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Ethnic differences in Ankle Brachial Index are Present in Middle-Aged Individuals without Peripheral Arterial Disease

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Abstract

Introduction—To better understand the basis for previously reported ethnic differences in ankle brachial index (ABI), we investigated whether these differences were present in individuals without known peripheral arterial disease (PAD).

Methods—We used data from National Health and Nutrition Examination surveys (NHANES 1999–2004) to determine whether ethnic differences were present in respondents without PAD (1 ABI 1.3). We assessed whether ethnicity was an independent predictor of ABI and ankle systolic blood pressure (SBP) in linear regression models that adjusted for conventional and novel cardiovascular risk factors. To minimize effects of atherosclerosis on ABI, we studied adults aged 60 years, and also repeated our analyses in a subset aged 50 years that did not have risk factors for PAD.

Results—3348 participants aged 60 years were included in the study. Mean ABI was 1.11 in non-Hispanic Blacks (NHB) and 1.13 in non-Hispanic Whites (NHW) ($P < 0.0001$). In multivariable linear regression analysis that adjusted for age, gender, ethnicity, smoking, height, diabetes, brachial SBP, dyslipidemia, diabetes, renal function, concurrent cardiovascular disease, and plasma levels of homocysteine, fibrinogen and C-reactive protein, NHB had lower ABI than NHW ($\beta = -0.03 \pm 0.004$, $P < 0.00001$). Although, NHBs had higher ankle SBP than NHWs (by 5.3 mm Hg), NHBs had a lower mean ankle SBP ($\beta = -3.663$ mm Hg ± 0.500 , $P < 0.0001$) after adjusting for clinical covariates, including brachial SBP, in multivariable analysis.

Conclusion—Ethnic differences in ABI are present in middle-aged adults at low risk for peripheral atherosclerosis.

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Keywords

ankle brachial index; ethnicity

INTRODUCTION

Peripheral arterial disease (PAD) affects about 8 million adults in the United States and is associated with significant morbidity and mortality in the affected population.^{1–3} Major risk factors for PAD include smoking, diabetes, dyslipidemia, hypertension and chronic kidney disease (CKD).^{4, 5} Inflammatory markers like C- reactive protein (CRP) and fibrinogen have also been associated with PAD.^{6,7} Ethnic differences in burden of PAD have been previously reported.^{8,9} Existing evidence suggests that non-Hispanic Blacks (NHB) are at two-to three-fold higher risk for PAD (defined as ABI <0.90) than non-Hispanic whites (NHW).¹ Although NHBs have a higher prevalence of several cardiovascular risk factors than NHWs, these risk factors do not entirely explain why NHBs have a higher prevalence of PAD.¹⁰

Ankle brachial index (ABI) is a well validated measure that is commonly used in clinical and epidemiological setting to diagnose PAD.¹¹ Most clinical studies use ABI < 0.9 to identify patients with PAD. ABI has been showed to have good sensitivity and specificity for diagnosing PAD when compared to arteriography as the reference standard.¹² In subjects without clinically significant peripheral arterial atherosclerosis, ABI is usually between 1.0 and 1.3.

There are sparse data on ethnic differences in distribution of ABI in healthy subjects without PAD. In the Multi-Ethnic Study of Atherosclerosis, Aboyans et al¹³ have previously reported that NHB ethnicity was associated with a lower ABI in subjects with ABI between 1.0 and 1.3 after adjustment for multiple risk factors. However mechanisms responsible for lower ABI in NHBs are not completely understood. The objective of our study was to evaluate whether ethnic differences (among NHBs and NHWs) are present in ABI in individuals without PAD. Simply put ABI is a ratio of brachial and ankle blood pressures. Ethnic variation in ABI could be driven by differences in brachial and ankle systolic blood pressure. Non-Hispanic blacks have a higher prevalence of hypertension (and mean brachial systolic blood pressure) in United States. Hence we also evaluated whether ethnic differences are present in ankle systolic pressure, which is a determinant of ABI. We used data from National Health and Nutritional Examination Surveys (NHANES) for this study.

