Published in final edited form as:
Hypertension. 2010 May ; 55(5): 1210–1216. doi:10.1161/HYPERTENSIONAHA.109.143123.

ENDOTHELIAL DYSFUNCTION AND THE RISK OF HYPERTENSION: THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

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Abstract

Hypertension is associated with impaired endothelial function in cross-sectional studies. However, few longitudinal data exist on whether endothelial dysfunction precedes the development of hypertension. We examined the cross-sectional and longitudinal relationships between endothelial-dependent brachial artery flow-mediated dilation (FMD) and hypertension prevalence and incidence in 3,500 participants from the Multi-Ethnic Study of Atherosclerosis (MESA), an ethnically diverse, community-based cohort study. At baseline, the prevalence ratios (95% CI) of hypertension from the highest to the lowest quartile of FMD were 1.00 (referent), 1.26 (1.12 – 1.40), 1.35 (1.21 – 1.52), and 1.68 (1.50 – 1.87) (linear trend $P < 0.001$). This association remained ($P = 0.017$) after adjustment for demographics (age, gender, ethnicity), MESA site, and other risk factors. Of the 1,869 participants without hypertension at baseline, 584 (31.3%) developed hypertension over a median follow-up of 4.8 years. The unadjusted relative risks (95% CI) of incident hypertension from the highest to the lowest quartile of FMD were 1.00 (referent), 1.38 (1.14 – 1.67), 1.44 (1.19 – 1.74), and 1.64 (1.36 – 1.97) (linear trend $P < 0.001$). However, after adjustment for demographics and MESA site, the relationship between FMD and incident hypertension was attenuated and not statistically significant: 1.00 (referent), 1.26 (1.04 – 1.52), 1.19 (0.98 – 1.44), and 1.18 (0.97 – 1.44). The longitudinal results also did not appreciably change after adjustment for additional risk factors and baseline blood pressure levels. In this sample, reduced FMD was not an independent predictor of hypertension incidence, suggesting that impaired endothelial function does not play a major role in the development of hypertension.

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Conflicts of Interest There are no conflicts of interest.

Keywords

hypertension; blood pressure; endothelium; atherosclerosis; epidemiology

Introduction

The normal endothelium senses hemodynamic forces and biochemical signals from the blood, and, in turn, responds by synthesizing and releasing vasoactive substances.[1] Endothelial-dependent flow-mediated vasodilation (FMD) is predominantly modulated by endothelium-derived nitric oxide (NO) which stimulates soluble guanylyl cyclase activity in vascular smooth muscle cells.[2] In addition to inducing vasodilation, NO inhibits leukocyte adhesion, thrombosis, and cellular proliferation in the vessel wall.[3] Endothelial dysfunction is considered to be an early process in the development of atherosclerosis.[4]

Hypertension is an established risk factor for incident cardiovascular disease (CVD) including coronary artery disease, peripheral arterial disease, stroke, and heart failure.[5] The etiology of essential hypertension has been investigated, and the underlying dysregulations are complex and likely multi-factorial. As several studies have shown that hypertension is associated with impaired brachial artery FMD,[6-9] some investigators have proposed that endothelial dysfunction is mechanistically implicated in a sustained increase in blood pressure.[10] However, virtually all of the published studies linking hypertension to impaired FMD have been cross-sectional, making it difficult to ascertain whether endothelial dysfunction precedes the onset of hypertension.

Prospective data on the relation between FMD and the subsequent risk of incident hypertension are limited. Rossi et al.[11] found that lower levels of FMD were associated with an increased risk of incident hypertension in an outpatient cohort of 952 apparently healthy postmenopausal women. Few longitudinal data are available on the relationship of FMD to incident hypertension in men, in minorities, or in population-based epidemiologic samples. Also, it is not known whether FMD is associated with hypertension incidence independent of other risk factors that are associated with both impaired FMD and hypertension. We, therefore, sought to evaluate whether FMD is an independent predictor of new onset hypertension in a multi-ethnic, population-based cohort of middle-aged and elderly men and women.

