordance with the Registrar General's (ONS) 1990 coding manual. Ethnicity was based on appearance, cross-checked with parental place of birth.

Vascular Measurements

Brachial artery distension during the cardiac cycle was measured for each child at rest, between 9 AM and 3:30 PM. The subject lay supine on a couch, and room temperature was recorded. After 10 minutes' rest, the right brachial artery was imaged in longitudinal section at 10 to 15 cm above the antecubital fossa with a 7-MHz linear-array transducer and Acuson 128XP[2].[27,28] The M-mode cursor was positioned at right angles to the arterial lumen over the clearest defined section of the artery on the B-mode image. A 5-second segment of the radiofrequency signal was recorded by a separate commercially available wall tracking system (Ingenious Medical Systems) at a rate of 800 Hz (1 frame/ms).[27] Arterial distensibility was measured as the mean diameter change (distension) between diastole and systole, standardized for pulse pressure (see below). Coefficients of variation for diameter and distension measurements with this technique are reported as 2% to 3%.[27,29] Pulse pressure was measured in the left brachial artery with a Dinamap 1846SX oscillometric blood pressure recorder (Critikon Inc) concordant with distensibility measurements in the right arm. Scan quality analysis was performed by independent observers as described previously.[16]

Earlier Measurements of Vascular Function and Cardiovascular Risk Factors at 9 to 11 Years

Among the participants in these studies, 188 had had earlier measurements of their cardiovascular risk profile in 1994 and measurements of arterial distensibility during 1995; of these, 152 provided blood samples on each occasion. These earlier measurements had been performed in an identical way to those described above, with the exception of blood lipid measurements, which had been made with a Technicon Dax analyser.[16]

Insulin Resistance and the Metabolic Syndrome

The degree of insulin resistance was defined by the homeostatic model assessment (HOMA), which uses the product of the fasting insulin concentration (mU/L) and the fasting glucose level (mmol/L) divided by 22.5.[30] Subjects were defined as having components of the metabolic syndrome in accordance with criteria used in a previous study in adolescents.[31] The individual components included the following: waist circumference >90th percentile, triglyceride level >90th percentile, and HDL cholesterol <10th percentile (all standardized for age and sex); systolic or diastolic blood pressure >90th percentile (standardized for age, sex, and height); and impaired fasting glucose >6.1 mmol/L.

Statistical Analysis

Analyses were performed with the SAS Statistical Analysis package (version 8.1). Standard *t* tests were used to compare gender differences in variable means (Table 1), which were log transformed where necessary. Standard linear regression modeling with ordinary least squares was used to model the change in diameter of the brachial artery between diastole and systole (a measure of distension, normally distributed), which was regressed on mean pulse pressure to provide a measure of distensibility, as in our previous study.[16] The roles of potential determinants of distensibility were explored by adding them to this basic linear regression model, fitting them both as fifths and as continuous variables. The regression coefficients presented (Tables 2, 3, and 4) are expressed in terms of a 1-SD increase in the independent variable or, in the case of variables that required log transformation, the SD of the natural logarithm of the variable. This approach, which used the SDs for both sexes combined at 13 to 15 years throughout, facilitates comparison of the strengths of associations of different independent variables with distension. The relation between the metabolic syndrome and arterial distensibility was examined differently, with regression of arterial distension on the number of components of the metabolic syndrome present (0, 1, 2, or 3) in a model that also included pulse pressure. Terms for observer (2 levels), room temperature (fifths), town (4 levels), age (5 levels), sex (2 levels), and ethnicity (3 levels: European white, South Asian, and other) were fitted in all models. Pubertal status was fitted as a 10-level score (by adding the 2 Tanner scores used for each sex). The comparisons of the determinants of arterial distensibility at 9 to 11 years and 13 to 15 years (Table 4) were produced with a repeated-measures regression model with PROC MIXED in SAS. The intercepts and slopes were allowed to differ at the 2 ages, which enabled us to test for a difference in the regressions relating distensibility to the explanatory factor at the 2 ages while taking account of the correlation in an individual's results at the 2 ages. This was achieved by fitting a block diagonal

TABLE 1. Summary of Key Variables

	Boys		Girls		*P* (No Sex Difference)†
	Mean	SD	Mean	SD	
Age, y	15.4	0.6	15.5	0.5	0.09
Height, cm	168.6	9.0	161.7	6.1	<0.001
Body mass index, kg/m^2	20.6	3.8	21.5	3.8	0.009
% Body fat (bioimpedance)	23.5	7.3	29.4	4.4	<0.001
Skinfold sum, mm	44.5	22.7	62.1	22.4	<0.001
Waist circumference, cm	72.4	9.6	69.0	8.8	<0.001
Waist:hip ratio	0.79	0.05	0.73	0.05	<0.001
Systolic blood pressure, mm Hg	124	14	118	12	<0.001
Diastolic blood pressure, mm Hg	67	7	67	7	0.49
Total cholesterol, mmol/L	4.09	0.65	4.29	0.71	0.004
LDL cholesterol, mmol/L	2.23	0.54	2.33	0.62	0.08
HDL cholesterol, mmol/L	1.44	0.27	1.52	0.31	0.005
Triglyceride, mmol/L	0.96	0.40	0.99	0.43	0.58
Glucose, mmol/L	5.27	0.39	5.13	0.42	0.002
Insulin, mU/L*	7.77		9.78		<0.001
Insulin resistance (HOMA)	2.06	1.13	2.49	1.43	0.002
CRP, mg/L*	0.23		0.21		0.43
Homocysteine, μmol/L	8.77	3.51	8.48	2.95	0.37
Cotinine, ng/mL*	0.76		0.87		0.55
Arterial distension, μm	160	58	115	49	<0.001
Pulse pressure, mm Hg	58	10	49	7	<0.001
Arterial diameter, mm	3.53	0.42	2.94	0.32	<0.001

*Variable log transformed, geometric mean presented.

