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Arterial stiffness in adolescents and young adults with and without type 1 diabetes: the SEARCH CVD study

Amy S. Shah[a], **R. Paul Wadwa**[b], **Dana Dabelea**[c], **Richard F. Hamman**[c], **Ralph D'Agostino Jr**[d], **Santica Marcovina**[e], **Stephen R. Daniels**[b], **Lawrence M. Dolan**[a], **Nora F. Fino**[d], and **Elaine M. Urbina**[a]

[a]Department of Pediatrics, Cincinnati Children's Hospital and University of Cincinnati, Cincinnati, OH, USA

[b]Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA

[c]Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Aurora, CO, USA

[d]Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, NC, USA

[e]Northwest Lipid Research Laboratories, University of Washington, Seattle, WA, USA

Abstract

Background—Arterial stiffness is a useful parameter to predict future cardiovascular disease.

Objective—We sought to compare arterial stiffness in adolescents and young adults with and without type 1 diabetes (T1D) and explore the risk factors associated with the differences observed.

Subjects and methods—Carotid-femoral pulse wave velocity (PWV), augmentation index (AI75), and brachial distensibility (BrachD) were measured in 402 adolescents and young adults with T1D (age 18.8 ± 3.3 yr, T1D duration 9.8 ± 3.8 yr) and 206 non-diabetic controls that were frequency-matched by age, sex, and race/ethnicity in a cross-sectional study. General linear models were used to explore variables associated with an increase in arterial stiffness after adjustment for demographic and metabolic covariates.

Results—T1D status was associated with a higher PWV (5.9 ± 0.05 vs. 5.7 ± 0.1 m/s), AI75 (1.3 ± 0.6 vs. −1.9 ± 0.7%), and lower BrachD (6.2 ± 0.1 vs. 6.5 ± 0.1%Δ/mmHg), all $p < 0.05$. In multivariate models, age, sex, race, adiposity, blood pressure, lipids, and the presence of microalbuminuria were found to be independent correlates of increased arterial stiffness. After adjustment for these risk factors, T1D status was still significantly associated with arterial stiffness ($p < 0.05$).

Corresponding author: Amy S Shah, MD, MS, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave ML 7012, Cincinnati, OH 45229, USA. Tel: (513) 636-4744; fax: (513) 803-1176; amy.shah@cchmc.org.

Conflict of interest

The authors have no conflict of interest to declare.

Conclusions—Peripheral and central subclinical vascular changes are present in adolescents and young adults with T1D compared to controls. Increased cardiovascular risk factors alone do not explain the observed differences in arterial stiffness among cases and controls. Identifying other risk factors associated with increased arterial stiffness in youth with T1D is critical to prevent future vascular complications.

Keywords

arterial stiffness; pediatrics; type 1 diabetes; vascular disease

Vascular disease is an important cause of morbidity and mortality in patients with type 1 diabetes (1, 2). Arterial stiffness is a useful parameter to study because an increase in arterial stiffness predicts cardiovascular disease and mortality in adults (3, 4) and may serve as a useful indicator of youth needing more intensive therapy to prevent future vascular complications. Emerging data suggest that subclinical vascular damage including increased arterial stiffness is present in youth with type 1 diabetes well before signs of vascular disease are present (5–7). For a comprehensive review, please see references (8, 9). Our group has previously published data demonstrating increased arterial stiffness in youth with type 1 diabetes compared to non-diabetic youth, but a limitation of that study was the use of a non-age and sex-matched control group (7). Therefore, in this study, we sought to compare pulse wave velocity (PWV), augmentation index (AI75), and brachial distensibility (BrachD) (three measures of arterial stiffness) in a large study population of adolescents and young adults with and without type 1 diabetes frequency matched by age, race, sex/ethnicity, and explore the risk factors associated with differences observed.

Materials and methods

Participants

SEARCH CVD is an ancillary study to the SEARCH for Diabetes in Youth Study that was conducted in Ohio and Colorado (10). For this study, 402 youth with type 1 diabetes were recruited. Participants with type 1 diabetes had a physician diagnosis of type 1 diabetes and a duration of type 1 diabetes of at least 5 yr. A total of 206 non-diabetic controls frequency matched by age, sex, and race/ethnicity were also recruited. Control participants without a history of diabetes were recruited from the primary care offices in the same geographical areas (Ohio and Colorado) and were confirmed to be non-diabetic based on fasting glucose levels < 126 mg/dL. The study was reviewed and approved by the local institutional review boards in Ohio and Colorado and all participants provided signed informed consent or assent.