Methods

Study Population

The current analysis included participants from the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based study of 6,814 community dwelling adults aged 45 to 84 years at baseline. Details of the MESA study design have been described elsewhere.[12] Participants from 4 ethnic groups (Caucasian, African American, Hispanic, and Asian primarily of Chinese descent) were recruited from 6 U.S. communities including Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St. Paul, Minnesota. Participants were excluded if they had a history of clinically evident cardiovascular disease, were under treatment for cancer, pregnant, weighed more than 300 lbs, had any serious medical condition which would prevent long-term participation in MESA, had significant cognitive deficits, were living in a nursing home or on the waiting list for a nursing home, had plans to leave the community within five years, spoke a language other than English, Spanish, Cantonese or Mandarin, and/or had a chest computed tomography (CT) scan in the previous year. Written informed

consent was obtained from all participants, and the study was approved by the Institutional Review Boards of all participating sites.

FMD assessment was performed at baseline (Exam 1). Of the 6,814 MESA participants, 6,489 (95.2%) successfully underwent FMD testing. Participants were excluded from FMD testing if they had a history of Raynaud's phenomenon (n=55), a congenital abnormality of the arm or hand (n=12), or a radical mastectomy on either side (n=100). Participants (n=158) were also excluded at the time of the FMD examination, if they had blood pressures in the left and right arms that differed by more than 15 mmHg, or had uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg). FMD studies were analyzed by the Wake Forest University Cardiology Image Processing Laboratory. Images from 5,731 participants were of sufficient quality for reading. Due to financial constraints, images were read for only a subset of participants (n=3,501). For our analyses, a single participant with a sex-specific FMD greater than six standard deviations above the mean was excluded, resulting in available data from 3,500 participants.

Baseline Risk Factor Measures

Information on demographics, current smoking, education level, current alcohol intake, physical activity and medical history were obtained using standardized questionnaires.[12] Education level was assessed by determining the highest level achieved. Physical activity was defined as the total of all light, moderate, and vigorous activities multiplied by individual metabolic equivalent values (METS) for these activities. Anthropometric measurements of height and weight were determined by the use of calibrated scales. Body mass index was calculated as weight in kilograms divided by height in meters squared. Levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose were measured from blood samples obtained after a 12-hour overnight fast and under standardized conditions. The Friedwald equation was used to calculate low-density lipoprotein (LDL) cholesterol. Diabetes was defined as a fasting serum glucose ≥ 126 mg/dL or use of hypoglycemic drugs or insulin. Serum creatinine was measured, and estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) equation.[13] High sensitivity C-reactive protein was measured using a particle enhanced immunonepholometric assay on a BNII nephelometer.

Flow-Mediated Dilation Assessment

FMD was determined using high resolution ultrasonography of the brachial artery.[7, 8, 14, 15] In brief, participants were asked to abstain from food, consumption of vitamin E or C, and smoking for at least six hours prior to the scan. A standard blood pressure cuff was positioned around the right arm, 2 inches below the antecubital fossa, and the brachial artery of the right arm was imaged 5 to 9 cm above the antecubital fossa using a 9 MHz linear array transducer (M12L transducer, GE Healthcare, Waukesha, WI) at rest and during a 2-minute period beginning immediately before cuff deflation. To induce reactive hyperemia, the brachial artery was occluded for 5 minutes at an occlusion cuff pressure of at least 50 mmHg above the participant's systolic blood pressure. Images were digitized, and data were analyzed using a validated semi-automated system.[15, 16] FMD was expressed as the percentage increase in brachial artery diameter (media-adventitial interface to the media-adventitial interface) with reactive hyperemia: FMD = ((peak brachial artery diameter after cuff deflation – diameter at rest)/diameter at rest) × 100. A more detailed description of the scanning and reading protocol can be found at the MESA website (www.mesa-nhlbi.org).

To evaluate intra-reader reproducibility for resting brachial artery diameter, peak diameter, and FMD, ultrasound studies from 40 MESA participants (30 males, 18 White, 2 Chinese

American, 10 African American, 10 Hispanic) were re-examined.[15] The intra-class-correlation coefficients were 0.99, 0.99 and 0.93 respectively.

Blood Pressure Measurements and Hypertension Ascertainment

Blood pressure measurements were performed at each MESA exam, which were conducted at 18-month intervals. Data from Exams 1-4 were available for our analyses. After resting for 5 minutes in the seated position, participants' blood pressure was measured three times at two-minute intervals using an automated oscillometric device (Dinamap Monitor Pro 100, GE Healthcare, Milwaukee, WI). Appropriate sized cuffs were utilized for blood pressure assessment. Blood pressure was defined as the average of the second and third readings. Participants were asked about their prior diagnoses of hypertension, and the use of antihypertensive medications was also assessed.