†*P* values based on *t* tests.

All analyses are based on 249 boys and 222 girls, except for blood-based measurements, which are based on 198 boys and 185 girls.

covariance structure (with identical blocks as the covariance parameters are assumed to be the same for all individuals).

Results

In all, 471 children (249 boys, 222 girls) took part in the study (69% response); 383 of these children had provided a blood sample in the cardiovascular risk factor survey. The mean age of the study population was ≈15.5 years; most participants (70% of both boys and girls) were at Tanner stages 4 or 5. Population characteristics are summarized in Table 1. Mean arterial distension, pulse pressure, and resting arterial diameter were significantly higher among boys. Baseline risk factor measures in nonresponders (not presented) showed no material differences from those of responders.

The relationships between individual adiposity measures (fifths) and arterial distensibility are shown (with both sexes combined) in Figure 1, with the corresponding regression coefficients (sex-specific and combined) per SD increase in each variable in Table 2. There were strong inverse graded associations between all adiposity measures and arterial distensibility, which were statistically significant both in males and in the combined analyses. However, formal tests of sex interaction were not statistically significant (all $P>0.2$).

The relations of insulin resistance and the individual components of the metabolic syndrome (systolic and diastolic blood pressure, HDL cholesterol, triglyceride, and fasting plasma glucose) to arterial distensibility are shown in Figure 2, with the corresponding regression coefficients in Table 2. Insulin resistance (HOMA) showed an inverse association with arterial distensibility, which was particularly marked at high insulin concentrations; a similar association was seen for fasting insulin level (Table 2). Both associations were statistically significant both in the combined analyses and in males; again, formal tests of sex interaction were not statistically significant (all $P>0.2$).

Diastolic pressure showed a strong inverse association with distensibility, which was statistically significant in both sexes. Systolic pressure and triglyceride levels showed weaker inverse associations, which were not statistically significant. HDL cholesterol and plasma glucose showed no appreciable associations with distensibility. The relationship between the number of metabolic syndrome components and arterial distensibility was also explored. In an analysis among 383 males and females with the relevant measurements, 102 (27%) had 1 component of the metabolic syndrome, 27 (7%) had 2 components, and 8 (2%) had 3 components; no subjects had more than 3 components. There was a strong graded inverse association between the number of metabolic syndrome components and arterial distensibility (Figure 3), with a highly statistically significant trend ($P=0.008$). The use of different thresholds for the definition of the metabolic syndrome (for example, the use of highest or lowest 20% of the risk factor distribution) had little effect on this overall pattern of results. Similarly, the combination of 2 and 3 components in the model had no appreciable effect.

The relations of classic and novel vascular risk factors (CRP and homocysteine) to arterial distensibility are shown in Figure 4, with the corresponding regression coefficients in Table 2. In the combined analysis, total and LDL cholesterol showed inverse associations with distensibility, which were particularly marked in the top fifth of their distributions. CRP also showed an inverse association with distensibility, which was statistically significant for boys and for both sexes combined. In contrast, cotinine (a sensitive biomarker of both active and passive smoking) and homocysteine showed no consistent relations to distensibility. Further analyses that used a combination of questionnaire information and cotinine levels to group subjects as current active smokers (at least 1 cigarette/d), passive smokers (not current active smokers, cotinine 0.7 to 14.1 ng/mL), or unexposed (not current active smokers, cotinine <0.7 ng/mL) showed no difference in distensibility between groups ($P=0.83$).

Because the regression coefficients in Table 2 are all expressed per SD of the explanatory variable (or its logarithm), the sizes of the coefficients provide a guide to the relative strengths of association. The strongest associations were observed for diastolic blood pressure, followed by adiposity measures (particularly body fat percentage), followed by total and LDL cholesterol, insulin resistance, and CRP. The strength of association with the metabolic syndrome (based on numbers of metabolic syndrome components) cannot be directly compared with these estimates.

All adiposity measures were related to blood pressure, total and LDL cholesterol, and insulin resistance (for body mass

TABLE 2. Associations Between Physical and Biochemical Measures and Brachial Artery Distension at 13 to 15 Years of Age