METHODS

Study Population

NHANES surveys include the non-institutionalized civilian population of United States. Sampling for NHANES is performed in a complex and multistage probability design to provide nationally representative data. The 1999–2004 NHANES was reviewed and approved by National Center for Health Statistics Institutional Review Board. Informed consent was obtained from all participants. ABI with its components were measured in participants aged ≥ 40 years. For our primary analysis, we defined the main sample to include healthy participants aged ≥ 60 years with an ABI of 1–1.3. To further elucidate the association between ethnicity and ABI, we conducted additional analyses on a subset of our main sample that included adults who were aged ≥ 50 years and did not have any major risk factors for PAD, i.e. hypertension, diabetes, dyslipidemia, current smoking and chronic kidney disease (CKD). We also excluded subjects with self-reported history of cardiovascular disease (CVD) in this subset. By choosing a selected subset of the main

sample population we aimed to reduce confounding introduced by known risk factors for PAD that may be differentially distributed by ethnicity.

Laboratory methods

Standard automated biochemical analysis was used to measure biomarkers in NHANES, as has been published by Centers for Disease Control and Prevention (CDC).¹⁴ Heparin-MN assay was used to measure high-density lipoprotein (HDL) cholesterol values. In participants with limited sample volume, direct immunoassay for HDL cholesterol was used. Total cholesterol was measured using the peroxide assay.¹⁵ Creatinine was measured using the Jaffe reaction. Because of change in assay from 1999–2000 to later study periods, creatinine values for 1999–2000 were corrected for laboratory technique per recommendations by CDC. High-sensitivity CRP was measured with latex-enhanced nephelometry. Homocysteine was measured using automated fluorescence polarization immunoassay and fibrinogen was measured using Clauss clotting method.

ABI measurement

ABI measurements were conducted on selected adult participants aged ≥40 years. Systolic blood pressures (SBP) were measured in the right brachial artery and both posterior tibial arteries. Ankle blood pressure was measured twice at each site for participants aged 40–59 years and once at each site for participants aged 60 years and older. The right and left ABI were obtained by dividing the mean SBP in the right and left ankles by the mean brachial SBP in the arm respectively. We used lower of the two ABIs for this analysis. The lower mean ankle SBP has been used in this analysis as well. Participants with ABI ≤0.9 were considered to have definite PAD and excluded. Participants with ABI between 0.9 and 1.0 were also excluded as this ABI is considered to be borderline low, and is associated with peripheral atherosclerosis.¹⁶ Participants with ABI >1.3 were excluded from this analysis because elevations in ABI above 1.3 may result from non-compressibility of arteries due to vascular calcification.¹⁷

Blood pressure measurements

Systolic and diastolic blood pressures were measured in the right arm, except for cases where it was not possible due to technical or anatomic reasons. A total of 3 or 4 measurements were taken on a given day. For analysis in this paper a participant was considered to be hypertensive if his/her average brachial SBP was ≥140 mm Hg or diastolic blood pressure was ≥90 mm Hg or the respondent reported that he/she was taking prescription medications for hypertension or had been told by a physician that he/she had hypertension. Two brachial SBPs were used in this analysis: one was taken at the same time as ankle SBP for calculation of ABI (concurrent brachial SBP) and the other was taken non-concurrently with ankle SBP for the purpose of blood pressure measurement in NHANES.

Other measurements

Respondents who reported that they had been told by a physician that they were diabetic, reported that they were taking prescription medications for diabetes (insulin or oral hypoglycemics or both) or had fasting blood glucose ≥126 mg/dl were classified as diabetic. Dyslipidemia was diagnosed if a participant had a total cholesterol/HDL cholesterol ratio ≥5.0 and/or was on lipid-lowering medications (prescription medications were ascertained separately in NHANES). Glomerular Filtration Rate (GFR) was calculated using the Modification of Diet in Renal Disease Equation.¹⁸ Participants with GFR ≤60 ml/min/m² were considered to have CKD.

