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Original Contribution

Structural and Functional Vascular Alterations and Incident Hypertension in Normotensive Adults

The Multi-Ethnic Study of Atherosclerosis

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Vascular abnormalities may exist before clinical hypertension. Using Poisson regression, the authors studied the association of coronary artery calcium (CAC), common carotid intima-media thickness (CIMT), aortic distensibility, and large and small arterial elasticity with incident hypertension among 2,512 normotensive US adults free of cardiovascular disease. Incidence rate ratios for incident hypertension (blood pressure $\geq$140/90 mm Hg or new antihypertensive medication) were calculated. Increased CAC was associated with incident hypertension in demographics-adjusted models (incidence rate ratio (IRR) = 1.35, 95% confidence interval (CI): 1.04, 1.75; IRR = 1.35, 95% CI: 1.02, 1.78; and IRR = 1.59, 95% CI: 1.12, 2.25 for CAC scores of 30–99, 100–399, and $\geq$400, respectively) but was attenuated after further adjustment. Increased common CIMT was associated with incident hypertension (IRR = 1.77, 95% CI: 1.28, 2.46 for quintile 4; IRR = 1.80, 95% CI: 1.28, 2.53 for quintile 5). Participants with the lowest, compared with the highest, aortic distensibility had an increased risk of hypertension (IRR = 1.75, 95% CI: 1.10, 2.79), as did those with the lowest large arterial elasticity (IRR = 1.49, 95% CI: 1.11, 1.99). Lower small arterial elasticity was incrementally associated with incident hypertension starting at quintile 2 (IRR = 2.01, 95% CI: 1.39, 2.91; IRR = 2.47, 95% CI: 1.71, 3.57; IRR = 2.73, 95% CI: 1.88, 3.95; and IRR = 2.85, 95% CI: 1.95, 4.16). Structural and functional vascular abnormalities are independent predictors of incident hypertension. These findings are important for understanding the pathogenesis of hypertension.

arteries; elasticity; hypertension

Abbreviations: MESA, Multi-Ethnic Study of Atherosclerosis; MRI, magnetic resonance imaging.

Hypertension affects almost 30% of the US population and is associated with increased risk of stroke, cardiovascular disease, and mortality (1, 2). Despite this high prevalence and serious health consequences, the pathogenesis of essential hypertension remains largely unknown. One possible mechanism to explain the initiation of hypertension may be vascular abnormalities that develop before the systolic or diastolic pressures become persistently elevated.

Hypertension is characterized by increased arterial stiffness and endothelial dysfunction, which themselves are associated with increased cardiovascular risk (3, 4). Studies suggest that structural and functional blood vessel abnormalities predate the development of clinical hypertension in prehypertensive patients (5, 6). Most recently, large-vessel stiffness (measured by pulse wave velocity) has been associated with rising systolic blood pressure levels among hypertensives and may also predict incident hypertension longitudinally (7). The relation of structural and/or functional vascular abnormalities to incident clinical hypertension is not well understood.

We designed these analyses to study the association between comprehensive subclinical measurements of blood vessel structure and function and the development of incident hypertension in a large, community-based, multiethnic