		Boys			Girls			Both Sexes		
Variable	SD	Regression Coefficient	95% CI	*P*	Regression Coefficient	95% CI	*P*	Regression Coefficient	95% CI	*P*
Age, y	0.54	−3.95	−10.92, 3.01	0.27	−1.58	−9.35, 6.18	0.69	−2.72	−7.77, 2.34	0.29
Height, cm	8.46	1.18	−6.68, 9.05	0.77	1.10	−8.71, 10.83	0.83	0.68	−5.16, 6.60	0.81
Body mass index, kg/m^2	3.83	−11.72	−19.53, −3.94	0.003	−7.89	−15.36, −0.38	0.040	−9.04	−14.29, −3.79	<0.001
Body fat % (bioimpedance)	6.80	−13.33	−20.40, −6.26	<0.001	−10.06	−21.15, 0.95	0.07	−11.15	−16.73, −5.51	<0.001
Skinfold sum, mm	24.19	−13.55	−22.01, −5.32	0.001	−6.77	−14.51, 0.97	0.09	−9.43	−15.00, −3.87	<0.001
Waist circumference, cm	9.36	−11.33	−18.81, −3.84	0.003	−10.02	−17.78, −2.25	0.012	−10.20	−15.44, −5.05	<0.001
Waist:hip ratio	0.06	−7.47	−16.00, 1.06	0.09	−8.86	−17.04, −0.69	0.034	−7.78	−13.50, −2.06	0.008
Systolic blood pressure, mm Hg	13.03	−2.87	−11.34, 5.60	0.51	−1.95	−10.29, 6.38	0.64	−2.74	−8.47, 3.00	0.35
Diastolic blood pressure, mm Hg	7.07	−16.47	−23.76, −9.12	<0.001	−9.05	−16.26, −1.84	0.014	−13.43	−18.38, −8.55	<0.001
Total cholesterol, mmol/L	0.68	−10.29	−19.02, −1.55	0.021	−4.34	−11.55, 2.88	0.24	−6.87	−12.30, −1.43	0.013
LDL cholesterol, mmol/L	0.58	−9.69	−18.54, −0.83	0.032	−4.31	−11.22, 2.59	0.22	−6.14	−11.48, −0.81	0.024
HDL cholesterol, mmol/L	0.29	−0.15	−8.62, 8.32	0.97	0.86	−5.93, 7.64	0.80	−0.03	−5.30, 5.23	0.99
Triglyceride, mmol/L	0.41	−7.62	−16.05, 0.82	0.08	−2.26	−9.35, 4.83	0.53	−4.75	−10.10, 0.59	0.08
Glucose, mmol/L	0.41	−1.80	−11.87, 8.27	0.73	2.72	−5.44, 10.88	0.51	0.71	−5.58, 6.99	0.83
Insulin, mU/L*	0.45	−10.29	−18.72, −1.85	0.017	−0.53	−8.90, 7.84	0.90	−5.98	−11.79, −0.17	0.044
Insulin resistance (HOMA)	1.30	−12.57	−22.57, −2.56	0.014	−2.29	−9.20, 4.63	0.51	−6.16	−11.84, −0.49	0.033
CRP, mg/L*	1.23	−8.36	−16.31, −0.40	0.04	−2.68	−10.08, 4.72	0.48	−5.71	−11.03, −0.40	0.035
Homocysteine, μmol/L	3.25	1.79	−6.21, 9.78	0.66	−0.49	−8.52, 7.54	0.91	0.07	−5.36, 5.49	0.98
Cotinine, ng/mL*	2.32	4.34	−3.54, 12.21	0.28	−1.01	−7.76, 5.73	0.78	1.95	−3.11, 7.02	0.45

The table shows linear regression coefficients and their 95% CIs for the regression of arterial distension on each individual variable, with pulse pressure, age, sex, room temperature, ethnicity, town, and observer included in the model; units of the coefficients are micrometers per SD change in the explanatory variable. Analyses are based on 249 boys and 222 girls, except for blood-based measurements, which are based on 198 boys and 185 girls. SDs (left-hand column) are based on boys and girls combined.

*Variable transformed with natural logarithms. Regression coefficients therefore relate to the change in distension (micrometers) per SD change in logged variable.

index, r=0.38, 0.09, 0.17, and 0.38, respectively). The extent to which the relations between adiposity and arterial distensibility could be accounted for by these factors and by pubertal status was examined (illustrated for body mass index in Table 3). The relation between body mass index and distensibility was somewhat strengthened by adjustment for puberty but was partly attenuated by cumulative adjustment for the other factors, particularly insulin resistance and CRP. Further adjustment for other components of the metabolic syndrome had little further effect on the association (data not presented). We also examined whether the relations between diastolic pressure, cholesterol, insulin resistance, CRP, and arterial distensibility were affected by taking pubertal status and adiposity into account (Table 3). Although adjustment for pubertal status had little effect on any of these associations, the relations of insulin resistance and CRP to arterial distensibility were markedly reduced and became statistically nonsignificant after adjustment for adiposity markers. In contrast, the relations of diastolic blood pressure and total cholesterol to distensibility were little affected by adjustment for adiposity.

Using data from 188 subjects who took part in the consecutive surveys at 9 to 11 and 13 to 15 years of age (152 of whom had blood measurements on both occasions), we used a repeated-measures analysis to examine the consistency of the associations with distensibility at the 2 age points. Arterial distension standardized for pulse pressure was correlated at the 2 points (r=0.27), although not as strongly as risk factor measurements including body mass index (r=0.79), total cholesterol (r=0.67), diastolic pressure (r=0.50), and fasting insulin (r=0.40). A comparison of the determinants of arterial distensibility at 13 to 15 and 9 to 11 years of age (Table 4) showed that the associations of total and LDL cholesterol and diastolic blood pressure to distensibility were present and of very similar strength on both occasions, with no formal evidence of any difference in the relationships between the 2 age groups. In contrast, the associations between body mass index, insulin resistance (assessed both by fasting insulin and the HOMA model), and distensibility observed at 13 to 15 years did not appear to have been present to the same degree at 9 to 11 years; there were statistically significant differences between the strengths of relations at 9 to 11 years and 13 to 15 years. These findings were not affected by analyzing BMI results as z scores rather than as absolute values. A similar (but statistically nonsignificant) pattern was observed for waist circumference.