Respondents were classified as having cardiovascular disease (CVD) if they reported that they had been told by physician they had coronary heart disease, angina pectoris, myocardial infarction, heart failure and/or stroke. Age, gender and ethnicity were assessed by self-report. Ethnicity in this analysis has been classified as NHB, NHW, Hispanic and others.

Participants who reported that they currently smoked were classified as current smokers. Those who did not meet this criterion were asked if they had ever smoked 100 or more cigarettes in life. Those who replied yes were classified as former smokers. Others were classified as never smokers. Based on participants' responses about the level of education they had completed, they were classified as those who had completed less than high school, had received high school diploma or equivalent and had completed more than high school.

Statistical Analysis

NHANES uses a complex, multistage and probability sample design to select participants. To account for this sampling design we used sample weights per National Center for Health Statistics (NCHS) recommendations. We generated a combined six year weight variable by assigning 2/3 of the 4-year weight for 1999–2002 data and 1/3 of the 2-year weight for 2003–04 data. Analyses were performed using SAS version 9.1 (SAS Institute, Inc, Cary, NC) and SAS-callable SUDAAN version 10 (Research Triangle Park, NC). We used linear regression models to evaluate association of ethnicity with ABI. Regression coefficients have been reported as β in results. In the first step linear models were constructed for each variable of interest and estimates were adjusted for age and gender. In the next step we constructed multivariable models that included relevant variables - age, gender, ethnicity, income, education smoking, height, BMI, brachial SBP, dyslipidemia, diabetes, GFR and presence of CVD. Brachial SBP that was used in this part of analysis was not measured concurrently with ankle SBP, due to concern for over adjustment in regression (given that concurrent brachial SBP would be included in the denominator of ABI which was a dependent variable in regression model). In the final step we included novel cardiovascular biomarkers (CRP, fibrinogen and homocysteine) in the multivariable model in a single step. Since fibrinogen was not measured in NHANES 2003–04, our sample sizes decreased almost by a third for the third model. Novel biomarkers (CRP, fibrinogen and homocysteine) showed a skewed distribution in the population. Hence logarithmic transformations were done and used in linear models.

ABI is the ratio of ankle SBP to brachial SBP. NHB have a higher prevalence of hypertension in United States than NHW.¹⁹ As a corollary they would have higher mean brachial SBP. A lower ABI in NHB could merely be a function of higher brachial SBP in this ethnic group. To investigate this, we ascertained whether differences existed in ankle SBP by ethnicity. We constructed linear models for ankle SBP in our study population with demographic and clinical predictors. Crude estimates were adjusted for age and gender, while multivariate estimates were adjusted for all relevant clinical variables (including age, gender, ethnicity, smoking, height, BMI, GFR, CVD and diabetes), and brachial SBP. For this analysis we used both brachial SBPs measured concurrently and non-concurrently with ankle SBP, in separate analyses (only results for concurrent brachial SBP are shown). Correlation between the two brachial SBPs measured concurrently and non-concurrently with ankle SBP was only 0.79 ($P < 0.0001$).

All analyses were also repeated in the subset of our main sample aged ≥ 50 years with ABI 1–1.3 that did not have known major risk factors for PAD and CVD.

RESULTS

We identified 7564 respondents who had ABIs measured in NHANES 1999–04 and had information available on conventional cardiovascular risk factors. Of these, 3348 participants aged 40–60 years formed our main sample. After excluding subjects aged >50 years, and those with hypertension, diabetes, current smoking, CKD, dyslipidemia and CVD, 628 subjects formed our low-risk subset. The mean age of the main sample was 48 years. Women comprised about 48% of participants in the main sample. Sociodemographic and clinical characteristics of the main sample are shown in Table 1.

The distribution of ABI by ethnicity in men and women aged 40–60 years with normal fitted curves are shown in figures 1 and 2 respectively. Mean ABI was 1.116 in NHB men and 1.151 in NHW men (difference = -0.036 , t test $P < 0.0001$). Among women, ABI for NHB was also significantly lower than NHW (1.094 and 1.125 respectively, difference = -0.032 , t -test $P < 0.00001$).