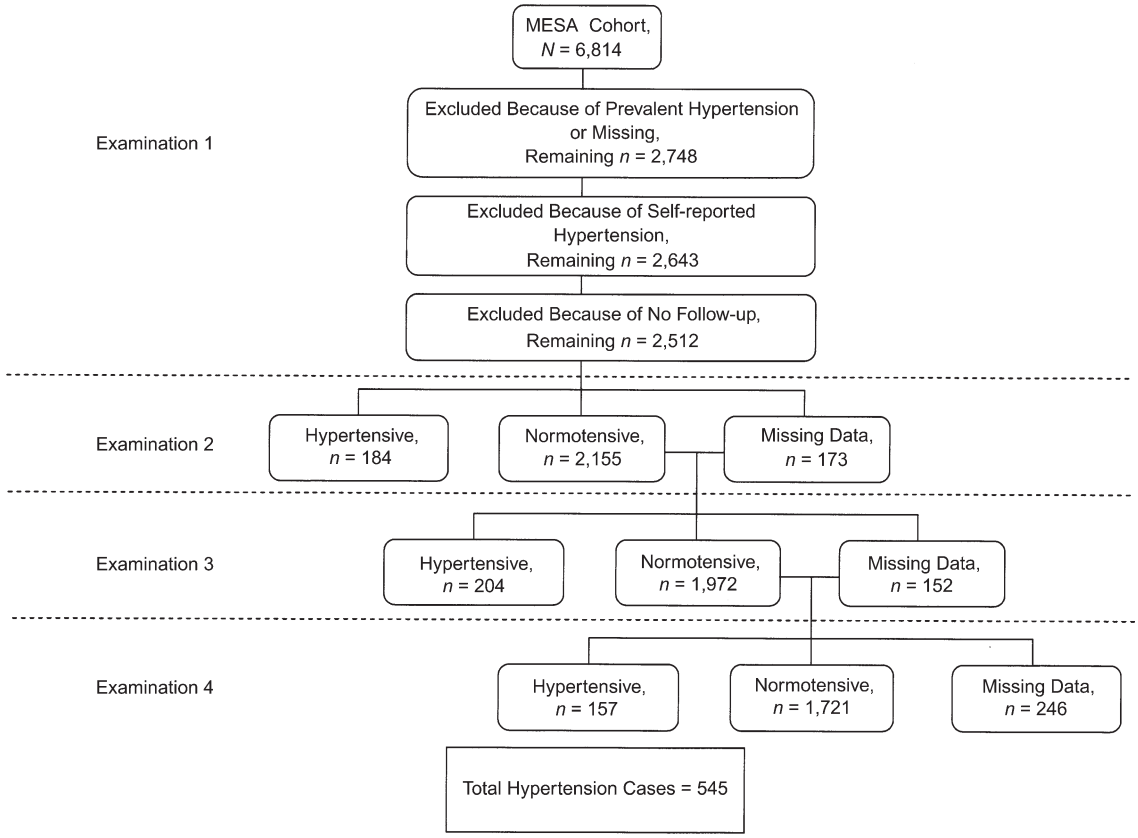

Figure 1. Case ascertainment for each examination of participants in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, United States, 2000–2007. Cohort definition: baseline blood pressure—<130 systolic blood pressure and <80 diastolic blood pressure.

cohort. Understanding associations between subclinical measures of vascular changes and incident hypertension may suggest potential mechanisms of disease, may help in identifying persons at high risk, and may be important in developing prevention strategies.

MATERIALS AND METHODS

Subjects

The Multi-Ethnic Study of Atherosclerosis (MESA), a large study sponsored by the National Heart, Lung, and Blood Institute, aimed to understand subclinical cardiovascular disease and its progression in a multiethnic cohort. Details on study recruitment and design have been previously published (8). Briefly, MESA recruited 6,814 men and women who were aged 45–84 years, who were free of cardiovascular disease, and who self-identified as white, African American, Hispanic, or Chinese American. Subjects were recruited from Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan and the Bronx, New York; and St. Paul, Minnesota, between July 2000 and August 2002. Individuals were excluded from this study if they had physician-diagnosed heart attack, angina, heart failure, stroke, or transient ischemic attack; had atrial fibrillation or had undergone coronary artery bypass grafting, angioplasty, or valve replacement; had a pacemaker; or weighed more than 300 pounds (136 kg). The institutional review boards at all participating centers approved the study, and all participants gave informed consent.