Anthropometric and laboratory measurements

Participants were invited for an outpatient research visit after an 8-h overnight fast. Short acting insulin and oral medications were withheld the morning of the visit until after the blood draw and vascular studies were complete. All participants were asked to refrain from any strenuous exercise, smoking, or any caffeinated drinks 12 h prior to the visit. Race/ethnicity was self-reported using 2000 U.S. Census– based questions. Cigarette smoking was assessed with questions based on Youth Risk Behavior Surveillance instruments, and

behaviors were characterized as current (smoking cigarettes at least 1 d in the past 30 d), former (smoking history but not smoking in the last 30 d), and never smoking. Height was measured in centimeters using a stadiometer and weight in kilograms using a standardized weighing machine. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, and age- and sex-specific BMI z scores were derived based on the 2000 Centers for Disease Control and Prevention age and gender national standards. Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times, using an aneroid sphygmomanometer, after the participants were seated for at least 5 min. Mean arterial pressure (MAP) was calculated as two thirds times DBP plus one third SBP (in mmHg).

Blood and urine samples were obtained under conditions of metabolic stability, defined, for subjects with type 1 diabetes, as no episode of diabetic ketoacidosis during the previous month. A fasting blood draw was conducted for the assessment of the metabolic parameters including hemoglobin A1c (HbA1c), total cholesterol, high-density lipoprotein cholesterol cholesterol (HDL-C) and triglyceride levels. High-performance liquid chromatography (TOSOH Bioscience, Inc., San Francisco, CA, USA) was used to measure HbA1c. Measurements of triglycerides and HDL-C were performed enzymatically on a Roche Modular P (Roche Molecular Biochemicals Diagnostics, Indianapolis, IN, USA). Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation for individuals with triglyceride concentration <400 mg/dL and by the Beta Quantification procedure for those with triglycerides ≥ 400 mg/dL. Urine was collected for the presence of albumin. Microalbumuria was defined as urine albumin to creatinine ratio ≥ 30 mg/g. Blood and urine samples were processed locally and shipped to a central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle) (10). Insulin sensitivity was estimated using the following equation:

$$\mathrm{Exp}\ [4.647252-(02032\times[\mathrm{waist,\ cm}])-(0.002350\times[\mathrm{TG,\ mg/dL}])-(0.09779\times[\mathrm{HbAlc,\ \%}])]$$

This equation was developed and validated using direct measurements of glucose disposal rate from euglycemic-hyperinsulinemic clamps conducted among participants with type 1 and type 2 diabetes and controls (11).

Arterial stiffness measures

Arterial stiffness measures included carotid-femoral vascular segment PWV and AI75 using the SphygmoCor Cardiovascular System (AtCor Medical, Lisle, IL, USA) and BrachD using the DynaPulse 2000 (PulseMetric, San Diego, CA, USA). All measurements were conducted in a room with a stable room temperature after the participant rested for >10 min.

PWV calculates the speed of pressure waves generated by cardiac ejection to reach the periphery. A higher PWV indicates increased arterial stiffness. Three ECG leads are applied to the torso of each participant. The distances from the lowest portion of the sternal notch to the carotid and femoral artery sites are then measured to the nearest 0.1 cm three times using a tape measure and averaged. A pressure wave form obtained from the proximal site (carotid artery) is recorded followed by a second arterial waveform recorded from the distal site

(femoral artery) using a tonometer. Waveforms are also recorded on a simultaneous electrocardiogram. PWV is the difference in the carotid-to-femoral path distance divided by the time delay measured between the feet of the two waveforms reported in meters per second. The average of at least 10 beats was used in the analysis to cover a complete respiratory cycle. Three PWV recordings were obtained per participant and averaged. Repeat measures show a coefficient of variation of <7% (12)

AI75 is a measure of wave reflections and systemic arterial stiffness (10, 11). A higher AI75 suggests increased arterial stiffness. For measurement of AI75, the SphygmoCor tonometer is placed over the right radial artery and pressure waves were recorded. The device then analyzes the pressure waves using a validated generalized transfer function (13). Transfer function is valid in those with normal cardiac anatomy. Wave forms collected over a 10-s period are averaged to produce peripheral and corresponding central (ascending aortic) pressure waveforms. AI75 is calculated as the difference between the main outgoing peripheral wave and the reflected wave of the central arterial waveform, expressed as a percentage of the central pulse pressure. Because AI75 is affected by heart rate, all values are adjusted to a standard heart rate of 75 beats/min, hence AI75. An average of three AI75 measurements was used in the analysis. A negative AI75 indicates that wave reflection happened late in cardiac cycle consistent with more pliable (less stiff) arteries. Reproducibility studies demonstrated intraclass correlation coefficient of 0.9 (12).