Results of linear models for predictors of ABI in the main sample are shown in Table 2. In age-adjusted models women had lower ABI than men ($\beta = -0.024 \pm 0.004$, $P < 0.00001$). NHB ethnicity was associated with a lower ABI in age and gender adjusted models ($\beta = -0.034 \pm 0.003$, $P < 0.00001$). Increasing height (in cm) was also associated with increasing ABI, although this effect was very small ($\beta = 0.0007 \pm 0.0002$, $P = 0.0009$). Other variables associated with ABI in age and gender adjusted linear regression included: current smoking ($\beta = -0.028 \pm 0.004$, $P < 0.001$), dyslipidemia ($\beta = -0.006 \pm 0.003$, $P = 0.05$) and history of CVD ($\beta = -0.012 \pm 0.005$, $P < 0.001$). Participants who had completed education less than high school also had a lower ABI than those who had completed education beyond high school. Among novel cardiovascular risk factors, fibrinogen and CRP levels also showed significant association with lower ABIs ($\beta = -0.0001 \pm 0.00003$, $P = 0.0002$ for fibrinogen, $\beta = -0.008 \pm 0.003$, $P = 0.004$ for CRP).

In a multivariate model that adjusted for confounders including conventional cardiovascular risk factors, NHBs had lower ABI than NHWs ($\beta = -0.032 \pm 0.004$, $P < 0.0001$). Other predictors of lower ABI included female gender ($\beta = -0.021 \pm 0.006$, $P = 0.0007$), increasing brachial SBP ($\beta = -0.0006 \pm 0.0002$, $P = 0.001$), and history of CVD ($\beta = -0.012 \pm 0.005$, $P = 0.013$). Lower GFR (0.0002 ± 0.00007 , $p = 0.002$) and current smoking ($\beta = -0.028 \pm 0.004$, $P < 0.00001$) were also associated with lower ABI. We did not find any significant association of schooling with ABI in our multivariable model. Associations found in multivariate analysis were consistent after adjustment for novel cardiovascular risk factors. Among novel markers, increasing fibrinogen tended to be associated with lower ABI in multivariable model ($\beta = -0.017 \pm 0.010$, $P = 0.09$).

Results of linear regression for predictors of ABI for the low risk subset are shown in supplemental appendix. In all linear models, NHB had lower ABI than NHW.

Mean ankle SBP in NHBs and NHWs were 147.2 mm and 141.8 mm Hg respectively. In age and gender adjusted linear models, ankle SBP was higher in NHBs. However, in multivariate analysis, NHB ethnicity was associated with lower ankle SBP in the overall sample population ($\beta = -3.663 \pm 0.500$, $P < 0.00001$) and in the subset of population aged 50 years without any major risk factors for PAD ($\beta = -3.422 \pm 0.869$, $P = 0.0003$, see supplemental appendix). For brachial SBP measured non-concurrently with ankle SBP, a 5.5 mm Hg difference was noted between adjusted means for NHB and NHW ethnicities (127.4 and 121.9 mm Hg respectively, $P < 0.0001$). However only a 2.5 mm Hg difference was noted in mean ankle SBP between two ethnicities (NHB = 139 mm Hg, NHW = 141.5 mm Hg, $P < 0.0001$), regardless of a very strong association between ankle SBP and concurrent brachial SBP ($\beta = 0.988 \pm 0.013$, $P < 0.001$ in multivariate models). This suggests that the

central blood pressure wave is attenuated more in lower extremity arteries of NHBs than NHWs.

DISCUSSION

Our results show that in a sample of middle aged adults who were at low risk for PAD, NHBs had lower ABI than NHWs after adjusting for conventional and novel cardiovascular risk factors. The magnitude of effect of NHB ethnicity on ABI was similar in various linear regression models, and was also consistent in the subset that was less likely to have peripheral atherosclerosis. Our results suggest that lower ABI in middle-aged NHBs may not be due to atherosclerotic vascular disease. Although NHBs had a higher ankle SBP than NHWs, the difference between the two was less than that would be expected from a higher brachial SBP in NHBs (assuming that there was no difference in conductance of central aortic pressure wave to lower extremity arteries).

