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Association of Normal Systolic Blood Pressure Level With Cardiovascular Disease in the Absence of Risk Factors

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IMPORTANCE The risk of atherosclerotic cardiovascular disease (ASCVD) at currently defined normal systolic blood pressure (SBP) levels in persons without ASCVD risk factors based on current definitions is not well defined.

OBJECTIVE To examine the association of SBP levels with coronary artery calcium and ASCVD in persons without hypertension or other traditional ASCVD risk factors based on current definitions.

DESIGN, SETTING, AND PARTICIPANTS A cohort of 1457 participants free of ASCVD from the Multi-Ethnic Study of Atherosclerosis who were without dyslipidemia (low-density lipoprotein cholesterol level ≥160 mg/dL or high-density lipoprotein cholesterol level <40 mg/dL), diabetes (fasting glucose level ≥126 mg/dL), treatment for hyperlipidemia or diabetes, or current tobacco use, and had an SBP level between 90 and 129 mm Hg. Participants receiving hypertension medication were excluded. Coronary artery calcium was classified as absent or present and adjusted hazard ratios (aHRs) were calculated for incident ASCVD. The study was conducted from March 27, 2018, to February 12, 2020.

EXPOSURES Systolic blood pressure.

MAIN OUTCOMES AND MEASURES Presence or absence of coronary artery calcium and incident ASCVD events.

RESULTS Of the 1457 participants, 894 were women (61.4%); mean (SD) age was 58.1 (9.8) years and mean (SD) follow-up was 14.5 (3.9) years. There was an increase in traditional ASCVD risk factors, coronary artery calcium, and incident ASCVD events with increasing SBP levels. The aHR for ASCVD was 1.53 (95% CI, 1.17-1.99) for every 10-mm Hg increase in SBP levels. Compared with persons with SBP levels 90 to 99 mm Hg, the aHR for ASCVD risk was 3.00 (95% CI, 1.01-8.88) for SBP levels 100 to 109 mm Hg, 3.10 (95% CI, 1.03-9.28) for SBP levels 110 to 119 mm Hg, and 4.58 (95% CI, 1.47-14.27) for SBP levels 120 to 129 mm Hg.

CONCLUSIONS AND RELEVANCE Beginning at an SBP level as low as 90 mm Hg, there appears to be a stepwise increase in the presence of coronary artery calcium and the risk of incident ASCVD with increasing SBP levels. These results highlight the importance of primordial prevention for SBP level increase and other traditional ASCVD risk factors, which generally seem to have similar trajectories of graded increase in risk within values traditionally considered to be normal.

Invited Commentary
Author Audio Interview
Supplemental content

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The 2017 American College of Cardiology/American Heart Association Blood Pressure Treatment Guidelines reduced the systolic blood pressure (SBP) level that defines hypertension from 140 to 130 mm Hg.[1] However, while guideline recommendations focus on the cut point at which there is likely to be a net benefit to pharmacologic treatment, many individuals classified as having low risk based on traditional atherosclerotic cardiovascular disease (ASCVD) risk factors have subclinical atherosclerosis as measured by the presence of coronary artery calcium and may therefore not truly be at the lowest risk.[2-5]

Populations in nonindustrialized countries have little to no increase in SBP levels with age, while SBP levels typically increase with age in countries with industrialized diets and lifestyles.[6-9] This age-associated increase in SBP level among persons living in industrialized areas is generally attributed to differences in modifiable risk factors, including increased sodium intake, decreased fruit/vegetable intake, obesity, and low physical activity level. These differences in SBP level trajectories between populations in industrialized and nonindustrialized countries have important implications, because atherosclerosis is a slowly progressive disease and the lower an individual's lifetime exposure to ASCVD risk factors, such as increased SBP level, the lower their probable risk for a future ASCVD event.[10-12] However, it is uncertain whether the association between SBP level and an increased risk for ASCVD is present among healthy individuals without either hypertension or other traditional ASCVD risk factors. In addition, prior studies have typically used a reference SBP level less than 115 mm Hg or less than 120 mm Hg to define a normal SBP level, and it is uncertain whether there is a lower SBP level at which the risk for incident ASCVD plateaus or increases (eg, a J-point).[13-16]

The identification and better understanding of the SBP level at which the risk for subclinical atherosclerosis and incident ASCVD increases among healthy individuals without hypertension or ASCVD risk factors based on current definitions is important to understand whether there is a threshold below which SBP level is not associated with an increased risk for ASCVD and whether population-level primordial prevention strategies may be important for individuals with a normal SBP level and without traditional ASCVD risk factors based on current definitions.

Key Points

Question Is there an association between normal systolic blood pressure values as currently defined and atherosclerotic cardiovascular disease among persons without traditional cardiovascular disease risk factors?