For these analyses, we included those participants who had their blood pressure measured at baseline and were not hypertensive at the baseline visit—defined as having a systolic blood pressure of <130 mm Hg and a diastolic blood pressure of <80 mm Hg—were not using any antihypertensive medication, and reported no history of hypertension. We chose the cutpoint 130/80 mm Hg to increase the likelihood that participants were free of the outcome at the beginning of the study. We excluded participants who had no follow-up data for all subsequent MESA examinations, for a total 2,512 participants available for these analyses (Figure 1).

Primary outcome ascertainment: incident hypertension

Blood pressure and medication use were assessed during the second, third, and fourth follow-up MESA examinations. During each examination, 3 blood pressure measurements

were obtained 5 minutes apart in the seated position by using an automated oscillometric sphygmomanometer (Dinamap; Critikon, General Electric, Madison, Wisconsin). The mean of the second 2 measurements was used for analysis. Participants were asked to bring all medications to each examination, and medication use was assessed by medication inventory. Incident hypertension was defined as a systolic blood pressure of $\geq$140 mm Hg, a diastolic blood pressure of $\geq$90 mm Hg, or the use of medication for hypertension during the second, third, or fourth follow-up examinations. Because angiotensin-converting enzyme inhibitors and angiotensin II antagonists may be prescribed to diabetics who do not have hypertension, sensitivity analyses were conducted to explore whether study findings were similar after excluding participants who had diabetes at baseline. A flowchart of case ascertainment for each examination is presented in Figure 1.

Primary predictors

Subclinical measures of structural vascular changes. We defined structural measures as those that assess the anatomy of the vessel, including calcification and intima size. Coronary artery calcification was measured by using computed tomography of the chest. Three field centers used an electrocardiogram-triggered electron-beam scanner (Imatron C-150; Imatron, San Francisco, California), and the others used prospectively electrocardiogram-triggered scan acquisition at 50% of the R-R interval with a multidetector computed tomography system (Lightspeed; General Electric Medical Systems, Waukesha, Wisconsin, or Volume Zoom; Siemens, Erlanger, Germany). All participants are scanned over phantoms of known physical calcium concentration. Scans were read centrally at the Harbor-UCLA Research and Education Institute in Torrance, California, to identify and quantify coronary calcification, calibrated according to the readings of the calcium phantom. Details on measurement of coronary artery calcification in MESA have been previously published (8, 9).

The intima-media thickness of the common and internal carotid arteries was measured on the right and left sides of the neck by using high-resolution B-mode ultrasound (Logiq 700 ultrasound machine; General Electric Medical Systems). This procedure has previously been described in detail (8, 9). In brief, 4 longitudinal images were obtained on each side of the neck: 1 of the common carotid artery and 3 of the internal carotid artery centered on the carotid bulb. All scans were read in a central location, using a standard protocol at the Tufts Medical Center, Boston, Massachusetts.

Subclinical measures of functional vascular changes. We defined measures of functional vascular changes as those that assess the ability of vessels to adapt to distending pressures throughout the cardiac cycle. For the large and small artery elasticity index, MESA investigators used the HDI PulseWave CR-2000 Research CardioVascular Profiling Instrument (Hypertension Diagnostics, Inc., Eagen, Minnesota) to acquire and analyze pulse waveforms from the radial artery. Using the pulse contour analysis technique, this method enables both large and small arterial characteristics to be studied. By incorporating pressure fluctuations, it provides a way to study changes in large and small arteries by measuring their response to distending pressures throughout the cardiac cycle. This process is accomplished by analyzing the diastolic pulse contour and calculating each parameter by using a third-order, 4-element Windkessel modified model. Briefly, this model divides total systemic arterial compliance into contributions from the pool of large arteries (capacitive) and from the pool of small arteries (oscillatory). The elasticity indices are then estimated by multiplying these parameters by systemic vascular resistance, which is estimated by dividing the mean arterial pressure by cardiac output (in liters/minutes). Cardiac output was calculated after directly measuring ejection time (in milliseconds) from the pulse waveform and including heart rate, height, age, and body surface area (in square millimeters). These estimates have been shown to be comparable to corresponding findings using direct invasive techniques (10), with high degrees of correlation and high reproducibility in repeated measures (11, 12).