Multiple mechanisms to explain the supposedly increased burden of PAD in NHBs have been proposed. These include higher prevalence of risk factors (hypertension and diabetes), health-care access disparities, under-treatment of risk factors and genetic polymorphisms.^{20,21} Ix et al, using data from the San Diego population study, have shown that including novel cardiovascular risk factors only adds modestly to the predictive accuracy of conventional risk factors for predicting increased prevalence of PAD in NHBs in a mixed ethnic sample.²² They utilized three of nine novel biomarkers that were differentially distributed among NHBs and NHWs in their study population. These included lipoprotein(a), CRP and fibrinogen. Previously Khwaja et al²³ and Allison et al¹⁰ have also shown that adjustment for novel risk markers (CRP, fibrinogen, lipoprotein(a) and homocysteine) only modestly attenuated odds ratios for PAD attributed to NHB ethnicity. Residual confounding due to unmeasured risk factors can not be ruled out in these studies. However, to the best of our knowledge literature on ethnic differences in ABI in normal population is limited. Similar to the PAD population, existing cardiovascular risk factors do not completely account for ethnic differences in ABI among apparently healthy adults. Differential atherosclerosis in peripheral beds in African Americans than Non Hispanic whites is another speculative mechanism that may account for differences seen in this study.

In healthy adults there is reflection of the pulse pressure from the vascular bed of the feet, producing a higher ankle SBP than brachial SBP (ABI>1). In our study, although brachial SBP was 5.5 mm Hg higher in NHB, only a 2.5 mm Hg difference was noted in ankle SBP among the two ethnicities suggesting that there was greater attenuation of the arterial pressure wave in the lower extremity vessels in NHBs. Due to limited data collected in NHANES it is not clear if this is due to differential peripheral atherosclerosis or differences in stiffness or wave reflection.

Besides atherosclerosis, arterial stiffening can affect the ABI. Ethnic differences in arterial compliance have been demonstrated in normotensive adolescents.²⁴ Collins et al found that among healthy adolescents, NHBs had mean brachial-ankle pulse wave velocities that were higher by 40 cm/s than in NHW adolescents. They hypothesized that these results could reflect “inherent phenotypic variation in arterial structure and function.” Moreover using data from Bogalusa Heart Study, Li et al have shown that childhood systolic blood pressure is significantly predictive of adult brachial pulse wave velocity.²⁵ Interestingly in the subsample that they evaluated for differences in arterial compliance as adults, mean childhood SBP was not different in NHBs and NHWs. Whether ethnic differences in arterial stiffness at a younger age translate into differences in arterial stiffness and ABI in middle age is not known.

Our findings extend those of Aboyans et al. We observed that women on an average had ABIs that were lower than men by 0.02, and that the difference in ABIs among NHBs and NHWs was about 0.03. Although these differences are small, using gender and ethnicity-based cutoffs for diagnosing PAD leads to substantial change in estimation of disease burden in specific groups in population, as Aboyans et al have suggested. However our analysis utilizes a much younger sample, shows that ethnic variation in ABI may exist in apparently healthy middle aged adults. Our study's strengths also include the large sample size of NHANES. Given that the data have been derived from a nationally representative sample our results can be generalized to the general American adult population. From a clinical stand point our results have diagnostic implications for patients with borderline ABIs. Ethnicity and gender-specific criteria for diagnosing PAD based on ABI may be needed. However it is not known and is difficult to predict if such small changes in ABI could affect clinical outcomes.