Brachial artery distensibility was obtained with the DynaPulse Pathway instrument. This instrument uses pulse dynamic analysis of arterial pressure signals obtained from a standard cuff sphygmomanometer (14). The pressure waveform obtained is incorporated into a physical model of the cardiovascular system, assuming a straight tube brachial artery and T-tube aortic system. Brachial artery compliance is then derived from waveform parameters and brachial artery distensibility is calculated using an empirical model to estimate baseline brachial artery diameter from gender, height, weight, and MAP. A lower BrachD indicates increased arterial stiffness. Off-line analyses of brachial artery pressure curve data were then performed by Pulse Metric, Inc., using an automated system to derive parameters from the pulse curves to calculate brachial artery distensibility. Three measurements of BrachD were obtained per participant and averaged. Repeat measures show coefficients of variation of < 9% (12).

Statistical analysis

Statistical analyses were performed using SAS for Windows (version 9.3; SAS Institute, Cary, NC, USA). p Values of <0.05 were considered significant. Data are mean and standard deviation. *T*-tests and chi-squared tests were used to test for differences in continuous and categorical variables between youth with and without type 1 diabetes, respectively. Variables with a skewed distribution were log transformed (triglycerides). Using each arterial stiffness measure as the outcome, linear regression models were used to assess the relationship between the arterial stiffness measures and type 1 diabetes status after adjusting for age, race, and sex. To explain the arterial stiffness differences between cases and controls, multiple linear regression models were built for each arterial stiffness outcome while adjusting for age, race/ethnicity, sex, smoking, microalbuminuria, mean arterial

pressure, waist-to-height ratio (as measure of central adiposity) (15), and triglyceride to HDL-C ratio (representing small dense LDL particles) (16). An additional model was created that included insulin sensitivity (see above for formula) as decreased insulin sensitivity (or insulin resistance) is thought to explain some of the increased cardiovascular disease risk in youth with type 1 diabetes (17). When insulin sensitivity was included in the model, waist-to-height ratio and triglyceride to HDL-C ratio were excluded (because waist and triglycerides are part of the insulin sensitivity measurement) and instead LDL and HDL cholesterol were added. Age, race/ethnicity, sex, smoking, microalbuminuria, and mean arterial pressure remained in this model. Each of the above cardiovascular risk factors were chosen because they have been previously shown to be highly associated with arterial stiffness. HbA1c was not included in any model because it was collinear with type 1 diabetes status. Duration of diabetes was also omitted because the goal of the analyses was to evaluate risk factors that explain the differences in arterial stiffness between cases and controls.

Results

Clinical characteristics of the study participants (by type 1 diabetes status) are presented in Table 1. The mean age of the study population was 18.9 ± 3.3 yr (age range 11–26) and included 50% male and 83% non-Hispanic whites. Subjects with type 1 diabetes were more likely to be non-Hispanic white, have lower triglycerides, and had higher LDL-C and HDL-C, DBP and HbA1c values than non-diabetic control participants (all $p < 0.05$).

After adjusting for age, sex, and race (and height for AI75 because height directly influences distance of wave reflection sites from the heart), participants with type 1 diabetes were found to have higher PWV (5.9 ± 0.05 vs. 5.7 ± 0.1 m/s), AI75 (1.3 ± 0.6 vs. −1.9 ± 0.7%), and lower BrachD (6.2 ± 0.1 vs. 6.5 ± 0.1%Δ/mmHg) indicating increased arterial stiffness (all $p < 0.05$).