Findings In this cohort study including 1457 participants without atherosclerotic cardiovascular disease, beginning with a systolic blood pressure level of 90 mm Hg, there was a stepwise increase in the prevalence of traditional atherosclerotic cardiovascular disease risk factors, coronary artery calcium, and the risk of atherosclerotic cardiovascular disease. For every 10-mm Hg increase in systolic blood pressure, there was a 53% higher risk for atherosclerotic cardiovascular disease.

Meaning These results highlight the importance of primordial prevention to maintain optimal systolic blood pressure levels as well as optimal values of other traditional atherosclerotic cardiovascular disease, all of which generally have similar trajectories of risk within conventionally considered normal ranges.

Methods

The present study was conducted from March 27, 2018, to February 12, 2020. This analysis included participants with an SBP level of 90 to 129 mm Hg who had a baseline coronary artery calcium scan as part of the Multi-Ethnic Study of Atherosclerosis (MESA), which is a community-based, multiethnic cohort free from known ASCVD at enrollment that has been described in detail elsewhere.[17] The MESA cohort was designed to include a racially diverse group of participants and they self-reported their race/ethnicity according to the following prespecified groups: white (non-Hispanic), black (non-Hispanic), Chinese, or Hispanic. The institutional review board at each MESA study site approved the protocol; the present study is approved within the MESA protocol. Data are deidentified. All participants provided written informed consent and received reimbursement for travel expenses. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

We defined ASCVD risk factors for this analysis based on traditional categorical ASCVD risk factors that are included in the 2013 pooled cohort equations, the 2018 American Heart Association/American College of Cardiology Guideline on the Management of Blood Cholesterol, 2019 Guideline on the Primary Prevention of Cardiovascular Disease, and prior studies that have defined the absence of ASCVD risk factors.[18-21] We used participant variables measured at MESA visit 1 (2000-2002) and excluded participants if they had dyslipidemia (low-density lipoprotein cholesterol [LDL-C] level ≥160 mg/dL, high-density lipoprotein cholesterol [HDL-C] level <40 mg/dL [to convert to millimoles per liter, multiply by 0.0259], or reported use of a cholesterol-lowering medication, n = 2945), had diabetes (fasting glucose level ≥126 mg/dL [to convert to millimoles per liter, multiply by 0.0555] or use of blood glucose–lowering medication, n = 344), or currently used tobacco products (n = 442). Participants with an SBP level less than 90 mm Hg (n = 56), 130 mm Hg or higher (n = 1155), or were prescribed medication for hypertension (n = 416) were also excluded, leaving a total of 1457 participants included in this analysis. After these exclusions, there were no participants missing an SBP level reported at MESA visit 1. We did not exclude participants with isolated diastolic hypertension (n = 91) among whom the mean (SD) diastolic BP (DBP) was 83.1 (2.9) mm Hg, because it is uncertain whether isolated diastolic hypertension is associated with a significantly increased risk for ASCVD.[22-24]

An automated sphygmomanometer (Dinamap Pro 100, GE Healthcare) was used to measure resting, seated BP in the participants' right arm.[25] Three BP measurements were taken, with the mean of the second and third measurements used for

this analysis. A history of ever smoking was defined as having smoked 100 or more cigarettes in a participant's lifetime. Hemoglobin A_{1c} level, which was measured at MESA visit 2 (but not visit 1), was used to define prediabetes based on a reference range of 5.7% to 6.4% (to convert to proportion of total hemoglobin, multiply by 0.01). Carotid distensibility was calculated via B-mode ultrasonographic scanning in 1409 MESA participants (98%) for this study and aortic distensibility was measured via magnetic resonance imaging using the descending thoracic aorta in 887 MESA participants (53%) for this study. A larger or higher distensibility value indicates a more elastic artery, while a lower distensibility value indicates a stiffer artery. The measurement techniques for determining distensibility have been described in detail elsewhere.[26]

Coronary artery calcium was measured using the Agatston method at MESA visit 1, with half the study sites using electron beam computed tomographic imaging and half using multidetector computed tomographic imaging.[27-29] A calcium phantom was scanned alongside participants to standardize results between field centers, and all coronary artery calcium scans were read at a central reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA). There was an interobserver κ value of 0.90 (95% CI, 0.81-0.99) and interscan κ value of 0.92 (95% CI, 0.90-0.94) for the presence of coronary artery calcification.[29] The number of coronary arteries with any coronary artery calcium was summed and diffuse coronary artery calcium was defined as the presence of coronary artery calcium in 2 or more coronary arteries.[30]