Our study's limitations stem from its cross-sectional design. Information on risk factors was collected at the same time as ABI were measured. Hence causal inferences cannot be conclusively drawn. Residual confounding due to unmeasured risk factors and subclinical atherosclerosis can also not be excluded in our analysis. Moreover, major risk factors may not help completely account for variation in distribution of ABI in an apparently healthy population. For example, a modest degree of variability in ABI is explained by genetic factors.^{26,27} However genetic factors' impact on ABI cannot be evaluated in NHANES. The method of ABI measurement employed in NHANES may overlook a proportion of patients at higher risk for cardiovascular events.²⁸ ABI calculation based on unilateral brachial artery pressure measurement can result in falsely normal ABI (due to subclavian stenosis).^{29,30} We also excluded subjects with self-referred history of CVD and risk factors for PAD in the limited subset. This does not completely exclude participants who could have had peripheral arterial atherosclerosis.

Multiple studies have suggested an increased prevalence of PAD in NHB.^{31–33} Our analysis shows that ethnic differences in mean ABI are present in middle-aged adults at low risk for PAD. To what extent this phenomenon may contribute to the higher observed prevalence of PAD in NHB relative to NHW in the elderly age group is not definitely known, as prospective studies are lacking. More research in to mechanisms explaining lower ABI in NHBs, especially physiologic properties of lower extremity arteries, is needed.

CONCLUSION

Our results show that in a nationally representative middle-aged sample of the American population that was at a low risk for PAD and had 1.0 ABI 1.3, NHB ethnicity was associated with a lower mean ABI. Ethnic differences in ABI in middle-aged adults may not be a manifestation of varying atherosclerotic vascular burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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LIST OF ABBREVIATIONS

ABI ankle brachial index

BMI	body mass index
CKD	chronic kidney disease
CVD	cardiovascular disease
GFR	glomerular filtration rate
hsCRP	high-sensitivity C-reactive protein
NHANES	National Health and Nutritional Examination Survey
NHW	non-Hispanic Whites
NHB	non-Hispanic Blacks
PAD	peripheral arterial disease
SBP	systolic blood pressure

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Figure 1.

Figure 2.

Table 1

Baseline characteristics of the sample aged 40–60 years

Characteristic	Mean $\pm$ SE ^a
Mean age years $\pm$ SE ^a	48.4 $\pm$ 0.15
Gender	
Male	1747 (51.6)
Female	1601 (48.4)
Ethnicity	
Non-Hispanic White	1693(76.3)
Non-Hispanic Black	885 (10.0)
Hispanic American	650 (9.1)
Others	120 (4.6)
Smoking	
Current	850 (24.4)
Former	926 (29.1)
Never	1570 (46.5)
Height in cm $\pm$ SE ^a	170.24 $\pm$ 0.19
Systolic blood pressure in mm Hg $\pm$ SE ^a	122.6 $\pm$ 0.43
BMI ^b kg/m ² $\pm$ SE ^a	28.35 $\pm$ 0.16
Central obesity	1712 (52)
Dyslipidemia	1197 (37.8)
Diabetes	302 (6.8)
GFR ^c ml/min/m ²	97.8 $\pm$ 0.75
hs CRP (mg/dl) $\pm$ SE ^a	0.38 $\pm$ 0.01
Homocysteine (μ mol/l) $\pm$ SE ^a	8.73 $\pm$ 0.09
Fibrinogen (mg/dl) $\pm$ SE ^a	348.3 $\pm$ 3.38

