American Journal of Hypertension, 2023, **36**, 593–601
https://doi.org/10.1093/ajh/hpad064
Advance access publication 17 July 2023
Original Article

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Standing Blood Pressure and Risk of Falls, Syncope, Coronary Heart Disease, and Mortality

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BACKGROUND: ACC/AHA guidelines caution against the use of antihypertensive therapy in the setting of low standing systolic BP (SBP) < 110 mm Hg due to unclear benefits.

METHODS: The Atherosclerosis Risk in Communities (ARIC) Study measured supine and standing SBP in adults aged 45–64 years between 1987 and 1989. We used Cox regression to evaluate the associations of low standing SBP (<110 mm Hg) with risk of falls, syncope, coronary heart disease (CHD), and mortality through December 31, 2019. Falls and syncope were ascertained by hospitalization and outpatient claims; CHD events were adjudicated. Associations were examined overall and in strata of hypertension stage, 10-year atherosclerotic cardiovascular disease (ASCVD) risk, age, and sex.

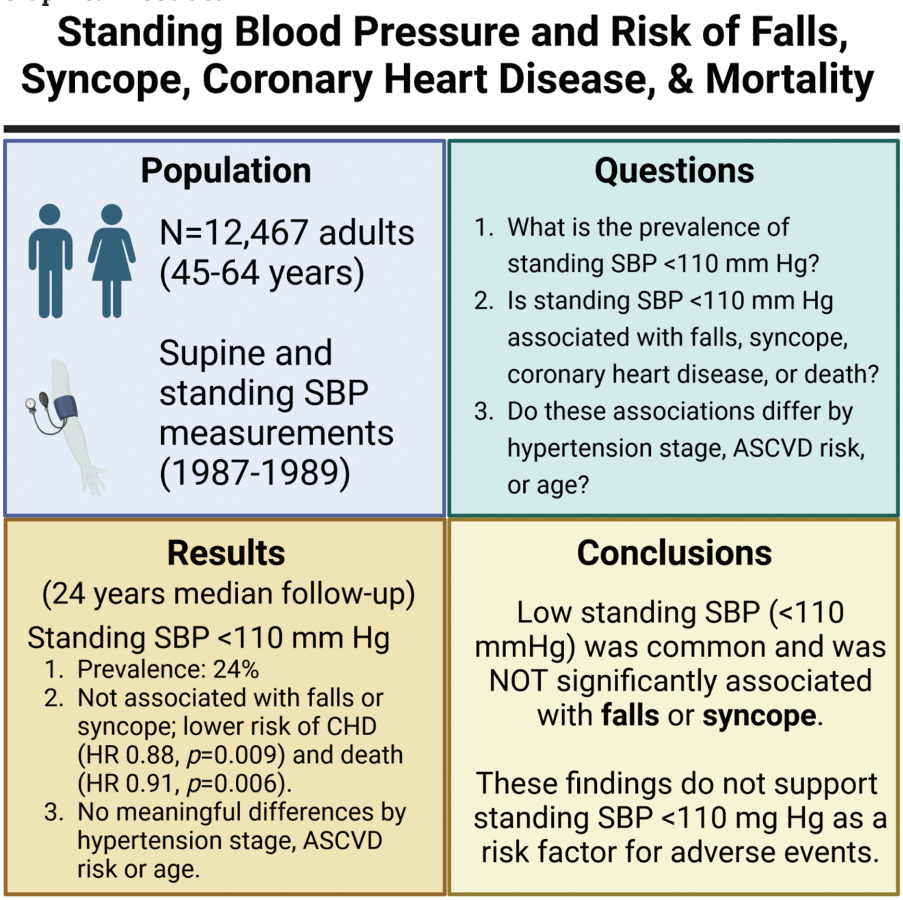
RESULTS: Among 12,467 adults followed a median of 24 years (mean age at enrollment 54.1 ± 5.8 years, 55% women, 26% Black adults), 3,000 (24%) had a standing SBP < 110 mm Hg. A standing SBP < 110 mm Hg compared to standing SBP ≥ 110 mm Hg was not significantly associated with falls or syncope, and was associated with a lower risk of CHD events and mortality with HRs of 1.02 (95% CI 0.94, 1.11), 1.02 (0.93, 1.11), 0.88 (0.80, 0.97), and 0.91 (0.86, 0.97), respectively. There were no clinically meaningful differences when stratified by hypertension stage, 10-year ASCVD risk, age, and sex.

CONCLUSIONS: In this community-based population, low standing SBP was common and not significantly associated with falls or syncope, but was associated with a lower risk of CHD and mortality. These findings do not support screening for low standing BP as a risk factor for adverse events.