Because the estimates of large arterial elasticity and small arterial elasticity were calculated based on measures including mean arterial blood pressure, heart rate, age, weight, and height, easily obtained physical measures that may be associated with hypertension, we performed 2 sensitivity analyses in an attempt to isolate the information given by the pulse waveform only. Because these values estimate large arterial elasticity and small arterial elasticity only by estimating systemic vascular resistance, in our first sensitivity analysis, we multiplied large arterial elasticity and small arterial elasticity by systemic vascular resistance to isolate the information from the pulse waveform only. In our second sensitivity analysis, we constructed a model adjusting for age, gender, race/ethnicity, income, education, diabetes, height, weight, heart rate, pulse pressure, C-reactive protein, urine albumin/creatinine ratio, and cystatin C. This procedure was performed to adjust for variables included in the formulae to estimate elasticity.

The magnetic resonance imaging (MRI) aortic distensibility index was calculated by assessing the diameter of the aorta at end systole and end diastole using MRI (1.5 T whole-body MRI systems, Signa CV/i or Signa LX; General Electric Healthcare, Chalfont St. Giles, United Kingdom) of the ascending aorta. Aortic wall measurements were performed by using FLOW software (Medis, Leiden, the Netherlands). A detailed description of the protocol has been previously published (13, 14). Briefly, these measures were incorporated into the following equation to estimate aortic distensibility throughout the cardiac cycle: aortic distensibility = [(maximum aortic cross-sectional area − minimum aortic cross-sectional area)/minimum area]/pulse pressure. Pulse pressure used was the average pulse pressure of measures immediately before and after the MRI examination in the supine position.

Covariates

Age, gender, race/ethnicity, socioeconomic status (i.e., income, education, occupation), past or present smoking, and diagnosed diabetes were ascertained by questionnaire at the baseline visit. Height and weight were measured with participants wearing light clothing and no shoes. Body

mass index was calculated as weight in kilograms divided by height in meters squared. Fasting blood was collected and stored at −70°F (−56.7°C) until needed for the appropriate assays, including high density lipoprotein cholesterol, triglycerides, glucose, and C-reactive protein. Low density lipoprotein cholesterol was calculated by using the Friedewald equation. Serum creatinine was measured by rate reflectance spectrophotometry using thin film adaptation of the creatinine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, New York) at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, Minnesota). Cystatin C was measured by using a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring Inc., Deerfield, Illinois). Estimated glomerular filtration rate was calculated by using the Modification of Diet in Renal Disease equation (15) for creatinine and the equation $76.7 \times \text{cys C}^{-1.19}$ for cystatin C (16). Urine albumin and creatinine were measured by nephelometry and the rate Jaffe reaction, respectively. A urine albumin to creatinine ratio was calculated, and a ratio of $\geq$30 mg/g was defined as albuminuria.

Statistical analysis

First, we evaluated sociodemographic and clinical characteristics of the study cohort. We then used Poisson (log-link) regression models to study the association of subclinical vascular changes and incident hypertension. We modeled the incidence rate ratio of hypertension as a function of each subclinical measure of vascular dysfunction with robust variance estimation and an offset for the log of follow-up time. Risk time was calculated as elapsed time from baseline to the fourth MESA examination, unless a participant either developed hypertension or was lost to follow-up at the time of the second or third MESA examination, in which case risk time was calculated as elapsed time from baseline to the second or third examination. We calculated unadjusted hypertension rates as the number of events divided by the person-years at risk and then examined their association with each of the vascular measures.

The primary predictors were examined as continuous variables (per standard deviation or per doubling for coronary artery calcification) and were also categorized into quintiles based on prior literature (9, 17–20). We used nested models, with the first model adjusted for sociodemographic variables: age, gender, and self-reported race/ethnicity. The second model adjusted for age, gender, race/ethnicity, income, education, diabetes, body mass index, C-reactive protein, urine albumin:creatinine ratio, cystatin C, and baseline systolic blood pressure. These variables were chosen a priori based on available literature on risk factors for hypertension (21).