^aStandard Error;^bBody Mass Index;^cGlomerular Filtration Rate

Table 2

Predictors of ankle brachial index in adults aged 40–60 years

Covariate	Model 1 (n=3348) Beta $\pm$ SE ^a	P	Model 2 (n=2874) Beta $\pm$ SE ^a	P	Model 3 (n=1972) Beta $\pm$ SE ^a	P
Age	-0.0006 $\pm$ 0.0003	0.04	0.0001 $\pm$ 0.0003	0.57	0.00001 $\pm$ 0.0003	0.97
Gender						
Men (<i>ref</i>)	-		-		-	
Women	-0.024 $\pm$ 0.004	<0.00001	-0.021 $\pm$ 0.006	0.001	-0.019 $\pm$ 0.007	0.01
Ethnicity						
Non Hispanic white (<i>ref</i>)	-		-		-	
Non Hispanic black	-0.034 $\pm$ 0.003	<0.00001	-0.032 $\pm$ 0.004	<0.00001	-0.030 $\pm$ 0.004	<0.00001
Hispanic	-0.009 $\pm$ 0.005	0.06	-0.010 $\pm$ 0.006	0.09	-0.010 $\pm$ 0.007	0.14
Education						
Less than high school (<i>ref</i>)	-		-		-	
High school	-0.010 $\pm$ 0.004	0.01	0.005 $\pm$ 0.005	0.28	0.005 $\pm$ 0.006	0.40
More than high school	-0.007 $\pm$ 0.003	0.04	0.002 $\pm$ 0.004	0.62	0.003 $\pm$ 0.005	0.63
Poverty income ratio						
Less than 1 (<i>ref</i>)	-		-		-	
1–2.5	0.005 $\pm$ 0.006	0.42	0.002 $\pm$ 0.007	0.82	-0.0006 $\pm$ 0.008	0.94
2.5–4	0.005 $\pm$ 0.007	0.51	-0.003 $\pm$ 0.008	0.71	-0.006 $\pm$ 0.009	0.52
>4	0.016 $\pm$ 0.006	0.01	0.002 $\pm$ 0.008	0.76	-0.0004 $\pm$ 0.009	0.96
Smoking						
Never (<i>ref</i>)	-		-		-	
Former	-0.001 $\pm$ 0.004	0.75	-0.0004 $\pm$ 0.004	0.25	-0.004 $\pm$ 0.004	0.33
Current	-0.025 $\pm$ 0.004	<0.00001	-0.028 $\pm$ 0.004	<0.00001	-0.025 $\pm$ 0.005	0.00003
Height	0.0007 $\pm$ 0.0002	0.001	0.0007 $\pm$ 0.0002	0.004	0.0005 $\pm$ 0.0003	0.09
BMI ^b	-0.0005 $\pm$ 0.0002	0.06	-0.00002 $\pm$ 0.0003	0.94	0.0007 $\pm$ 0.0004	0.04
Brachial SBP ^c	-0.0007 $\pm$ 0.00009	<0.00001	-0.0006 $\pm$ 0.0001	<0.00001	-0.0007 $\pm$ 0.0003	0.00001
Dyslipidemia	-0.008 $\pm$ 0.003	0.003	-0.006 $\pm$ 0.003	0.08	-0.003 $\pm$ 0.004	0.46
Diabetes	-0.006 $\pm$ 0.005	0.20	-0.0001 $\pm$ 0.006	0.91	0.006 $\pm$ 0.006	0.27
GFR ^d	0.00006 $\pm$ 0.00006	0.30	0.0002 $\pm$ 0.00007	0.002	0.0003 $\pm$ 0.00007	0.001

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Covariate	Model 1 (n=3348) Beta ± SE ^a	P	Model 2 (n=2874) Beta ± SE ^a	P	Model 3 (n=1972) Beta ± SE ^a	P
CVD ^e	−0.016 ± 0.005	0.001	−0.012 ± 0.005	0.01	−0.013 ± 0.006	0.02
Log(homocysteine)	−0.0008 ± 0.0005	0.09			0.005 ± 0.008	0.59
Log(fibrinogen)	−0.0001 ± 0.00003	0.0002			−0.017 ± 0.010	0.09
Log(CRP)	−0.008 ± 0.003	0.004			−0.003 ± 0.003	0.30

In model 1, estimates are adjusted for age and gender. In model 2, estimates are adjusted for age, gender, ethnicity, income, education smoking, height, BMI^b, brachial SBP^c, dyslipidemia, diabetes, GFR^d, and presence of CVD^e. In model 3, estimates are adjusted for all covariates as in model 2, and log values of homocysteine, fibrinogen, and C-reactive protein are adjusted for as well.

^aStandard Error;

^bBMI body mass index;

^cSystolic Blood Pressure;

^dGlomerular Filtration Rate;

^eCardiovascular Disease.