In multivariate models (Table 2) adjusted for type 1 diabetes status, age, race/ethnicity, sex, smoking, microalbuminuria, mean arterial pressure, waist-to-height ratio, and triglyceride to HDL ratio, higher PWV was significantly associated with type 1 diabetes status, older age, race/ethnicity other than non-Hispanic white, microalbuminuria, higher mean arterial pressure, and larger waist height ratio. Higher AI75 was significantly associated with type 1 diabetes status, race/ethnicity other than non-Hispanic white, female sex, higher mean arterial pressure, and higher triglyceride to HDL-C ratio. Lower BrachD (higher stiffness) was significantly associated with type 1 diabetes, male sex, younger age, and larger waist height ratio.

In multivariate models that included insulin sensitivity, similar results were seen for AI75. Higher AI75 was associated with type 1 diabetes status, race/ethnicity other than non-Hispanic white, female sex, higher mean arterial pressure, and lower HDL cholesterol. A higher PWV was associated with older age, race/ethnicity other than non-Hispanic white, female sex, higher mean arterial pressure, lower insulin sensitivity score, and the presence of microalbuminuria. Lower BrachD (higher stiffness) was associated with male sex and lower

insulin sensitivity. Because each of these models had a lower R^2 than the models presented in Table 2, they were omitted.

Discussion

We present data comparing PWV, AI75, and BrachD in adolescents and young adults with and without type 1 diabetes. Using these three different measures of central and peripheral arterial stiffness, our data demonstrate that type 1 diabetes adversely affects the vasculature by late adolescence. We also identify several modifiable risk factors including blood pressure, adiposity, lipids, and microalbuminuria that are independent risk factors for impaired vascular health in youth with type 1 diabetes. However, an important finding of our study is that despite adjustment for these known modifiable and non-modifiable cardiovascular disease risk factors, there is still an increased arterial stiffness in youth with type 1 diabetes compared to controls.

Arterial stiffness is recognized as a surrogate end point for cardiovascular disease (3) and can be measured reliably using non-invasive imaging modalities making it ideal for large scale studies in adolescents and young adults. In this report, we used three measures to assess arterial stiffness in adolescents and young adults. It should be noted that each is a slightly different measure of arterial stiffness; thus, the three measures should not be used interchangeably (3). Carotid femoral PWV, a measure of central arterial stiffness, is considered the gold standard measure of subclinical arterial stiffness in both adults and children (18, 19) and has been shown to predict future cardiovascular events and mortality. AI75 is an indirect mixed measure of arterial stiffness that is influenced by central stiffness (PWV) and peripheral wave reflections (3). AI75 has been used in both pediatric (20, 7) and adult studies (21, 22) of type 1 diabetes to assess arterial stiffness and has been shown to predict all-cause mortality in adults with end-stage renal disease (23) and hypertension (24). BrachD is a non-ultrasound measure of stiffness (arterial compliance) in a medium muscular artery (14). It is highly correlated with cardiovascular risk factors and may be a better measure of arterial stiffness in youth because it uses a term for baseline vessel diameter that corrects for body size and gender (14). In this study, we report increased arterial stiffness in youth with type 1 diabetes using all three measurements. This suggests that type 1 diabetes in youth affects both the central and peripheral vasculature.

We and others have evaluated arterial stiffness in youth with type 1 diabetes, but results have differed between studies (20, 25, 26, 7, 27). Haller et al. first reported increased arterial stiffness in youth (age range 10–18 yr) with type 1 diabetes using AI75. However, their group did not include measurements of PWV or BrachD and because of small sample size were unable to assess any relationships between cardiovascular risk factors and AI75 (20). Heilman et al. showed increased AI75 in cases vs. controls who were mean age of 13 ± 3 yr but found no differences in PWV (25). Palombo et al. noted increased PWV and AI in youth with type 1 diabetes and BrachD was not measured (26). We previously published data showing an increase in PWV, AI75, and lower BrachD (increased stiffness) in a younger cohort of youth with type 1 diabetes ages 14.6 ± 3.3 yr compared to controls (no overlap with the current study). However, as mentioned, the control group was recruited from another study and were older (17.8 ± 3.5 yr), more likely to be minority ethnicity and had

lower BMI score than the cases (7). Of note, our group has also published data focused on changes in arterial stiffness overtime in type 1 diabetes (5) and evaluating arterial stiffness in type 2 diabetes (28, 29, 7). Lastly, Yu et al. described no differences in brachial ankle PWV in youth with type 1 diabetes compared to age- and BMIz-matched controls, but this method of assessing arterial stiffness has not been validated in youth (27). Thus, we expand on the current cross-sectional data published in the literature in type 1 diabetes and demonstrate an increase in both central and peripheral measures of arterial stiffness in adolescents and young adults with a mean diabetes duration of 10 yr compared to controls that is larger than that previously observed. Furthermore, we found that this increase in arterial stiffness in youth with type 1 diabetes persists even after adjustment for known cardiovascular disease risk factors.