Hypertension at baseline (i.e., prevalent hypertension) was defined by the presence of any of the following criteria: (1) self-reported history of hypertension, (2) systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, and/or (3) the use of antihypertensive medication.[17] Among participants without hypertension at baseline, the incidence of hypertension was defined as the first follow-up study visit with the presence of: (1) systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, and/or (2) the use of antihypertensive medication.

Statistical Analyses

We first examined the cross-sectional relation between FMD and prevalent hypertension in the 3,500 MESA participants with a FMD measurement at baseline. We then examined the longitudinal relation between baseline FMD and incident hypertension at follow-up (Exams 2-4). After excluding participants who had hypertension at baseline (n=1,624) and those who did not attend at least one follow-up visit (n=7), a total of 1,869 MESA participants were available for the analysis of incident hypertension. To account for the sampling of participants for reading of FMD images, following the MESA analytic guidelines, we used probability sampling weights for all analyses. In the current analysis, the unweighted estimates did not differ markedly from the weighted estimates (data not shown). Therefore, we only report the weighted estimates.

For the analysis of FMD and prevalent hypertension, we divided the study population into quartiles based on the distribution of FMD in the MESA cohort. Characteristics of participants and the prevalence of hypertension were calculated by quartile of FMD. Next, the unadjusted prevalence ratios of hypertension and the prevalence ratios adjusted for age, gender, ethnicity, and MESA site associated with quartile of FMD were calculated using log-binomial regression models. An additional model with multivariable adjustment for covariates that might be related to FMD or hypertension was also fitted. In addition to demographics (age, gender, and ethnicity) and MESA site, the following covariates (all chosen a priori) were included: body mass index, diabetes, LDL and HDL cholesterol levels, cigarette smoking, current alcohol intake, education level (defined as high school education or higher), physical activity, eGFR, and C-reactive protein. Linear trends across quartiles were assessed by including quartile-specific median FMD values as a continuous variable in the regression models. The association between FMD, expressed as a continuous variable, and hypertension at baseline was also evaluated using prevalence ratios, which were modeled to reflect a standard deviation decrease in FMD.

Next, the population eligible for the incident hypertension analyses was divided into quartiles based on their distribution of FMD. Characteristics of the population included in the analysis of incident hypertension were calculated by quartile of FMD. The incidence of

hypertension was calculated for each FMD quartile. Unadjusted hypertension incidence rates were calculated as the number of events in each FMD quartile divided by the sum of person-years at risk. The time at risk was calculated as the number of days between the baseline exam and Exam 4, unless a participant developed hypertension at an earlier visit (i.e., Exams 2 or 3), or did not attend Exam 4, in which case we calculated the risk time as the elapsed time from baseline to the last Exam the participant attended (i.e. Exam 2 or 3 for n=6 and n=64 participants, respectively). For the analysis of incident hypertension, Poisson regression was used to calculate the adjusted relative risk and 95% confidence intervals of hypertension associated with FMD. In addition to the covariates described above, baseline blood pressure was included as an additional covariate in the multivariable adjusted models. Because the distribution of FMD may vary by gender, all analyses were repeated using gender-specific FMD quartiles. Results were markedly similar (data not shown), and therefore, we only report on non-gender-specific FMD quartiles.

We also examined the relationship between resting brachial artery diameter and incident hypertension. However, the results were not appreciably different than for FMD (data not shown). Therefore, herein, we only report on results utilizing FMD as a main predictor variable.

In an additional secondary analysis, we examined an outcome of incident sustained hypertension, defined as having hypertension at Exams 2, 3, and 4, or Exams 3 and 4. We also examined an outcome of a clinically meaningful increase in blood pressure, defined as an increase in systolic blood pressure ≥ 10 mm Hg, an increase in diastolic blood pressure ≥ 5 mm Hg, and/or the introduction of an antihypertensive medication during follow-up.[17] Finally, secondary analyses were performed after incorporating prehypertension in the outcome: incidence of crossing the threshold for prehypertension (≥120/80 mmHg) and/or the use of antihypertensive medication. However, as the results were similar (data not shown), we do not report on these latter analyses. Statistical analyses were conducted with SAS 9.2 (SAS Institute, Cary, NC).