RESULTS

Study cohort

Among the 2,512 MESA participants in these analyses, the mean age of our cohort was 58 years (standard deviation, 10), 19% had an income of less than $20,000 per year, and 58% had less than a college education. Approximately 48% (n = 1,215) were either past or current smokers, 145 (6%) had diabetes, and 123 (5%) had chronic kidney disease, which was defined as estimated glomerular filtration rate <60 mL/minute per 1.73 m^2 per the Modification of Diet in Renal Disease. Characteristics of study participants are detailed in Table 1.

We compared baseline participant characteristics with those of the 131 participants who did not return for any follow-up visits. Age, gender, baseline blood pressure, diabetes, body mass index, and cystatin C levels were similar. Those lost to follow-up were more likely to be of Hispanic origin.

Incident hypertension

Overall, 545 cases of incident hypertension were identified among the 2,512 participants, corresponding to 22% of the cohort. Forty percent (n = 218) were identified by high blood pressure alone, and 55% (n = 302) were identified by the use of a new antihypertensive medication alone. Mean follow-up time was 4.3 years (standard deviation, 1.1).

Structural vascular measures and incident hypertension

Increased coronary artery calcification was associated with incident hypertension in models adjusted for age, gender, and race/ethnicity, starting at a coronary artery calcification score of >30 (Table 2). However, this association was attenuated after further adjustment.

Increased maximum common carotid intima-media thickness was significantly and incrementally associated with incident hypertension starting at the third quintile after adjustment for age, gender, and race/ethnicity. This association was significant after full adjustment starting at the fourth quintile. Those in the fifth quintile of common carotid intima-media thickness were at an almost 2-fold risk of incident hypertension (Table 3).

Functional vascular measures and incident hypertension

Decreased aortic distensibility and decreased large and small arterial elasticity were significantly associated with increased risk of incident hypertension. The magnitude of these associations varied by vessel caliber.

Lower aortic distensibility was also associated with increased risk of hypertension. In analyses adjusted for age, gender, and race/ethnicity, risk of incident hypertension increased with lower distensibility. In the fully adjusted model, a graded association persisted, but only those with the lowest aortic distensibility (i.e., the highest aortic stiffness) were at higher risk of developing hypertension (Table 4).

Lower large arterial elasticity was also associated with incident hypertension, but this association was significant only for those in the fifth quintile (lowest elasticity) compared with those with the highest large arterial

Table 1. Characteristics of 2,512 MESA Study Cohort Participants Without Prevalent Hypertension at Baseline, United States, 2000–2007

	No.	%	Mean (SD)
Age, years			58.1 (9.6)
Female	1,368	54	
Race/ethnicity			
White	1,114	44	
Chinese American	347	14	
African American	467	19	
Hispanic	584	23	
Income group, $			
<20,000	458	19	
20,000–34,999	465	19	
35,000–49,999	373	15	
50,000–99,999	734	30	
≥100,000	434	18	
Education <college	1,460	58	
No health insurance	272	11	
Current smoker	376	15	
Current alcohol consumption	1,531	74	
Diabetes	145	6	
Impaired fasting glucose	234	9	
Body mass index, kg/m^2			27.0 (5.1)
Systolic blood pressure, mm Hg			110 (10)
Diastolic blood pressure, mm Hg			67 (8)
LDL cholesterol, mg/dL			119 (31)
HDL cholesterol, mg/dL			52 (15)
Triglycerides, mg/dL			122 (77)
C-reactive protein, mg/L[a]			1.5 (0.7, 3.6)
Serum creatinine, mg/dL			0.93 (0.18)
Cystatin C, mg/L			0.84 (0.15)
MDRD eGFR, mL/minute per 1.73 m^2			81.4 (15.0)
Cystatin C eGFR, mL/minute			98.6 (20.4)
Urine albumin:creatinine ratio, mg/g[a]			4.1 (2.9, 6.6)
Medication use			
Estrogen (among females)	362	26	
NSAIDs and/or COX_2 inhibitors	110	4	
Thyroid agents	151	6	