The other outcome of interest for this analysis was incident ASCVD, which was defined as fatal or nonfatal (1) incident coronary heart disease, (2) incident stroke, or (3) other incident ASCVD. Hospital and medical records were used to make a diagnosis of incident ASCVD, which was adjudicated by 2 trained physicians according to prespecified criteria.[31]

Statistical Analysis

We calculated the unadjusted and age-adjusted rates of incident ASCVD per 1000 person-years of observation by SBP groups and performed nonparametric testing to determine the significance of trends for ASCVD event rates across SBP levels. We performed progressively adjusted Cox proportional hazard ratio (aHR) testing to describe the risk for incident ASCVD for every 10-mm Hg increase in SBP. We also performed progressively adjusted Cox proportional HR testing to examine the hazard for incident ASCVD by SBP group with an SBP level of 90 to 99 mm Hg as the reference group. Model 1 includes age, sex, and race/ethnicity; model 2 additionally includes DBP level, total cholesterol level, HDL-C level, fasting blood glucose level, body mass index, income, and educational level. The proportional hazards assumption was met based on Schoenfeld residual testing.[32]

To further examine the association between SBP level and ASCVD, we calculated a restricted cubic spline with a reference value of 100 mm Hg allowing for 3 knots, which were selected based on Harrell's[33] recommended percentiles at SBP values of 97.5, 111.5, and 125 mm Hg. This restricted cubic spline was adjusted for age, sex, race/ethnicity, DBP level, total cholesterol level, HDL-C level, fasting blood glucose level, body mass index, income, educational level, ever-smoker status, and prediabetes.

We also performed sensitivity analyses excluding participants with a DBP level greater than or equal to 80 mm Hg (isolated diastolic hypertension) and those who did not meet the predefined categorical cut points, but who had risk factor values above what are typically defined as normal on a continuous scale: (1) LDL-C level 130 mg/dL or higher, (2) fasting glucose level 100 mg/dL, or (3) women with an HDL-C level less than 50 mg/dL. In addition, we tested age as a squared variable to evaluate for residual confounding by age. A 2-tailed, paired *P* value <.05 was considered statistically significant.

To examine whether changes in SBP levels and the burden of other traditional risk factors over time may bias our results, we determined the means of SBP levels and other traditional risk factor variables between MESA visit 1 (2000-2002), visit 2 (2002-2004), and visit 3 (2004-2005). To ensure that our results show the prospective association between SBP level and ASCVD events, we excluded participants with an ASCVD event between MESA visits 1 through 3 (n = 8). In addition, we did not include the SBP level from later MESA visits (eg, visit 5) in determination of the mean values, because doing so would significantly reduce the number of observed events and statistical power. Statistical analysis was performed using Stata, version 15.1 (StataCorp).

Results

The mean (SD) age of participants was 58.1 (9.8) years and 894 participants (61.4%) were women (**Table 1**). Overall, the mean SBP level was 111.3 (10.0) mm Hg, the mean DBP level was 67.5 (8.3) mm Hg, and the median 10-year pooled cohort equations ASCVD risk was 3.0% (interquartile range, 1.1%-6.7%). The proportion of women in each SBP decile decreased with increasing SBP level. There was an increase in the mean values for traditional ASCVD risk factors, but no difference in income or educational level with increasing SBP level. Carotid and aortic distensibility were significantly lower with higher SBP values, consistent with increasing carotid and aortic stiffness. Nearly a third of participants had coronary artery calcium detected at baseline. Over a mean follow-up of 14.5 (3.9) years, there were 94 incident ASCVD events. Among participants in our study with an SBP level less than 110 mm Hg, the median 10-year ASCVD risk was 1.7% (interquartile range, 0.7%-4.5%) and they experienced nearly a third of the total ASCVD events (27/94 [29%]). The proportion of participants with coronary artery calcium and diffuse coronary artery calcium increased in a stepwise manner with increasing SBP level in our sample from 19.7% for participants with an SBP level of 90 to 99 mm Hg to 40.8% for participants with an SBP level of 120 to 129 mm Hg (*P* < .001 for trend) (**Figure 1**). The rate of incident ASCVD events per 1000 person-years also increased in a graded manner with increasing SBP levels, with unadjusted SBP level 90 to 99 mm Hg, 1.3; 100 to 109 mm Hg, 3.8; 110 to 119 mm Hg, 4.3; and 120 to 129 mm Hg, 7.8 (*P* < .001 for trend). The overall age-adjusted event rate per 1000 person-years was low, at 4.7 per 1000 person-years; other age-