Results

Table 1 shows the baseline characteristics of the samples utilized for the cross-sectional (top panel) and longitudinal analyses (bottom panel), according to FMD quartiles. For the cross-sectional analyses, lower FMD quartile levels were associated with older age, African-American ethnicity, diabetes, higher levels of systolic and diastolic blood pressure and lower levels of eGFR. In contrast, higher FMD levels were associated with female gender, White or Chinese ethnicity, a high school education, alcohol intake, and a small but significant higher LDL-cholesterol levels. This latter relation was no longer significant after excluding participants on statins (data not shown). For the longitudinal analyses of incident hypertension, lower FMD levels were associated with older age, African-American ethnicity, diabetes, and higher baseline blood pressure levels, whereas higher FMD levels were associated with female gender and White or Chinese ethnicity.

FMD and Hypertension Prevalence

At baseline, lower FMD levels were significantly associated with a higher prevalence of hypertension (Table 2). After adjustment for age, gender, ethnicity and MESA site, the relation between FMD and hypertension was somewhat attenuated, but the trend across FMD quartiles remained statistically significant. This association did not change appreciably after inclusion of additional covariates. Each standard deviation decrease in FMD was associated with a 32% (95% CI 25% - 39%) greater unadjusted prevalence of hypertension (Table 3). In the fully adjusted model, each standard deviation decrease in FMD was associated with a 10% (95% CI 3% - 16%) higher prevalence of hypertension.

FMD and Hypertension Incidence

Over a median follow-up of 4.8 years (25th – 75th percentiles: 4.6 – 5.0 years), 584 (31.3%) of the 1,869 participants without hypertension at baseline developed hypertension. Lower FMD levels were significantly associated with an increased unadjusted risk of incident hypertension (Table 4). However, after adjustment for age, gender, ethnicity, and MESA site, these associations were substantially attenuated, and no longer statistically significant. Adjustment for additional covariates did not alter these findings. A similar pattern was observed when FMD was expressed as a continuous variable (Table 5). Each standard deviation decrease in FMD was associated with a 21% (95% CI 8% - 35%) higher unadjusted risk of incident hypertension. However, after further covariate adjustment, the relation was attenuated and not statistically significant. Exploratory analyses revealed that among age, gender and ethnicity, age had the greatest attenuating effect on the association between lower FMD levels and incident hypertension (data not shown). Table S1, available in an online supplement (please see http://hyper.ahajournals.org), shows the relative risk of incident hypertension for the covariates in the multivariable models.

FMD and Incident Sustained Hypertension

The incidence rates of incident sustained hypertension (per 1000 person-years) were 36.1 for the highest FMD quartile (≥ 6.5%), and 48.2, 43.2, and 59.5 for decreasing FMD quartiles (4.3 - 6.4%, 2.6 - 4.2%, and < 2.6% respectively; $P = 0.002$ for trend). However, these relations were attenuated and the trend was not statistically significant after adjustment for demographics, MESA site, and also other covariates (*P*-trend across quartiles = 0.673 after adjusting for age, gender, ethnicity, and MESA site; *P*-trend across quartiles = 0.907 after additional adjustment for body mass index, diabetes, LDL and HDL cholesterol levels, cigarette smoking, alcohol intake, education level, physical activity, eGFR, and C-reactive protein; and *P*-trend across quartiles = 0.922 after additional adjustment for baseline systolic and diastolic blood pressure levels).

FMD and a Clinically Meaningful Increase in Blood Pressure

There was no relationship between baseline FMD and a subsequent increase in systolic blood pressure ≥ 10 mmHg, diastolic blood pressure ≥ 5 mmHg, and/or the initiation of antihypertensive medication. The unadjusted relative risks (95% CI) from the highest to the lowest quartile of FMD were 1.00 (referent), 1.01 (0.89 – 1.15), 1.04 (0.92 – 1.18), and 1.09 (0.96 – 1.24) (*P*-trend = 0.181). After adjustment for demographics and MESA site, the relationship between FMD and incident hypertension became even weaker: 1.00 (referent), 1.00 (0.88 – 1.13), 0.99 (0.87 – 1.13), and 0.99 (0.87 – 1.14) (*P*-trend = 0.906). The results were unchanged after further covariate adjustment (data not shown).