Abbreviations: COX_2, cyclooxygenase-2; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; MDRD, Modification of Diet in Renal Disease; MESA, Multi-Ethnic Study of Atherosclerosis; NSAIDs, nonsteroidal antiinflammatory drugs; SD, standard deviation.

[a] Median (interquartile range).

elasticity, after full adjustment (Table 4). When we modeled our predictor as large arterial elasticity × systemic vascular resistance, the findings were not materially different.

In unadjusted and adjusted analyses, lower small arterial elasticity was significantly and incrementally associated with incident hypertension even at the second quintile. Those in the fifth quintile (lowest elasticity) had an almost 3-fold risk of developing hypertension compared with those with the highest elasticity levels (Table 4). When we modeled our predictor as small arterial elasticity × systemic vascular resistance, the findings were not materially different.

Sensitivity analyses

To avoid case misclassification by including participants who may have begun using an antihypertensive drug for an indication other than hypertension, we performed a sensitivity analysis as follows: we reassigned to ''noncase'' status those who were identified as having hypertension because they used an antihypertensive medication alone (angiotensin-converting enzyme/angiotensin receptor blockers) AND either had 1) diabetes at baseline or follow-up prior to hypertension diagnosis and chronic kidney disease (estimated glomerular filtration rate <60 mL/minute per 1.73 m^2) at baseline or 2) an adverse cardiovascular event during the follow-up period and prior to their hypertension diagnosis ($n = 82$). The findings were not significantly different.

Another sensitivity analysis of the whole cohort was performed for the elasticity measures by constructing a model adjusting for age, gender, race/ethnicity, income, education, diabetes, height, weight, heart rate, pulse pressure, C-reactive protein, urine albumin:creatinine ratio, and cystatin C. The results were not materially different.

DISCUSSION

Hypertension is a costly public health problem with a large burden of disease complications, including cardiovascular disease, chronic kidney disease, and increased mortality (22). However, the pathogenesis of essential hypertension is not known. In these analyses, we found that structural measures (higher common carotid intima-media thickness by ultrasound) and functional measures, lower aortic distensibility by MRI, and lower large and small arterial elasticity by pulse contour analysis are independent predictors of incident hypertension. Most importantly, we found that the strength of these associations varied significantly by vessel caliber, with the strongest associations observed for the index relating to the pool of small arteries. These findings suggest that subclinical vascular abnormalities present before the onset of hypertension may be important in the pathway of development of hypertension.

Our findings confirm prior findings that subclinical measures of central stiffness predict incident hypertension (7, 23, 24). Increased pulse wave velocity (a measure of central stiffness) predicted hypertension among only those participants followed up for more than 4 years in the Baltimore Longitudinal Study of Aging. Dernellis and Panaretou (23) found that aortic stiffness, measured by echocardiography, was associated with incident hypertension in a Greek cohort. Moreover, Liao et al. (24) found that arterial stiffness

Table 2. Association of Coronary Artery Calcification With Incident Hypertension Among MESA Participants, United States, 2000–2007

Baseline Group of Coronary Artery Calcification, Agatston units	No.	No. of Cases	Incidence Rate[a]	Model 1[b]		Model 2[c]	
				IRR	95% CI	IRR	95% CI
0	1,593	284	4.0	1.00		1.00	
1–29	354	90	6.1	1.26	0.99, 1.59	1.17	0.92, 1.47
30–99	216	63	7.0	1.35	1.04, 1.75	1.20	0.92, 1.56
100–399	238	67	7.0	1.35	1.02, 1.77	1.05	0.78, 1.40
≥400	111	41	9.7	1.59	1.12, 2.25	1.26	0.90, 1.77
Per doubling[d]	919	261	6.9	1.04	0.99, 1.09	1.01	0.96, 1.06

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; MESA, Multi-Ethnic Study of Atherosclerosis.