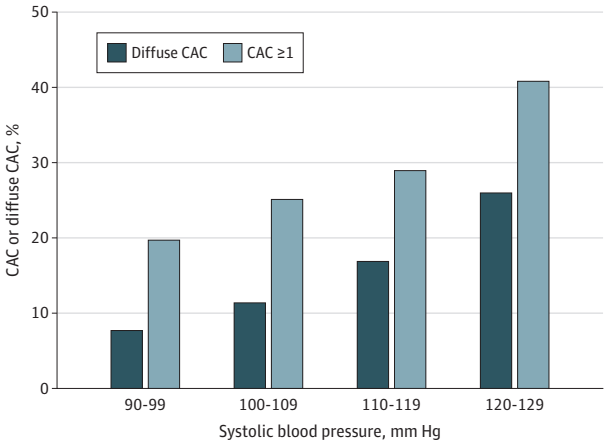
Table 1. Participant Characteristics

Characteristic	All participants (n = 1457)	SBP 90-99 (n = 208)	100-109 (n = 414)	110-119 (n = 504)	120-129 (n = 331)	*P* value for trend
Age, mean (SD), y	58.1 (9.8)	55.7 (8.9)	56.5 (9.0)	58.1 (9.7)	61.8 (10.2)	<.001
Women, No. (%)	894 (61.4)	169 (81.3)	258 (62.3)	286 (56.7)	181 (54.7)	<.001
Race/ethnicity, No. (%)						
White	654 (44.9)	109 (52.4)	172 (41.5)	222 (44.0)	151 (45.6)	.08
Black	271 (18.6)	18 (8.7)	82 (19.8)	99 (19.6)	72 (21.8)	<.001
Hispanic	309 (21.2)	40 (19.2)	90 (21.7)	110 (21.8)	69 (20.8)	.87
Chinese	223 (15.3)	41 (19.7)	70 (16.9)	73 (14.5)	39 (11.8)	.06
Blood pressure, mean (SD), mm Hg						
Systolic	111.3 (10.0)	95.3 (2.8)	104.8 (2.9)	114.6 (2.9)	124.6 (2.7)	
Diastolic	67.5 (8.3)	59.1 (6.4)	65.0 (6.7)	69.6 (7.0)	72.5 (8.1)	
Cholesterol, mean (SD), mg/dL						
Total	191.8 (26.6)	187.6 (28.0)	189.6 (27.0)	194.4 (26.7)	193.1 (24.5)	<.001
LDL	114.1 (23.5)	107.4 (25.5)	113.1 (23.8)	116.7 (22.9)	115.4 (22.0)	<.001
HDL	57.1 (14.2)	61.2 (15.1)	56.6 (14.0)	56.1 (14.3)	56.7 (13.4)	<.001
Fasting blood glucose, mean (SD), /dL	86.4 (9.4)	82.6 (8.1)	85.5 (87.2)	88.6 (9.9)	88.6 (9.9)	<.001
BMI, mean (SD)	26.6 (5.1)	24.2 (4.0)	26.5 (4.8)	27.0 (5.1)	27.8 (5.4)	<.001
Distensibility, mean (SD)						
Carotid, 10^{-3} kPa	2.9 (1.2)	3.5 (1.7)	3.2 (1.1)	2.8 (1.0)	2.5 (1.0)	<.001
Aortic, $\times 10^{-3}$ mm Hg^{-1}	2.2 (1.3)	2.6 (2.0)	2.5 (1.1)	2.1 (1.1)	1.8 (1.0)	<.001
Completed high school, No. (%)	1074 (73.7)	161 (77.4)	308 (74.4)	374 (74.2)	231 (69.8)	.24
Annual income ≥$40 000, No. (%)	867 (59.5)	130 (62.5)	248 (59.9)	303 (60.1)	186 (56.2)	.50
10-y PCEs ASCVD risk, median (IQR)	3.0 (1.1-6.7)	1.1 (0.5-3.0)	2.1 (0.8-5.0)	3.3 (1.5-6.7)	5.6 (2.5-12.5)	<.001
ASCVD events, No. (%)	94 (6.5)	4 (1.9)	23 (5.6)	31 (6.2)	36 (11.0)	<.001

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; PCEs, pooled cohort equations; SBP, systolic blood pressure.

SI conversion factors: To convert total, HDL, and LDL cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

Figure 1. Proportion of Participants With Coronary Artery Calcium (CAC) and Diffuse CAC by Systolic Blood Pressure Group



A stepwise increase was noted in the proportion of participants with prevalent coronary artery calcium (CAC ≥1) and diffuse CAC (CAC ≥1 in ≥2 coronary arteries).

adjusted rates were SBP 90 to 99 mm Hg, 1.3; 100 to 109 mm Hg, 4.0; 110 to 119 mm Hg, 4.5; and 120 to 120 mm Hg, 8.3. There was a 53% higher risk for incident ASCVD for every 10-mm Hg increase in SBP level, with an HR of 1.52 (95% CI, 1.15-2.00) using model 2 adjustment variables.