Discussion

A number of prospective studies including MESA[8, 15, 18] have shown that impaired FMD, a measure of NO bioavailability, predicts CVD events, independent of traditional risk factors. Given the important role of NO in blood pressure regulation and vascular function, a reduction in NO bioavailability, mediated by an increased generation of reactive oxygen species,[19, 20] may be a mechanism underlying chronic blood pressure elevation and hypertension onset. Several studies have demonstrated a consistent cross-sectional relation between impaired FMD and hypertension.[6-10] However, it remains unclear whether endothelial dysfunction predicts progression to hypertension.

In the current study, reduced FMD was associated with an increased prevalence of hypertension at baseline, and this relation was independent of several other possible explanatory factors. This finding is consistent with previous cross-sectional studies[6-10] that

have examined the relation between FMD and hypertension. Although reduced FMD was associated with incident hypertension in unadjusted analyses, this relationship was attenuated and not statistically significant in adjusted models. A European of Society Working Group[21] proposed in 2005 that impaired endothelial function is unlikely to be a direct causal mechanism of hypertension initiation and maintenance. Our results provide longitudinal evidence in support of this hypothesis.

At least one previous longitudinal study has examined the relation between impaired FMD and incident hypertension.[11] A total of 952 normotensive post-menopausal women, recruited from an outpatient center in Italy had FMD assessed and were followed for hypertension incidence over a mean period of 3.6 years. Participants were excluded if they had a history of overt cardiovascular disease or a history of traditional risk factors such as hyperlipidemia, smoking, diabetes, and obesity. Lower FMD levels predicted incident hypertension, even after adjusting for age, family history of hypertension, baseline blood pressure levels, body mass index, waist circumference, duration of menopausal period, years of education, alcohol use, and physical activity. The association between reduced FMD and incident hypertension was large in magnitude. Compared to the highest quartile of FMD (≥ 5.5%), the multivariable-adjusted relative risks (95% CI) associated with decreasing FMD quartiles (4.3 - 5.4%; 3.6 - 4.2%; and ≤ 3.5%) were 1.92 (1.62 – 3.55), 3.00 (2.43– 4.29), and 5.77 (4.34 – 8.10) respectively.

The contrary findings of our study may be explained by differences in the characteristics of the study population. Our study utilized a large multi-ethnic, community-based sample that included an equivalent number of men and women drawn from several geographically diverse communities. Participants in MESA were also not excluded on the basis of traditional CVD risk factors. Further, the quartile-stratified incident hypertension rates (per 1000 person-years), as shown in Table 4, were substantially greater than those observed in the study conducted by Rossi et al. (10.4 for Q4, 20.9 for Q3, 40.8 for Q3, 61.1 for Q1).[11] However, the cumulative incidence of hypertension in the current study (31.3% over a median of 4.8 years) is comparable to the proportions observed in other population-based studies including the Framingham Heart Study.[22-24]

Overall, the results of our study strongly suggest that endothelial dysfunction is not an independent predictor of hypertension in the general population. One explanation for this finding is that endothelial dysfunction may have influenced other risk factors for hypertension that were included in the multivariable-adjusted models. However, the relationship between lower FMD levels and incident hypertension became weaker and non-significant after adjustment for demographics and MESA site, which are factors that FMD could not have directly influenced. A more likely explanation is that endothelial dysfunction is a consequence of hypertension. In the Cardiovascular Risk in Young Finns Study,[25] FMD was assessed in adults aged 24 to 39 years, and the relation of blood pressure levels measured in childhood and adolescence with subsequent FMD levels was examined. In male participants, systolic blood pressure levels in adolescence predicted lower FMD levels in adulthood, independent of traditional risk factors. These findings suggest that blood pressure elevations, at least in adolescent males, may adversely affect the biological processes underlying endothelial function such as NO bioavailability in early adulthood. Therefore, a chronic increase in blood pressure may induce endothelial damage over time, thereby contributing to atherosclerosis development and CVD event onset.[4]

Limitations

There are several limitations to our study. The follow-up period was relatively short. However, hypertension incidence during follow-up was relatively common even among those in the highest FMD quartile. It is therefore possible that the relation between reduced