Our findings suggest that there are other risk factors that likely contribute to increased arterial stiffness in youth with type 1 diabetes. Hyperglycemia and its consequences including formation of advanced glycation end products (30) is one possible mechanism. Hyperglycemia was not explored because A1c status was collinear with type 1 diabetes status. Other risk factors may include insulin resistance, autonomic dysfunction, or increased pulse pressure.

Insulin resistance was sought after in regression models because insulin resistance in adults with type 1 diabetes has been independently associated with arterial stiffness (31) and it predicts the development of coronary artery disease (32). It appears that decreased insulin sensitivity may explain some of the case control differences in PWV and BrachD in youth with type 1 diabetes. For AI75, after adjustment for insulin sensitivity, the case control differences persisted. This suggests that insulin sensitivity may be a cardiovascular risk factor in youth with type 1 diabetes. Given the addition of insulin sensitivity, decreased the overall variance of the models, further work is needed to clarify this relationship.

Autonomic dysfunction is present in youth (mean age 18.8 yr) with type 1 diabetes with a mean diabetes duration of 9.8 yr (33) and has been shown to be associated with increased carotid and arterial stiffness (34, 35). Similarly, youth with type 1 diabetes have an increased in pulse pressure, suggesting impaired blood pressure regulation which is an independent risk for increased arterial stiffness (36). Autonomic or blood pressure dysfunction may be two important links to explain the higher vascular disease in persons with type 1 diabetes and are areas for future work.

We show several known modifiable risks factors are associated with an increase in arterial stiffness. The relationship between blood pressure and arterial stiffness is well described (3). Waist-to-height ratio, a measure of central adiposity, has been shown to be superior to BMI or percent body fat in its ability to predict cardiovascular risk factors (15, 37) and correlates with an increase in PWV and carotid intima media thickness in adults (38). Here, we show that waist-to-height ratio was associated with increased PWV and lower BrachD in youth. We also show that a higher triglyceride to HDL-C ratio was associated with an increase in AIx. Triglyceride to HDL-C ratio was chosen for our models because it correlates with small dense LDL particles (39, 16) which are elevated in youth with type 1 diabetes (40) and strongly predicts coronary artery disease (41). Finally, we show that presence of

microalbuminuria is associated with an increase in PWV. This is not surprising given that microalbuminuria is a significant risk factor for cardiovascular disease (42). Whether improving the above risk factors lowers arterial stiffness in type 1 youth needs to be established. However, recent cross-sectional analyses suggest that achieving ideal cardiovascular metrics such as a blood pressure lower than the 90th percentile, total cholesterol concentration of <170 mg/dL, and a fasting glucose of <100 mg/dL is associated with lower arterial stiffness (43).

The differential associations between cardiovascular risk factors and arterial stiffness are expected given that PWV, AI75, and BrachD are not interchangeable measurements. It should also be noted that while several modifiable risk factors are associated with arterial stiffness, the most consistent risk factors are type 1 diabetes status are non-modifiable age, race, and sex.

This study has some limitations. This is a cross-sectional study and, therefore, we cannot determine the order in which arterial stiffness develops (central vs. peripheral vs. muscular artery development) nor can we make conclusions about the causative factors of increased stiffness. Second, although we show increased arterial stiffness in youth with type 1 diabetes compared to controls, we are unable to conclude the degree of vessel abnormalities in youth with type 1 diabetes due to lack of normal values in this age group. Finally, we cannot assess whether the differences in cases and controls translates into clinically significant differences.

The strengths of this paper include our ability to compare three different measures of arterial stiffness in a large study population of cases and controls that are of similar age, sex, and BMI which has not previously been done and to demonstrate that differences in arterial stiffness exist among cases and controls despite adjustment for traditional cardiovascular risk factors.