Discussion

The present study shows that adiposity and its associated metabolic abnormalities have strong and in many cases graded adverse relations to vascular function in teenagers. The association between adiposity and distensibility appeared stronger than the previously documented relationship be-

TABLE 3. Associations Between Body Mass Index, Insulin Resistance (HOMA), Diastolic Blood Pressure, Total Cholesterol, CRP, and Brachial Artery Distension at 13 to 15 Years of Age: Effect of Cumulative Adjustment for Other Factors

Adjustment	Regression Coefficient	95% CI	P
Body mass index, kg/m^2			
Baseline variables only	−9.04	−14.29, −3.79	0.007
+ Puberty	−10.07	−15.59, −4.56	<0.001
+ Puberty, DBP,	−9.42	−15.05, −3.75	0.001
+ Puberty, DBP, TC	−10.34	−16.24, −4.40	<0.001
+ Puberty, DBP, TC, IR	−7.01	−13.86, −0.19	0.044
+ Puberty, DBP, TC, IR, CRP	−5.63	−13.02, 1.76	0.13
Insulin resistance (HOMA)			
Baseline variables only	−6.16	−11.84, −0.49	0.033
+ Puberty	−7.51	−13.52, −1.50	0.015
+ Puberty, all adiposity measures	−2.07	−9.01, 4.88	0.56
DBP, mm Hg			
Baseline variables only	−13.43	−18.38, −8.55	<0.001
+ Puberty	−12.94	−18.10, −7.78	<0.001
+ Puberty, all adiposity measures	−12.66	−18.17, −7.14	<0.001
Total cholesterol, mmol/L			
Baseline variables only	−6.87	−12.24, −1.43	0.013
+ Puberty	−6.99	−12.65, −1.28	0.017
+ Puberty, all adiposity measures	−6.24	−12.24, −0.21	0.043
CRP, mg/L*			
Baseline variables only	−5.71	−11.03, −0.40	0.035
+ Puberty	−5.20	−10.77, 0.38	0.07
+ Puberty, all adiposity measures	−2.34	−8.56, 3.89	0.46

DBP indicates diastolic blood pressure; TC, total cholesterol; and IR, insulin resistance.

The table shows linear regression coefficients and their 95% CIs for the regression of arterial distension on each explanatory factor of interest; units of the regression coefficients are micrometers per SD change in the explanatory variable (SDs shown in Table 2). Boys and girls are combined in analysis. Baseline variables (included in all models) include pulse pressure, age, sex, room temperature, ethnicity, town, and observer. Analyses are based on 471 subjects, except for blood-based measurements, which are based on 383 subjects.

*Variable transformed with natural logarithms. Regression coefficients therefore relate to the change in distension (micrometers) per SD change in the logged variable.

All adiposity measures=body mass index, body fat %, sum of 4 skinfolds, and waist circumference.

tween blood cholesterol and distensibility. The combination of classic risk factors, metabolic abnormalities, and CRP appeared to explain at least a part of the relation of adiposity to arterial distensibility. The findings are important for understanding the determinants of early atherosclerosis and could have major public health implications.

The observations on the relation between adiposity and arterial distensibility are consistent with the epidemiological evidence relating adiposity to vascular disease.[8,32] Obesity in young people has been related directly to pathological evidence of early atherosclerosis,[33] whereas obesity in adolescence has been related to impaired endothelial function[34,35] and increased vascular resistance.[36] However, few reports have related obesity to arterial distensibility. The present observations extend the findings of Tounian et al[14] in markedly obese French teenagers and those of Iannuzzi et al[15] in US children by showing a graded relationship with arterial distensibility from much lower levels than in these earlier studies. The mechanisms by which adiposity is linked to arterial disease remain uncertain. In adults, the relation of adiposity to atherosclerosis is largely mediated by the presence of raised blood pressure, dyslipidemia, insulin resistance, and impaired glucose tolerance.[8,37] Previous reports in adults have suggested that insulin resistance is related to diminished arterial distensibility, both in subjects with and in those without type 2 diabetes mellitus.[38,39] Hypertension is also related to reduced distensibility in adults,[40] whereas HDL cholesterol has protective vascular effects, and its acute administration can reverse endothelial dysfunction.[41] We now show that adiposity is related to similar changes in the metabolic profile in adolescents and that both adiposity and metabolic syndrome components are related to vascular function in adolescence, with a cumulative relationship between an increasing number of components of the metabolic syndrome and distensibility. Moreover, these factors together appeared to account for an appreciable part of the relationship between adiposity and distensibility. Adiposity (particularly central adiposity) is also associated with elevated levels of a range of acute-phase reactants and proinflammatory cytokines.[42] In the present study, it appeared that CRP level made a modest contribution to explaining the vascular consequences of adiposity, although its own modest association with vascular function was almost completely abolished after adjustment for adiposity.

The relationships between both total and LDL cholesterol and arterial distensibility are consistent with clinical, epidemiological, and experimental evidence demonstrating the causative role of blood cholesterol in the pathophysiology of atherosclerosis. Elevated LDL levels result in accumulation of lipoproteins in the vessel wall, which, when oxidized, are rapidly taken up by macrophages to form foam cells.[43,44] This process starts very early in life, possibly even before birth.[28] In animal models, arterial distensibility is reduced in the early stages of cholesterol accumulation in the arterial wall, before other changes develop.[13] The inverse association between cholesterol and distensibility was of a very similar strength to that in our previous study in 9- to 11-year-old children,[16] which suggests that the association is already established by adolescence. In both the present and previous study,[16] the relation between cholesterol and distensibility appeared to be concentrated at the upper fifth of mean cholesterol levels in this study population (total cholesterol >4.5 mmol/L, LDL cholesterol >2.5 mmol/L), at levels that are still low compared with the levels associated with high coronary heart disease risk in middle-aged populations. Reliable longitudinal analyses examining the relation of changes in cholesterol level to changes in distensibility (not possible in the present study because of limited statistical power) will help to clarify these observations.