FMD and hypertension onset may become even weaker over a longer follow-up period, as the incident hypertension rates between the highest and lowest FMD quartiles narrowed. Although non-significant, the adjusted relative risks of incident hypertension associated with lower FMD quartiles were not entirely negligible. Thus, despite our study being the largest to date (N=1,869) to examine the relation between FMD and incident hypertension, it is possible that an even larger sample size might have led to a statistically significant association between lower FMD quartile levels and incident hypertension. However, no clear association with incident hypertension was present when examining FMD as a continuous variable (adjusted relative risk of 1.00, p=0.935, Model 3, Table 5). Further, even if the results in the fully adjusted model (Model 3, Table 4) were to become statistically significant in a larger sample, the relative risk (95% CI) of 1.14 (0.93 – 1.38), comparing Q1 vs. Q4, is substantially weaker in magnitude than the relative risk of 5.77 (4.34 – 8.10) observed in the smaller study (N=952) by Rossi et al.[11] Endothelium-independent vasodilation, typically assessed by exogenous nitrate administration, was not assessed in this study. Thus, we cannot definitely exclude the possibility that reduced FMD was additionally explained by smooth muscle dysfunction. Similar to other large population-based studies,[8] we did not include this measure, because of limited feasibility in conducting this measure in a large number of participants. Blood pressures measured in the clinic environment are known to be variable. Therefore, it is possible that we included participants with hypertension at baseline in the analysis of FMD and incident hypertension. However, the results were not different when excluding those participants with baseline blood pressures in the prehypertensive range (systolic/diastolic blood pressure: 120-139/80-89 mmHg;[26] data not shown). The classification of hypertension at follow-up could also be affected by misclassification, but analyses defining the outcome as incident hypertension across consecutive visits (i.e., incident sustained hypertension) did not produce different results.

Strengths of the current study include the use of a large multi-ethnic cohort that was drawn from several communities in the United States, the longitudinal study design, and the careful and standardized assessment of cardiovascular risk factors including blood pressure readings across time. As limited data exist on the longitudinal relation between FMD and the subsequent risk of hypertension, the current study provides valuable new information.

Perspectives

As evidence from cross-sectional studies has shown that impaired NO-mediated endothelial-dependent vasodilation is associated with hypertension, it has been proposed that endothelial dysfunction may be an important underlying causal factor in hypertension onset. In an ethnically diverse, community-based population sample, no independent association was present between reduced FMD and the incidence of hypertension. These findings do not support the contention that endothelial dysfunction plays a major role in hypertension onset. Interventions designed to improve NO bioavailability may not reduce the incidence of hypertension in initially non-hypertensive individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Sources of Funding MESA was supported by contracts NO1-HC-95159 through NO1-HC-95166, and NO1-HC-95167; and R01-HL077612 from the National Heart, Lung, and Blood Institute.

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Table 1

Characteristics of MESA Participants Included in the Cross-sectional Analysis of Prevalent Hypertension (top panel) and the Longitudinal Analysis of Incident Hypertension (bottom panel)

Cross-sectional Analysis (N=3,500)					
	Quartiles of FMD*				
Characteristics	**Q4 (n =903)**	**Q3 (n =917)**	**Q2 (n =868)**	**Q1 (n =812)**	***P*-trend**
Levels of FMD, %	≥ 5.9	3.8 – 5.8	2.2 – 3.7	<2.2	-
Mean age (SD), years	57.5 (11.3)	60.7 (11.8)	63.9 (12.8)	65.7 (12.7)	< 0.001
Female, %	62.7	51.1	50.6	46.3	< 0.001
White, %	42.8	36.3	36.2	30.7	< 0.001
Chinese American, %	15.9	15.7	13.8	10.4	< 0.001
African American, %	16.0	19.2	23.5	35.9	< 0.001
Hispanic, %	25.4	28.8	26.5	23.1	0.295
High school education, %	84.9	82.8	80.1	80.0	< 0.001
Current smoker, %	12.5	13.1	13.2	13.0	0.744
Current alcohol intake, %	58.4	56.3	56.7	53.6	< 0.001
Diabetes, %	8.3	10.1	12.8	14.2	< 0.001
Mean BMI (SD), kg/m^2	28.2 (7.2)	28.1 (6.5)	27.8 (6.3)	28.0 (6.5)	0.392
Mean SBP (SD), mmHg	119.9 (24.1)	123.7 (23.5)	127.0 (25.4)	130.7 (26.8)	< 0.001
Mean DBP (SD), mmHg	70.1 (13.0)	71.7 (12.2)	71.7 (12.5)	73.0 (13.6)	< 0.001
Mean LDL-cholesterol (SD), mg/dL	119.0 (38.9)	117.8 (39.8)	116.5 (39.3)	115.7 (38.2)	0.019
Mean HDL-cholesterol (SD), mg/dL	51.4 (18.8)	49.9 (18.9)	51.6 (19.0)	50.9 (18.5)	0.611
Geometric mean CRP (95% CI), mg/L	1.9 (1.7 – 2.0)	1.9 (1.8 – 2.1)	1.8 (1.7 – 1.9)	1.9 (1.8 – 2.1)	0.978
Mean eGFR (SD), mg/dL	75.2 (18.9)	75.0 (19.0)	74.0 (19.4)	73.6 (21.5)	0.017
Geometric mean physical activity level (95% CI), 1000 METs-min/wk	7.2 (6.9 – 7.5)	7.2 (6.9 – 7.5)	7.2 (6.9 – 7.5)	7.4 (7.1 – 7.7)	0.481