Compared with participants with an SBP level of 90 to 99 mm Hg, adjusted Cox proportional hazards models showed a significant increase in the risk for incident ASCVD among participants with an SBP level of 100 to 109 mm Hg (aHR, 3.00; 95% CI, 1.01-8.88), 110 to 119 mm Hg (aHR, 3.10; 95% CI, 1.03-9.28), and 120 to 129 mm Hg (aHR, 4.58; 95% CI, 1.47-14.27) (**Table 2**). We also found a significant increase in the risk for ASCVD across SBP values when SPB was modeled as a continuous variable (**Figure 2**). The overall results were unchanged when we adjusted for age as a squared variable or when we excluded participants with (1) DBP level 80 mm Hg or higher, (2) LDL-C level 130 mg/dL or higher, (3) fasting glucose level 100 mm Hg or higher, or (4) women with an HDL-C level lower than 50 mg/dL. Using a mean of SBP values from MESA visits 1 to 3, the mean (SD) difference with the visit 1 baseline SBP values was −0.8 (6.8) mm Hg (eTable 1 in the Supplement). Overall, we also observed an increase in the mean values of traditional ASCVD risk factors with increasing SBP levels. For example, LDL-C level increased from a mean value of 110.6 mg/dL among participants with an SBP level of 90 to 99 mm Hg to 114.6 mg/dL among participants with an SBP level of 120 to 129 mm Hg (eTable 2 in the Supplement). In addition, using the mean SBP level, we observed similar ASCVD event rates across SBP groups, such as 7.9 using the mean SBP level vs 8.3 using the visit 1 SBP level per 1000 person-years follow-up among participants with an SBP level of 120 to

Table 2. Hazard of Cardiovascular Disease by Systolic Blood Pressure Group

Characteristic	Systolic blood pressure, mm Hg				*P* value for trend
	90-99	100-109	110-119	120-129	
Unadjusted	1 [Reference]	3.04 (1.05-8.80)	3.49 (1.23-9.90)	6.31 (2.24-17.73)	<.001
Model 1[a]	1 [Reference]	2.70 (0.93-7.85)	2.64 (0.93-7.82)	3.76 (1.33-10.69)	.07
Model 2[b]	1 [Reference]	3.00 (1.01-8.88)	3.10 (1.03-9.28)	4.58 (1.47-14.27)	.06

[a] Adjusted for age, sex, race/ethnicity.

[b] Model 1 adjustments plus diastolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, fasting blood glucose level, body mass index, income, educational level, ever smoking, and prediabetes.

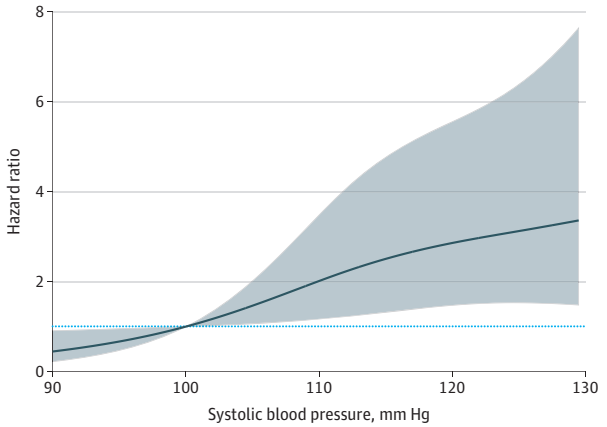
129 mm Hg (eTable 3 in the Supplement). However, there was a greater association between SBP level and the risk for incident ASCVD when the mean ASCVD values from visits 1 to 3 were used, but with wider 95% CIs owing to lower power (eFigure in the Supplement). For instance, the aHR for ASCVD was 4.58 (95% CI, 1.47-14.27) using visit 1 values vs aHR 15.23 (95% CI, 1.93-120.22) using the mean values from visits 1 to 3 (eTable 4 in the Supplement).

Discussion

Individuals without hypertension or other traditional ASCVD risk factors using current definitions are typically considered to have an ideal ASCVD risk profile based on the pooled cohort equation 10-year ASCVD risk score. However, our findings suggested that, among individuals without hypertension or other traditional ASCVD risk factors, there is a stepwise increase in both coronary artery calcium and incident ASCVD with increasing SBP levels. In addition, our results suggest that the association between SBP level, coronary artery calcium, and ASCVD events was present at an SBP level below the current definition of hypertension with a graded increase in both the prevalence of coronary artery calcium and risk of ASCVD starting from SBP levels as low as 90 mm Hg.