The relations of adiposity and classic risk factors (particularly total and LDL cholesterol) to arterial distensibility

TABLE 4. Factors Associated With Arterial Distensibility at 9 to 11 Years and 13 to 15 Years of Age: Repeated-Measures Analysis

		Relation at 9–11 Years			Relation at 13–15 Years			Difference Between 9–11 and 13–15 Years
Factor	No. of Subjects	Regression Coefficient	95% CI	*P*	Regression Coefficient	95% CI	*P*	*P*†
Body mass index, kg/m^2	188	4.25	−7.14, 15.64	0.46	−7.63	−15.13, −0.12	0.046	0.046
Waist circumference, cm	178	−1.43	−11.74, 8.87	0.78	−9.75	−17.86, −1.65	0.019	0.15
Diastolic blood pressure, mm Hg	188	−12.04	−19.29, −4.78	0.001	−10.45	−17.18, −3.72	0.003	0.74
Total cholesterol, mmol/L	152	−7.90	−16.41, 0.61	0.07	−7.98	−15.82, −0.13	0.046	0.99
LDL cholesterol, mmol/L	152	−8.12	−16.14, −0.10	0.047	−7.16	−15.03, 0.72	0.08	0.85
Fasting insulin, mU/L*	71	3.48	−3.85, 10.81	0.35	−14.00	−27.04, −0.96	0.036	0.015
Insulin resistance (HOMA)	71	4.81	−8.73, 18.36	0.48	−17.00	−34.14, 0.15	0.05	0.025

The table shows linear regression coefficients and their 95% CIs for the regression of arterial distension on each individual variable in each age group, derived from a repeated-measures analysis. Analyses are based on boys and girls together. Pulse pressure, age, sex, room temperature, ethnicity, town, and observer are included in all models; units of the regression coefficients are micrometers per SD change in the explanatory variable (as shown in Table 2).

*Variable transformed with natural logarithms. Regression coefficients therefore relate to the change in distension (micrometers) per SD change in log (insulin).

†Testing for a difference in regression coefficients between the 2 ages.

appeared to differ in important respects. The adiposity association was stronger than that of blood cholesterol and was graded, whereas the cholesterol relationship appeared particularly marked at high total cholesterol levels, with the possibility of a threshold effect around 4.5 mmol/L. Furthermore, the emergence of the relations of adiposity and blood lipids to distensibility appeared to be different. For LDL cholesterol, the strength of the association with arterial distension was similar at 9 to 11 and 13 to 15 years of age, which suggests that the consequences of cholesterol exposure on the arterial wall are cumulative during the childhood years. In contrast, the relation of adiposity to arterial distensibility was substantial at 13 to 15 years but did not appear to have been present at 9 to 11 years of age. Larger population-based prospective studies of arterial function in children will help to define further the relations of weight, body mass index, and lipid trajectories to arterial structure and function at this key period of development.[45]

We selected populations of children and teenagers to have risk factor profiles representative of British children living in areas of widely differing adult cardiovascular mortality. Importantly, subjects were not selected on the basis of their levels of obesity or blood lipids. We have developed several tests of arterial function that can be used to examine the early phases of atherosclerosis. Arterial distensibility provides a marker of the structure and function of the arterial wall that diminishes with age and with increasing risk factor burden in older subjects.[46] Reduced distensibility predicts adverse cardiovascular outcomes in adults.[47,48] The lower arterial distension and distensibility observed in females in the present study is consistent with previous reports and may reflect the different properties of the muscular brachial artery compared with the aorta.[49] The relations between obesity, blood lipids, blood pressure, and distensibility do not appear to be artifacts of associations between risk factors and pulse pressure. With the exception of systolic blood pressure (which showed little relationship to distensibility), the factors studied showed little or no relation to pulse pressure (including diastolic pressure, $r=0.09$). The extent of tracking of arterial distensibility over a 4-year period was modest and generally weaker than that of

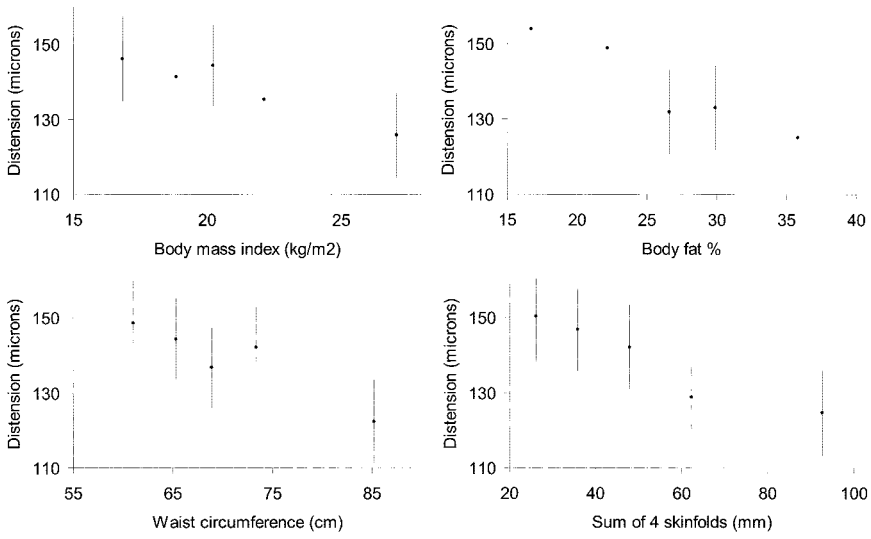

Figure 1. Relations of arterial distensibility (mean, 95% CI) to adiposity markers (fifths). All analyses show arterial distension (micrometers) standardized for pulse pressure, age, sex, room temperature, ethnicity, town, and observer. Analyses are based on 471 children.