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Longitudinal Analysis (N=1,869)

Characteristics	Q4 (n =477)	Q3 (n =470)	Q2 (n =484)	Q1 (n =438)	*P*-trend
Levels of FMD, %	≥ 6.5	4.3 – 6.4	2.6 – 4.2	< 2.6	-
Mean age (SD), years	55.3 (10.4)	57.8 (11.0)	59.6 (12.3)	62.8 (12.7)	< 0.001
Female, %	64.0	51.4	49.5	46.8	< 0.001
White, %	43.5	39.9	37.6	36.9	0.004
Chinese American, %	17.1	16.2	17.0	11.4	0.013
African American, %	12.7	13.7	19.9	24.5	< 0.001
Hispanic, %	26.7	30.3	25.5	27.2	0.789
High school education, %	85.7	80.7	82.9	82.3	0.112
Current smoker, %	12.6	14.4	17.2	13.2	0.269
Current alcohol intake, %	61.4	57.4	61.7	57.5	0.318
Diabetes, %	3.9	6.2	8.6	7.4	< 0.001
BMI (SD), kg/m^2	27.1 (6.9)	27.2 (6.0)	27.5 (6.6)	27.0 (5.6)	0.890
Mean SBP (SD), mmHg	111.6 (17.2)	114.6 (16.2)	116.3 (16.0)	116.4 (16.1)	< 0.001
Mean DBP (SD), mmHg	67.2 (11.5)	69.3 (10.6)	69.5 (10.8)	69.2 (11.5)	< 0.001
Mean LDL-cholesterol (SD), mg/dL	119.3 (39.2)	120.2 (39.6)	118.9 (38.1)	119.4 (39.0)	0.918
Mean HDL-cholesterol (SD), mg/dL	52.4 (19.6)	49.9 (19.1)	51.6 (19.1)	51.5 (18.9)	0.490
Geometric mean CRP (95% CI), mg/L	1.6 (1.4 – 1.8)	1.7 (1.5 – 1.9)	1.6 (1.4 – 1.8)	1.7 (1.5 – 1.9)	0.663
Mean eGFR (SD), mg/dL	76.4 (17.9)	77.5 (18.6)	76.6 (18.1)	75.1 (18.8)	0.193
Geometric mean physical activity level (95% CI), 1000 METs-min/wk	7.5 (7.0 – 7.9)	7.3 (7.0 – 7.7)	7.0 (6.6 – 7.4)	7.3 (7.0 – 7.7)	0.647

* Quartile cut-points were based on the weighted distribution of FMD (see Methods section). For this reason, the number of participants in each quartile is not equal.

BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FMD = flow-mediated dilation, HDL = high-density lipoprotein, LDL = low-density lipoprotein, MET = metabolic equivalent value, SBP = systolic blood pressure, SD = standard deviation.

Table 2

Prevalence and Prevalence Ratios of Hypertension at Baseline by FMD Quartile

Characteristics	Q4	Q3	Q2	Q1	*P* value*
Levels of FMD, %	≥ 5.9	3.8 – 5.8	2.2 – 3.7	< 2.2	-
Cases of hypertension	319	405	415	485	-
N, at risk	903	917	868	812	-
Prevalence, %	35.6%	44.7%	48.2%	59.7%	< 0.001
Model	**Prevalence Ratio (95% CI)**				
Unadjusted	1.00 (ref)	1.26 (1.12 – 1.40)	1.35 (1.21 – 1.52)	1.68 (1.50 – 1.87)	< 0.001
Model 1†	1.00 (ref)	1.11 (0.98 – 1.24)	1.04 (0.93 – 1.17)	1.17 (1.04 – 1.32)	0.030
Model 2‡	1.00 (ref)	1.12 (0.99 – 1.26)	1.06 (0.94 – 1.20)	1.19 (1.05 – 1.34)	0.017

**P* value represents the linear trend across quartiles (with each quartile represented by the median value within the quartile).