[a] Per 100 person-years.

[b] Adjusted for age, gender, and race/ethnicity.

[c] Adjusted for age, race/ethnicity, gender, income, education, diabetes, body mass index, ln(C-reactive protein), ln(albumin:creatinine ratio), cystatin C, and baseline systolic blood pressure.

[d] Includes those with a baseline coronary artery calcification score of >0.

measured by ultrasound of the left common carotid artery was associated with hypertension defined as >160/95 mm Hg, which already represents stage II hypertension (22), or the use of an antihypertensive medication. Our study extends these findings to both structural and functional measures of subclinical vascular disease in a large multiethnic cohort.

It is noteworthy that, in our study, the strength of the associations varied by vessel caliber. Even small changes in small arterial elasticity (the second quintile) were independently associated with hypertension, whereas only the highest quintiles of large arterial elasticity and aortic distensibility had independent associations. It is possible that the small arteries, which represent the oscillatory compliance of the vascular tree, are uniquely important in the development and initiation of hypertension, relative to the vascular stiffness and atherosclerotic plaque deposition of the larger vessels.

The fact that increased coronary artery calcification was not associated with incident hypertension after adjustment for comorbidities and inflammation suggests that deposition of calcium may play a less important, independent role in the incidence of hypertension than do other changes in the endothelium that affect function or structure of arteries. However, it is also possible that vascular calcium is an important contributor to hypertension only at much higher levels than those observed in MESA.

Our study is novel in that it includes different techniques to measure subclinical cardiovascular disease (ultrasound, MRI, and pulse contour analysis), which significantly

Table 3. Association of Common Carotid Intima-Media Thickness (mm) With Incident Hypertension Among MESA Participants, United States, 2000–2007

Baseline Group of Maximum Common Carotid Intima-Media Thickness, mm[a]	No.	No. of Cases	Incidence Rate[b]	Model 1[c]		Model 2[d]	
				IRR	95% CI	IRR	95% CI
0.44–0.67	508	50	2.2	1.00		1.00	
0.67–0.75	502	66	2.9	1.21	0.85, 1.73	1.10	0.77, 1.56
0.75–0.83	496	96	4.5	1.73	1.24, 2.43	1.33	0.95, 1.87
0.83–0.93	490	142	6.9	2.48	1.79, 3.42	1.78	1.28, 2.46
0.93–2.16	498	185	9.4	2.93	2.10, 4.08	1.80	1.28, 2.53
Per 1 SD	2,494	539	5.0	1.36	1.24, 1.48	1.22	1.12, 1.32

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation.

[a] Categories overlap because all values were rounded to 2 decimal places.

[b] Per 100 person-years.

[c] Adjusted for age, gender, and race/ethnicity.

[d] Adjusted for age, race/ethnicity, gender, income, education, diabetes, body mass index, ln(C-reactive protein), ln(albumin:creatinine ratio), cystatin C, and baseline systolic blood pressure.

Table 4. Association of Functional Vascular Measures With Incident Hypertension Among MESA Participants, United States, 2000–2007