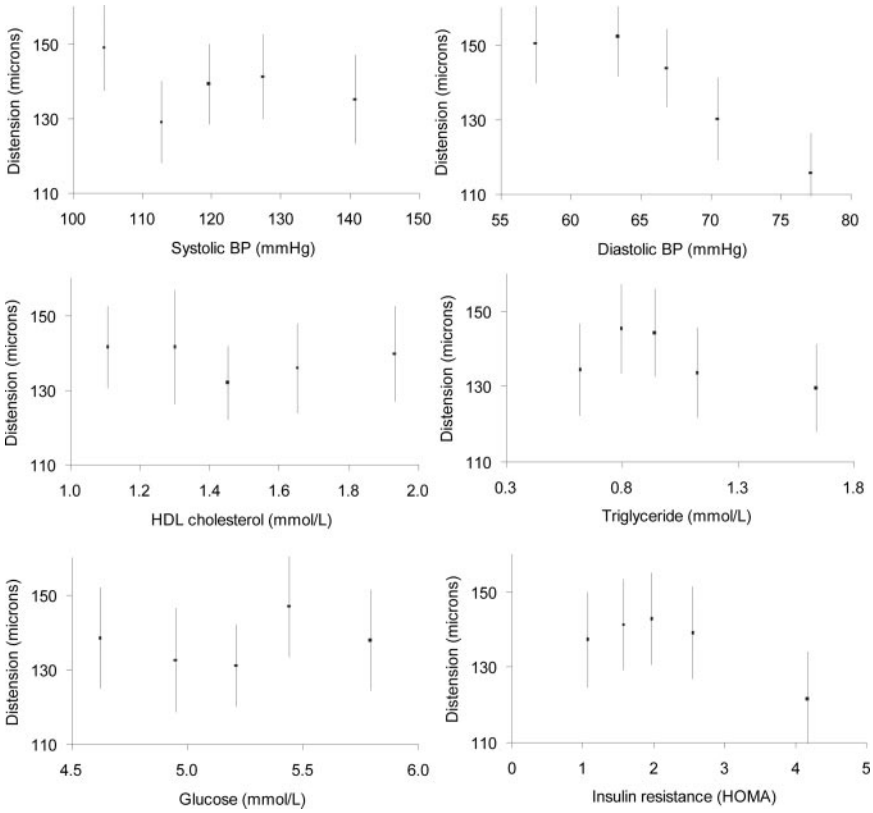

Figure 2. Relations of arterial distensibility (mean, 95% CI) to systolic and diastolic blood pressure, HDL cholesterol, triglyceride, plasma glucose, and HOMA insulin resistance (fifths). All analyses show arterial distension (micrometers) standardized for pulse pressure, age, sex, room temperature, ethnicity, town, and observer. Analyses are based on 471 children (blood pressure) and 383 children (all other measurements). BP indicates blood pressure.

other risk markers. The limited degree of tracking was not affected by adjustment either for pubertal status or for factors related to circumstances of measurement and may reflect the marked potential for reversibility of reductions in distensibility at this stage of the life course.

Our findings in the present study suggest that higher levels of several vascular risk factors are associated with adverse relations to arterial distensibility by the time of adolescence, in either a graded or a threshold manner. In particular, adiposity is becoming a more important determinant of vascular disease than blood lipids, at least in the present study population. The application of this finding to other study populations will depend on the balance of adiposity and blood lipid exposures that occurs in those populations. However, the results are of considerable concern in the context of the marked secular increases in adiposity and obesity in children, particularly in the United States.[5] The graded nature of the relationships observed here between adiposity and arterial distensibility occurred well below the levels of body mass index regarded as overweight in adolescents (only 14% of the subjects studied here were defined as overweight by current US criteria).[50] These observations emphasize the importance of population-wide strategies directed to the reduction of levels of childhood adiposity by a combination of changes in diet and physical activity. The low tracking coefficient observed for arterial distensibility suggests that reductions in distensibility that occur in childhood and adolescence are reversible. This would be consistent with the results of earlier studies that suggested that obesity-related vascular dysfunction can be reversed by weight loss[36] and increased physical activity.[34,35] Such approaches are likely to be important for the prevention both of cardiovascular disease and type 2 diabetes mellitus in the next generation. In the meantime, arterial distensibility may provide a valuable marker of the early cardiovascular consequences of adiposity and obesity both in future observational studies and in clinical trials examining the effects of adiposity reduction in young people.

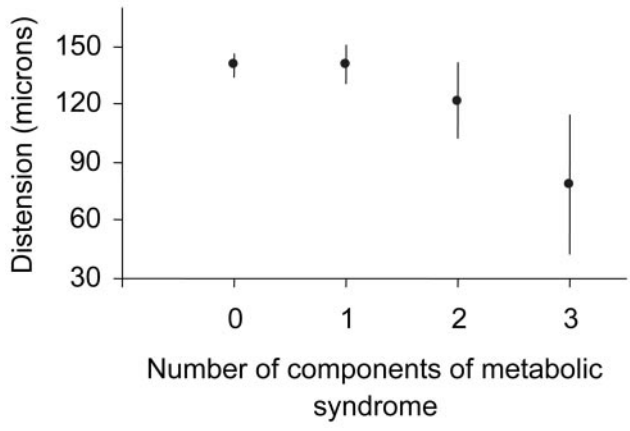

Figure 3. Relations of arterial distensibility (mean, 95% CI) to number of components of the metabolic syndrome present (see text). All analyses show arterial distension (micrometers) standardized for pulse pressure, age, sex, room temperature, ethnicity, town, and observer. Analyses are based on 383 children.