While the association between SBP level, coronary artery calcium, and ASCVD is well established at higher SBP levels,[13-16] the optimal SBP levels for a healthy adult and whether there is a J-shaped relationship or lower limit of SBP level necessary to maintain adequate organ perfusion has been uncertain.[34] Excluding participants with traditional ASCVD risk factors based on current definitions enabled our analyses to have a more focused insight into the independent contribution of SBP levels to atherosclerosis by minimizing outcomes associated with non-BP-related atherosclerotic pathophysiologic mechanisms that commonly occur in tandem, such as hyperlipidemia and diabetes. In addition, we examined these associations among individuals without hypertension by the updated and lower 2017 American College of Cardiology/American Heart Association definition, which is in contrast to other studies that have predominantly focused on the association at higher SBP levels and/or among patients using antihypertensive medications.[10,15,16,25,35,36] However, we acknowledge that the levels of other traditional ASCVD risk factors were higher with higher SBP levels and that there may be residual confounding not accounted for by our adjusted modeling methods. Accordingly, primordial prevention strategies should focus on broad risk factor control rather than any single ASCVD risk factor.

Figure 2. Adjusted Cubic Spline for the Hazard of Incident Cardiovascular Disease by Systolic Blood Pressure



Adjusted for age, sex, race/ethnicity, diastolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, fasting blood glucose level, body mass index, income, educational level, ever smoking, and prediabetes.

Among studies that have examined SBP values considered to be normal or near normal, the results were compatible with our analysis. For example, a report by Bild et al[37] suggested a borderline significant association between SBP level and coronary artery calcium with an adjusted odds ratio of 1.31 (95% CI, 0.98-1.74) per 10-mm Hg increase in SBP level among young participants (mean age, 35 years) with a mean SBP level of approximately 112 mm Hg. In addition, in an unadjusted analysis, Taylor et al[38] reported a significant association between SBP level and coronary artery calcium among young United States Army personnel who were predominantly men and had a mean SBP level of approximately 122 mm Hg. However, neither of these studies excluded participants with ASCVD risk factors or hypertension. In addition, neither study examined incident ASCVD events.

Results from the Heart Outcomes Prevention Evaluation (HOPE)-3 trial demonstrated no benefit for treatment (HR, 0.93; 95% CI, 0.79-1.10) with a fixed antihypertensive medication regimen among participants at intermediate ASCVD risk and an SBP level of approximately 138 mm Hg.[39] However, the relatively small absolute difference in SBP levels of 6.0 mm Hg between the treatment and control groups is likely a contributor to these nonsignificant findings. Comparing our results with the findings from HOPE-3, it is also necessary to take into account that the median follow-up time for HOPE-3 was 5.6 years compared with 16.1 years for our study. Therefore, the findings from HOPE-3 and our study suggest that, among individuals at low or intermediate ASVCD risk, it may be more efficacious to focus on a life-course approach for preventing an

increase in SBP levels rather than treatment of established hypertension to lower SBP levels. Further implementation research on the primordial prevention of SBP level increases and other traditional ASCVD risk factors is needed.

Our findings may have implications for primordial prevention strategies to maintain optimal SBP for several reasons. First, the data suggest that, in otherwise healthy adults, individuals with an SBP level between 90 and 99 mm Hg have a low cardiovascular disease event rate. In fact, these participants also had the lowest prevalence of coronary artery calcium and lowest incident rate of ASCVD. In an isolated population of nonindustrialized areas of Brazil and Venezuela, the mean SBP level was 95 mm Hg.[8,9] Second, our data appear to confirm that the continuum of risk associated with SBP level is graded with no nadir or J-point observed for SBP levels as low as 90 mm Hg. Third, we observed that the levels of other traditional ASCVD risk factors were higher with higher SBP levels and that there may be residual confounding not accounted for by our adjusted modeling methods. Accordingly, primordial prevention strategies should focus on broad risk factor control rather than any single ASCVD risk factor.

Limitations and Strengths

Limitations of this study include the use of only a baseline SBP level measurement, although the BP was measured in a standardized manner by trained investigators, along with the reported value being the mean of the second and third measurements. In addition, our sensitivity analyses using mean SBP values determined over 3 visits did not significantly change the results. There was also a significant age difference between the lower and higher SBP level groups, although we found no statistically significant difference in our results when we performed a sensitivity analysis to examine residual confounding by age. In addition, we focused on traditional ASCVD risk factors based on current definitions as used for risk prediction in the pooled cohort equations, but did not include behavioral risk factors, such as diet and physical activity, which are more difficult to accurately measure. We also acknowledge that there are different definitions or cut points for specific categorical variables, such as hyperlipidemia, and that in general there is a continuum of risk with increasing values of traditional ASCVD risk factors. However, we excluded individuals with other traditional ASCVD risk factors to focus on the association of SBP level with ASCVD, and participants had a low 10-year ASCVD score, with a median (SD) value of 3.0% (interquartile range, 1.1%-6.7%). In addition, our results were robust even after adjusting for risk factors as continuous variables and performing sensitivity analyses using lower categorical cut points for other traditional ASCVD risk factors, such as lipid levels.