Baseline Group[a]	No.	No. of Cases	Incidence Rate[b]	Model 1[c]		Model 2[d]	
				IRR	95% CI	IRR	95% CI
Aortic distensibility, mm $Hg^{-1} \times 10^3$							
3.05–24.2	289	26	1.9	1.00		1.00	
2.29–3.05	289	41	3.2	1.41	0.87, 2.28	1.12	0.70, 1.81
1.72–2.29	289	60	4.8	1.99	1.26, 3.14	1.45	0.93, 2.27
1.24–1.71	289	67	5.4	1.95	1.22, 3.09	1.44	0.91, 2.26
0–1.24	290	95	8.1	2.61	1.65, 4.15	1.75	1.10, 2.79
Per −1 SD	1,446	289	4.6	1.53	1.25, 1.88	1.31	1.08, 1.59
Large artery elasticity, mL/mm Hg × 10							
19.0–55.8	467	72	3.4	1.00		1.00	
15.8–19.0	467	69	3.3	1.04	0.76, 1.43	0.91	0.67, 1.24
13.3–15.8	467	84	4.1	1.22	0.90, 1.65	0.96	0.71, 1.30
10.8–13.3	467	116	5.7	1.67	1.24, 2.24	1.22	0.90, 1.63
3.3–10.8	468	166	9.0	2.25	1.67, 3.03	1.49	1.11, 1.99
Per −1 SD	2,336	507	5.0	1.34	1.17, 1.54	1.15	1.03, 1.29
Small artery elasticity, mL/mm Hg × 10							
7.86–17.32	467	35	1.6	1.00		1.00	
5.67–7.86	467	87	4.2	2.48	1.70, 3.62	2.01	1.39, 2.91
4.06–5.67	467	116	5.8	3.17	2.19, 4.60	2.47	1.71, 3.57
2.70–4.06	467	123	6.2	3.34	2.28, 4.87	2.73	1.88, 3.95
0.81–2.70	468	146	7.8	3.68	2.52, 5.38	2.85	1.95, 4.16
Per −1 SD	2,336	507	5.0	1.57	1.40, 1.75	1.48	1.32, 1.66

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation.

[a] Some categories overlap because all values were rounded to 2 decimal places.

[b] Rate per 100 person-years.

[c] Adjusted for age, gender, and race/ethnicity.

[d] Adjusted for age, race/ethnicity, gender, income, education, diabetes, body mass index, ln(C-reactive protein), ln(albumin:creatinine ratio), cystatin C, and baseline systolic blood pressure.

strengthens our conclusions and reduces the bias that may occur from using only one technique. Moreover, these measures have been associated with adverse events. For example, common carotid intima-media thickness has been shown to predict adverse cardiovascular events (18, 25), and lower arterial elasticity has been found to be associated with cardiovascular risk factors in healthy adults (26), with early kidney dysfunction (20), and with cardiovascular disease (27). In addition, this large, multiethnic cohort is fairly representative of the US population, free of cardiovascular disease at baseline. To minimize noise from those close to the threshold, we also included only those participants with blood pressures of <130/80 mm Hg.

Our study has certain limitations. We did not have invasive measures of endothelial function. We used pulse contour analysis to estimate large and small arterial elasticity. This method makes certain assumptions about the arterial tree when using the modified Windkessel model of circulation. Although some studies have suggested low reliability of the estimates, which may reduce the validity of the methodology (28), this method has been shown to correlate with invasive measures of arterial compliance, and it has high reproducibility (10, 11). Moreover, lower elasticity by this measure has been associated with higher prevalence of cardiovascular risk factors among young adults (26), with early kidney dysfunction (20) and reported adverse cardiovascular events in one US cohort (27). We ascertained some cases by the use of a newly prescribed antihypertensive medication, which may result in misclassification due to other indications for some of these medicines, including the report of subclinical abnormalities to treating physicians. Misclassification may also have occurred if a participant started and then stopped using a medication before a follow-up visit. However, our sensitivity analyses reclassifying diabetics, those with kidney disease, or those who had an adverse cardiovascular event during follow-up showed similar results.

In summary, we found that structural and functional measures of subclinical vascular disease are independent predictors of incident hypertension in a multiethnic cohort and that small arterial elasticity is the earliest predictor. Our findings are an important step in elucidating possible

pathways for the development of idiopathic hypertension. Future studies should focus on elucidating whether these measures may be cost-effective in identifying persons at risk of hypertension and who may benefit from earlier treatment.

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