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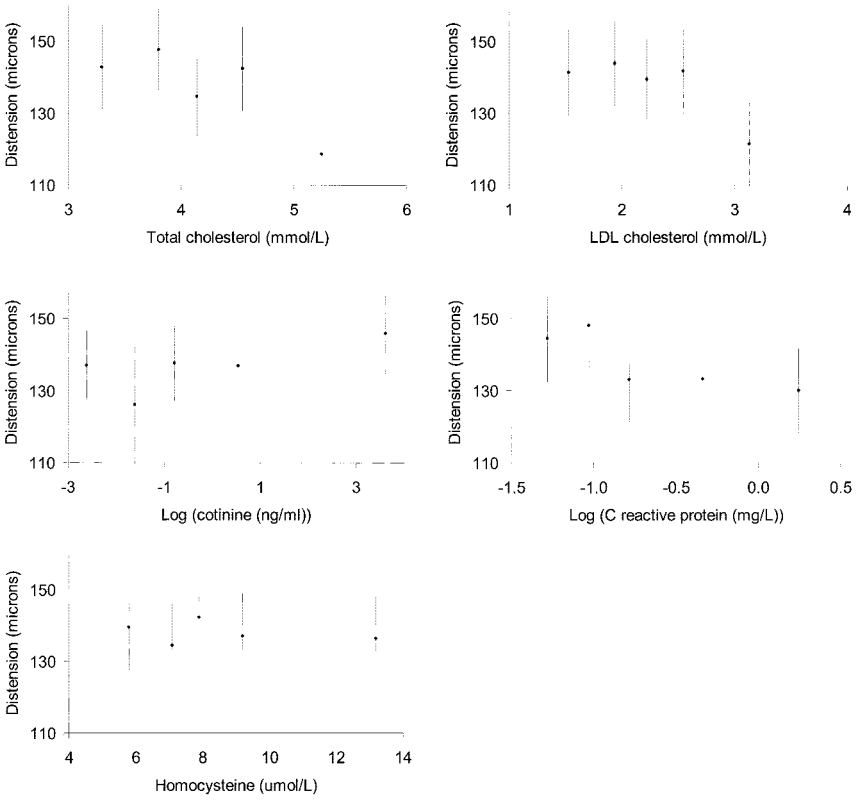

Figure 4. Relations of arterial distensibility (mean, 95% CI) to total and LDL cholesterol, salivary cotinine, CRP, and homocysteine level (fifths). All analyses show arterial distension (micrometers) standardized for pulse pressure, age, sex, room temperature, ethnicity, town, and observer. All analyses are based on 383 children.

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References

1. Kannel WB. The Framingham Study: its 50-year legacy and future promise. *J Atheroscler Thromb*. 2000;6:60–66.
2. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*. 1992;340:1111–1115.
3. McGill HC Jr, McMahan CA, Malcom GT, et al. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women: the PDAY Research Group: Pathobiological Determinants of Atherosclerosis in Youth. *Arterioscler Thromb Vasc Biol*. 1997;17:95–106.
4. Ogden CL, Flegal KM, Carroll MD, et al. Prevalence and trends in overweight among US children and adolescents, 1999–2000. *JAMA*. 2002;288:1728–1732.
5. Troiano RP, Flegal KM, Kuczmarski RJ, et al. Overweight prevalence and trends for children and adolescents: the National Health and Nutrition Examination Surveys, 1963 to 1991. *Arch Pediatr Adolesc Med*. 1995; 149:1085–1091.
6. World Health Organization. *Report of the WHO Consultation: Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, Switzerland: World Health Organization, Department of Noncommunicable Disease Surveillance; 1999.
7. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.
8. Shaper AG, Wannamethee SG, Walker M. Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men. *BMJ*. 1997;314:1311–1317.
9. Srinivasan SR, Myers L, Berenson GS. Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: the Bogalusa Heart Study. *Diabetes*. 2002;51: 204–209.
10. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. 2004;350:2362–2374.
11. Bank AJ, Wang H, Holte JE, et al. Contribution of collagen, elastin, and smooth muscle to in vivo human brachial artery wall stress and elastic modulus. *Circulation*. 1996;94:3263–3270.
12. Sudhir K, Mullen WL, Hausmann D, et al. Contribution of endothelium-derived nitric oxide to coronary arterial distensibility: an in vivo two-dimensional intravascular ultrasound study. *Am Heart J*. 1995;129: 726–732.
13. Hironaka K, Yano M, Kohno M, et al. In vivo aortic wall characteristics at the early stage of atherosclerosis in rabbits. *Am J Physiol*. 1997;273: H1142–H1147.
14. Tounian P, Aggoun Y, Dubern B, et al. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet*. 2001;358:1400–1404.
15. Iannuzzi A, Licenziati MR, Acampora C, et al. Increased carotid intima-media thickness and stiffness in obese children. *Diabetes Care*. 2004;27:2506–2508.
16. Leeson CP, Whincup PH, Cook DG, et al. Cholesterol and arterial distensibility in the first decade of life: a population-based study. *Circulation*. 2000;101:1533–1538.
17. Singhal A, Farooqi IS, Cole TJ, et al. Influence of leptin on arterial distensibility: a novel link between obesity and cardiovascular disease? *Circulation*. 2002;106:1919–1924.
18. Durnin JV, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thickness. *Br J Nutr*. 1967; 21:681–689.
19. Smye SW, Sutcliffe J, Pitt E. A comparison of four commercial systems used to measure whole-body electrical impedance. *Physiol Meas*. 1993; 14:473–478.
20. Deurenberg P, Kusters CS, Smit HE. Assessment of body composition by bioelectrical impedance in children and young adults is strongly age-dependent. *Eur J Clin Nutr*. 1990;44:261–268.