†Model 1 includes adjustment for age, gender, ethnicity, and MESA site.

‡Model 2 includes adjustment for variables in Model 1 and baseline information on body mass index, diabetes, low-density lipoprotein and high-density lipoprotein cholesterol levels, cigarette smoking, current alcohol intake, education level, physical activity, estimated glomerular filtration rate, and C-reactive protein. ref = referent category.

Table 3

Prevalence Ratios of Hypertension at Baseline Per Each Standard Deviation* Decrease in FMD

Model	Prevalence Ratio (95% CI)	*P* value
Unadjusted	1.32 (1.25 – 1.39)	<0.001
Model 1†	1.09 (1.03 – 1.16)	0.003
Model 2‡	1.10 (1.03 – 1.16)	0.003

*Standard deviation of FMD = 3.6%.

†Model 1 adjusted for age, gender, ethnicity, and MESA site.

‡Model 2 adjusted for variables in Model 1 + body mass index, diabetes, low-density lipoprotein and high-density lipoprotein cholesterol levels, cigarette smoking, current alcohol intake, education level, physical activity, estimated glomerular filtration rate, and C-reactive protein.

Table 4

Incident Rates and Relative Risks of Incident Hypertension by FMD Quartile

Characteristics	Q4	Q3	Q2	Q1	*P* value*
Levels of FMD, %	≥ 6.5	4.3 – 6.4	2.6 – 4.2	< 2.6	-
Cases of hypertension	109	148	164	163	-
N, at risk	477	470	484	438	-
Incidence, per 1000 person-years	50.8	70.0	72.8	82.9	< 0.001
Model	**Relative Risk (95% CI)**				
Unadjusted	1.00 (ref)	1.38 (1.14 – 1.67)	1.44 (1.19 – 1.74)	1.64 (1.36 – 1.97)	< 0.001
Model 1†	1.00 (ref)	1.26 (1.04 – 1.52)	1.19 (0.98 – 1.44)	1.18 (0.97 – 1.44)	0.126
Model 2‡	1.00 (ref)	1.20 (0.99 – 1.46)	1.10 (0.90 – 1.34)	1.18 (0.96 – 1.44)	0.180
Model 3§	1.00 (ref)	1.14 (0.93 – 1.38)	1.02 (0.84 – 1.25)	1.14 (0.93 – 1.38)	0.360

**P* value represents the linear trend across quartiles (with each quartile represented by the median value within the quartile).

†Model 1 includes adjustment for age, gender, ethnicity, and MESA site.

‡Model 2 includes adjustment for variables in Model 1 + baseline information on body mass index, diabetes, low-density lipoprotein and high-density lipoprotein cholesterol levels, cigarette smoking, current alcohol intake, education level, physical activity, estimated glomerular filtration rate, and C-reactive protein.

§Model 3 includes adjustment for variables in Model 2 + baseline systolic and diastolic blood pressure levels. ref = referent category.

Table 5

Relative Risk of Incident Hypertension Per Each Standard Deviation* Decrease in FMD

Model	Relative Risk (95% CI)	*P* value
Unadjusted	1.21 (1.08 – 1.35)	<0.001
Model 1†	1.04 (0.93 – 1.16)	0.400
Model 2‡	1.03 (0.92 – 1.15)	0.517
Model 3§	1.00 (0.89 – 1.11)	0.935

*Standard deviation of FMD = 3.6%.

†Model 1 includes adjustment for age, gender, ethnicity, and MESA site.

‡Model 2 includes adjustment for variables in Model 1 + baseline information on body mass index, diabetes, low-density lipoprotein and high-density lipoprotein cholesterol levels, cigarette smoking, current alcohol intake, education level, physical activity, estimated glomerular filtration rate, and C-reactive protein.

§Model 3 includes adjustment for variables in Model 2 + baseline systolic and diastolic blood pressure levels.