In conclusion, global subclinical vascular differences using three different measures of arterial stiffness are present in adolescents and young adults. While management of cardiovascular risk factors including blood pressure, adiposity (waist-to-height ratio), microalbuminuria, and possibly lipids is likely beneficial to prevent early vascular disease in this group, our data emphasize the need to identify other potential modifiable risk factors in this high risk population. Whether improvement in these risk factors early in life will slow the progression of arterial stiffness also requires further study.

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Table 1

Clinical characteristics of study participants according to diabetes status

Variable	Type 1 diabetes (N = 402)	Controls (N = 206)	p-Value
Age (yr)*	18.8 (3.3)	19.2 (3.3)	0.10
Race/ethnicity, n (%)			<0.01
Non-Hispanic white†	348 (87%)	155 (75%)	
Black	22 (6%)	18 (9%)	
Hispanic	28 (7%)	28 (14%)	
Sex, n (%) male†	211 (53%)	94 (46%)	0.11
Smoking status, n (%)			0.75
Never†	252 (58)	115 (56)	
Former†	88 (22)	51 (25)	
Current†	80 (20)	40 (19.4)	
Body mass index (kg/m^2)*	25 (5)	25 (7)	0.13
BMI Z-score*	0.6 (0.9)	0.6 (1.1)	0.99
Waist-to-height ratio	0.5 (0.1)	0.5 (0.1)	0.22
LDL cholesterol (mmol/L)*	2.5 (0.7)	2.4 (0.7)	0.03
HDL cholesterol (mmol/L)*	1.4 (0.3)	1.3 (0.4)	<0.01
Triglycerides (mmol/L)‡	1.1 (0.6)	1.2 (0.7)	0.05
Systolic blood pressure (mmHg)*	111 (10)	110 (11)	0.59
Diastolic blood pressure (mmHg)*	70 (9)	69 (9)	0.04
Mean arterial blood pressure (mmHg)	83.8 (7.9)	82.7 (8.2)	0.09
Duration of type 1 diabetes (yr)	9.8 (3.8)	--	--
Glycosylated hemoglobin A1c (%)*	8.9 (1.8)	5.0 (0.3)	<0.01
Microalbuminuria†	26 (8)	3 (2)	0.04

All data are mean (standard deviation) except where noted.

* p-value by *t*-test;

† p-value by chi-squared test;

‡ p-value based on log distribution. Controls (2%) were classified as 'other' race/ethnicity.

Table 2

Multivariate regression models for arterial stiffness measures

	PWV (higher = stiffer)		AI75 (higher = stiffer)		BrachD (lower = stiffer)	
	Beta (SE)	**p-Value**	**Beta (SE)**	**p-Value**	**Beta (SE)**	**p-Value**
Intercept	4.47 (0.23)	<0.0001	4.29 (3.53)	0.23	9.52 (0.36)	<0.0001
Type 1 diabetes status (yes)	0.16 (0.07)	0.02	4.08 (1.02)	<0.0001	−0.25 (0.11)	0.02
Age (yr)	0.10 (0.01)	<0.0001	−0.18 (0.16)	0.26	0.05 (0.02)	0.006
Sex (female)	0.11 (0.07)	0.10	5.55 (1.02)	<0.0001	0.79 (0.10)	<0.0001
Race (non-Hispanic white)	−0.23 (0.08)	0.01	−6.06 (1.30)	<0.0001	0.003 (0.14)	0.97
Smoking (current)	0.03 (0.09)	0.72	0.92 (1.31)	0.49	0.14 (0.14)	0.31
Smoking (former)	−0.02 (0.08)	0.85	0.77 (1.25)	0.54	0.21 (0.13)	0.10
Mean arterial pressure (mmHg)	0.02 (0.004)	<0.0001	0.15 (0.07)	0.03	−0.003 (0.01)	0.62
Waist/height ratio	0.01 (0.002)	<0.0001	−0.07 (0.04)	0.07	−0.04 (0.004)	<0.0001
Triglycerides/HDL-C ratio	0.03 (0.02)	0.18	0.76 (0.31)	0.01	0.05 (0.03)	0.08
Microalbuminuria (yes)	0.38 (0.13)	0.004	1.40 (2.18)	0.52	0.16 (0.21)	0.44
Model R^2	0.43		0.15		0.30	

AI, augmentation index; BrachD, brachial distensibility; HDL, high-density lipoproteins; SE, standard error.

The above are beta-estimates (standard error) and p-values.