21. Taylor SJ, Whincup PH, Hindmarsh PC, et al. Performance of a new pubertal self-assessment questionnaire: a preliminary study. *Paediatr Perinat Epidemiol*. 2001;15:88–94.
22. Whincup PH, Bruce NG, Cook DG, et al. The Dinamap 1846SX automated blood pressure recorder: comparison with the Hawksley random zero sphygmomanometer under field conditions. *J Epidemiol Community Health*. 1992;46:164–169.
23. Refsum H, Ueland PM, Svardal AM. Fully automated fluorescence assay for determining total homocysteine in plasma. *Clin Chem*. 1989;35:1921–1927.
24. Andersen L, Dinesen B, Jorgensen PN, et al. Enzyme immunoassay for intact human insulin in serum or plasma. *Clin Chem*. 1993;39:578–582.
25. Highton J, Hessian P. A solid-phase enzyme immunoassay for C-reactive protein: clinical value and the effect of rheumatoid factor. *J Immunol Methods*. 1984;68:185–192.
26. Feyerabend C, Russell MA. A rapid gas-liquid chromatographic method for the determination of cotinine and nicotine in biological fluids. *J Pharm Pharmacol*. 1990;42:450–452.
27. Hoeks AP, Brands PJ, Smeets FA, et al. Assessment of the distensibility of superficial arteries. *Ultrasound Med Biol*. 1990;16:121–128.
28. Napoli C, D'Armiento FP, Mancini FP, et al. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia: intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. *J Clin Invest*. 1997;100:2680–2690.
29. Brands PJ, Hoeks AP, Rutten MC, et al. A noninvasive method to estimate arterial impedance by means of assessment of local diameter change and the local center-line blood flow velocity using ultrasound. *Ultrasound Med Biol*. 1996;22:895–905.
30. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419.
31. Cruz ML, Weigensberg MJ, Huang TT, et al. The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. *J Clin Endocrinol Metab*. 2004;89:108–113.
32. Rimm EB, Stampfer MJ, Giovannucci E, et al. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. *Am J Epidemiol*. 1995;141:1117–1127.
33. McGill HC Jr, McMahan CA, Herderick EE, et al. Obesity accelerates the progression of coronary atherosclerosis in young men. *Circulation*. 2002;105:2712–2718.
34. Watts K, Beye P, Siafarikas A, et al. Effects of exercise training on vascular function in obese children. *J Pediatr*. 2004;144:620–625.
35. Watts K, Beye P, Siafarikas A, et al. Exercise training normalizes vascular dysfunction and improves central adiposity in obese adolescents. *J Am Coll Cardiol*. 2004;43:1823–1827.
36. Rocchini AP, Moorehead C, Katch V, et al. Forearm resistance vessel abnormalities and insulin resistance in obese adolescents. *Hypertension*. 1992;19:615–620.
37. Abbasi F, Brown BW Jr, Lamendola C, et al. Relationship between obesity, insulin resistance, and coronary heart disease risk. *J Am Coll Cardiol*. 2002;40:937–943.
38. Salomaa V, Riley W, Kark JD, et al. 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.
39. Giltay EJ, Lambert J, Elbers JM, et al. Arterial compliance and distensibility are modulated by body composition in both men and women but by insulin sensitivity only in women. *Diabetologia*. 1999;42:214–221.
40. Benetos A, Laurent S, Hoeks AP, et al. Arterial alterations with aging and high blood pressure: a noninvasive study of carotid and femoral arteries. *Arterioscler Thromb*. 1993;13:90–97.
41. Spieker LE, Sudano I, Hurlimann D, et al. High-density lipoprotein restores endothelial function in hypercholesterolemic men. *Circulation*. 2002;105:1399–1402.
42. Yudkin JS, Stehouwer CD, Emeis JJ, et al. 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.
43. Faggiotto A, Ross R, Harker L. Studies of hypercholesterolemia in the nonhuman primate, I: changes that lead to fatty streak formation. *Arteriosclerosis*. 1984;4:323–340.
44. Witztum JL. The oxidation hypothesis of atherosclerosis. *Lancet*. 1994;344:793–795.
45. Charakida M, Donald AE, Terese M, et al. Endothelial dysfunction in childhood infection. *Circulation*. 2005;111:1660–1665.
46. van Popele NM, Grobbee DE, Bots ML, et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke*. 2001;32:454–460.
47. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*. 2001;37:1236–1241.
48. Cruickshank K, Riste L, Anderson SG, et al. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation*. 2002;106:2085–2090.
49. van der Heijden-Spek JJ, Staessen JA, Fagard RH, et al. Effect of age on brachial artery wall properties differs from the aorta and is gender dependent: a population study. *Hypertension*. 2000;35:637–642.
50. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat 11*. 2002;1–190.