Strengths of this study include the multiethnic diversity of participants without other traditional ASCVD risk factors. In addition, we suggest an association between SBP level and ASCVD both at baseline with coronary artery calcium and over a long-term, prospective follow-up with incident ASCVD events. Furthermore, we investigated the continuous association between SBP level and ASCVD at SBP level values lower than those of previous large-cohort studies.

Conclusions

In this study, there appeared to be a stepwise increase in traditional ASCVD risk factors, prevalence of coronary artery calcium, and risk of incident ASCVD with increasing SBP levels among individuals without hypertension or other traditional ASCVD risk factors. We demonstrated that this apparently positive graded association of SBP with coronary artery calcium and ASCVD begins at an SBP level as low as 90 mm Hg and that there did not appear to be a higher ASCVD risk at this low SBP level. Our results appear to support the importance of primordial prevention for SBP level increases along with other traditional ASCVD risk factors, all of which generally display similar trajectories of graded increase in risk within values traditionally considered to be normal.

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Acquisition, analysis, or interpretation of data: Whelton, McEvoy, Lima, Budoff, Szklo, Blumenthal, Blaha.
Drafting of the manuscript: Whelton, Lima.
Critical revision of the manuscript for important intellectual content: McEvoy, Shaw, Psaty, Lima, Budoff, Nasir, Szklo, Blumenthal, Blaha.
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REFERENCES

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):1269-1324. doi:10.1161/HYP.0000000000000066

2. Naqvi MA, Khan MK, Iqbal Z, et al. Prevalence and associated risk factors of haemoparasites, and their effects on hematological profile in domesticated chickens in District Layyah, Punjab, Pakistan. *Prev Vet Med*. 2017;143:49-53. doi:10.1016/j.prevetmed.2017.05.001

3. Pen A, Yam Y, Chen L, Dennie C, McPherson R, Chow BJ. Discordance between Framingham risk score and atherosclerotic plaque burden. *Eur Heart J*. 2013;34(14):1075-1082. doi:10.1093/eurheartj/ehs473

4. Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, et al. Prevalence, vascular distribution, and multiterritorial extent of subclinical atherosclerosis in a middle-aged cohort: the PESA (Progression of Early Subclinical Atherosclerosis) study. *Circulation*. 2015;131(24):2104-2113. doi:10.1161/CIRCULATIONAHA.114.014310

5. Nasir K, Clouse M. Role of nonenhanced multidetector CT coronary artery calcium testing in asymptomatic and symptomatic individuals. *Radiology*. 2012;264(3):637-649. doi:10.1148/radiol.12110810

6. He J, Klag MJ, Whelton PK, et al. Migration, blood pressure pattern, and hypertension: the Yi Migrant Study. *Am J Epidemiol*. 1991;134(10):1085-1101. doi:10.1093/oxfordjournals.aje.a116012

7. He J, Tell GS, Tang YC, Mo PS, He GQ. Effect of migration on blood pressure: the Yi People Study. *Epidemiology*. 1991;2(2):88-97. doi:10.1097/00001648-199103000-00002

8. Mueller NT, Noya-Alarcon O, Contreras M, Appel LJ, Dominguez-Bello MG. Association of age with blood pressure across the lifespan in isolated Yanomami and Yekwana Villages. *JAMA Cardiol*. 2018;3(12):1247-1249. doi:10.1001/jamacardio.2018.3676

9. Rodriguez BL, Labarthe DR, Huang B, Lopez-Gomez J. Rise of blood pressure with age: new evidence of population differences. *Hypertension*. 1994;24(6):779-785. doi:10.1161/01.HYP.24.6.779

10. Yano Y, Stamler J, Garside DB, et al. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. *J Am Coll Cardiol*. 2015;65(4):327-335. doi:10.1016/j.jacc.2014.10.060

11. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113(6):791-798. doi:10.1161/CIRCULATIONAHA.105.548206

12. Reinikainen J, Laatikainen T, Karvanen J, Tolonen H. Lifetime cumulative risk factors predict cardiovascular disease mortality in a 50-year follow-up study in Finland. *Int J Epidemiol*. 2015;44(1):108-116. doi:10.1093/ije/dyu235

13. Cupples LDAR. *The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease*. National Heart Lung and Blood Institute; 1971.

14. Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis, and Management*. 2nd ed. Raven Press Ltd; 1995.

15. Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med*. 2001;345(18):1291-1297. doi:10.1056/NEJMoa003417

16. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903-1913. doi:10.1016/S0140-6736(02)11911-8

17. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156(9):871-881. doi:10.1093/aje/kwf113

18. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25, pt B):2935-2959. doi:10.1016/j.jacc.2013.11.005

19. Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: executive summary—a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):3168-3209. doi:10.1016/j.jacc.2018.11.002

20. Fernández-Friera L, Fuster V, López-Melgar B, et al. Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. *J Am Coll Cardiol*. 2017;70(24):2979-2991. doi:10.1016/j.jacc.2017.10.024

21. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646. doi:10.1161/CIR.0000000000000678

22. Strandberg TE, Salomaa VV, Vanhanen HT, Pitkälä K, Miettinen TA. Isolated diastolic hypertension, pulse pressure, and mean arterial pressure as predictors of mortality during a follow-up of up to 32 years. *J Hypertens*. 2002;20(3):399-404. doi:10.1097/00004872-200203000-00014

23. Hozawa A, Ohkubo T, Nagai K, et al. Prognosis of isolated systolic and isolated diastolic hypertension as assessed by self-measurement of blood pressure at home: the Ohasama study. *Arch Intern Med*. 2000;160(21):3301-3306. doi:10.1001/archinte.160.21.3301

24. McEvoy JW, Daya N, Rahman F, et al. Association of isolated diastolic hypertension as defined by the 2017 ACC/AHA blood pressure guideline with incident cardiovascular outcomes. *JAMA*. 2020;323(4):329-338. doi:10.1001/jama.2019.21402

25. Psaty BM, Arnold AM, Olson J, et al. Association between levels of blood pressure and measures of subclinical disease multi-ethnic study of atherosclerosis. *Am J Hypertens*. 2006;19(11):1110-1117. doi:10.1016/j.amjhyper.2006.04.002

26. Whelton SP, Blankstein R, Al-Mallah MH, et al. Association of resting heart rate with carotid and aortic arterial stiffness: multi-ethnic study of atherosclerosis. *Hypertension*. 2013;62(3):477-484. doi:10.1161/HYPERTENSIONAHA.113.01605

27. Whelton SP, Silverman MG, McEvoy JW, et al. Predictors of long-term healthy arterial aging: coronary artery calcium nondevelopment in the MESA Study. *JACC Cardiovasc Imaging*. 2015;8(12):1393-1400. doi:10.1016/j.jcmg.2015.06.019

28. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15(4):827-832. doi:10.1016/0735-1097(90)90282-T

29. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. *Radiology*. 2005;234(1):35-43. doi:10.1148/radiol.2341040439

30. Shaw LJ, Min JK, Nasir K, et al. Sex differences in calcified plaque and long-term cardiovascular mortality: observations from the CAC Consortium. *Eur Heart J*. 2018;39(41):3727-3735. doi:10.1093/eurheartj/ehy534

31. Bluemke DA, Kronmal RA, Lima JA, et al. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol*. 2008;52(25):2148-2155. doi:10.1016/j.jacc.2008.09.014

32. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81(3):515-526. doi:10.1093/biomet/81.3.515

33. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. Springer; 2001. doi:10.1007/978-1-4757-3462-1

34. Kannel WB, Vasan RS, Levy D. Is the relation of systolic blood pressure to risk of cardiovascular disease continuous and graded, or are there critical values? *Hypertension*. 2003;42(4):453-456. doi:10.1161/01.HYP.0000093382.69464.C4

35. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Arch Intern Med*. 1993;153(5):598-615. doi:10.1001/archinte.1993.00410050036006

36. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet*. 2014;383(9932):1899-1911. doi:10.1016/S0140-6736(14)60685-1

37. Bild DE, Folsom AR, Lowe LP, et al. Prevalence and correlates of coronary calcification in black and white young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Arterioscler Thromb Vasc Biol*. 2001;21(5):852-857. doi:10.1161/01.ATV.21.5.852

38. Taylor AJ, Feuerstein I, Wong H, Barko W, Brazaitis M, O'Malley PG. Do conventional risk factors predict subclinical coronary artery disease? results from the Prospective Army Coronary Calcium Project. *Am Heart J*. 2001;141(3):463-468. doi:10.1067/mhj.2001.113069

39. Lonn EM, Bosch J, López-Jaramillo P, et al; HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374(21):2009-2020. doi:10.1056/NEJMoa1600175