Keywords: blood pressure; coronary heart disease; falls; hypertension; mortality; standing blood pressure; syncope.

Received 8 April 2023; **revised** 5 July 2023; **accepted** 13 July 2023.

Graphical Abstract



Blood pressure (BP) is an important modifiable risk factor for cardiovascular disease and mortality.[1] The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that a lower systolic BP (SBP) treatment goal reduced the risk of coronary heart disease (CHD) and death from any cause without increasing risk of falls and only mildly increasing risk of syncope among adults with hypertension at higher risk for CHD.[2] However, SPRINT excluded adults with a standing SBP < 110 mm Hg, raising questions about whether the risk of an intensive BP treatment goal may be underestimated for clinical populations that are not routinely screened for standing hypotension.[3] Indeed, the 2017 ACC/AHA hypertension management guidelines caution against the initiation of antihypertensive medications for patients with low standing BP (<110 mm Hg).[4] However, very little is even known about standing BP and clinical outcomes in the general adult population with hypertension and without hypertension.

The Atherosclerosis Risk in Communities (ARIC) Study was established to examine cardiovascular risk factors in community-dwelling, middle-aged U.S. adults. A significant number of ARIC participants further underwent standing BP measurement as part of an ancillary study focused on orthostatic hypotension. While prior ARIC studies demonstrated that orthostatic hypotension was an independent predictor of falls, syncope, CHD events, and all-cause mortality,[5–7] standing hypotension (defined here as SBP < 110 mm Hg) and standing SBP have not been studied. These standing BP assessments afford a unique opportunity to characterize standing hypotension and standing SBP in an ambulatory population and determine its association with adverse events often attributed to hypertension treatment.

The objectives of the present study were to (i) quantify the prevalence of standing hypotension (i.e., standing SBP < 110 mm Hg), (ii) characterize the association of standing hypotension and standing SBP with adverse clinical events, that is, falls, syncope, CHD events, and mortality, and (iii) determine whether the association between standing hypotension or standing SBP with adverse outcomes differed by hypertension stage, 10-year estimated atherosclerotic cardiovascular disease (ASCVD) risk, or age among community-dwelling middle-aged adults. We hypothesized that while standing hypotension would be common, it would not be significantly associated with adverse clinical events regardless of hypertensive stage, 10-year ASCVD risk, age, sex, change in BP upon standing, hypertension status, or antihypertensive medication use at baseline.

METHODS

Study population

The ARIC Study is an ongoing prospective study of 15,792 middle-aged mostly White and Black adults, described in depth elsewhere.[8–10] In brief, ARIC enrolled community-dwelling adults, aged 45–64 years, from four U.S. communities: Forsyth Country, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. Participants were enrolled between 1987 and 1989 (visit 1), and the original study protocol consisted of physical examinations, medical interviews, and laboratory tests. Participants have been followed for over three decades through active surveillance of community hospitals, annual or semiannual telephone interviews, and follow-up clinical examinations.[10]

The present analysis excluded participants who withdrew consent (*N* = 35), did not participate in standing BP measurements during visit 1 (*N* = 2,548), and those missing relevant covariate data at baseline (visit 1) (*N* = 742); the three most common missing covariates were relevant medication use data (*N* = 575), LDL-cholesterol (*N* = 82), and heart rate (*N* = 63). Our analytic sample included 12,467 participants.

All participants provided written informed consent and the study protocol was approved by institutional review boards from each study site. The Institutional Review Board at Beth Israel Deaconess Medical Center decided that this secondary analysis was human subjects exempt research.

Exposure: standing hypotension and standing SBP

During the baseline visit, after a 20-minute rest period, supine BP was measured up to five times following a standardized protocol using an automatic cuff (Dinamap 1846 SX oscillometric device) every 20–30 seconds for two minutes. Participants were then instructed to stand up from a supine position with their arm supported at heart level with a bedside table. They subsequently underwent up to five standing measurements (≥4 measurements obtained for 91% of participants) every 20–30 seconds within the first 2 minutes of standing, and the average of up to five measurements were used to determine standing BP. Measures occurred without a programmed pause between deflation and re-inflation. Further details for recording supine and standing BP have been described previously.[11] In this study, we defined standing hypotension as a mean standing SBP < 110 mm Hg. Our reference group was standing SBP ≥ 110 mm Hg. We also examined standing SBP as a continuous variable (per 10 mm Hg).

Clinical outcomes: falls, syncope, CHD, and death

The clinical outcomes in this study were falls, syncope, incident CHD events, and all-cause mortality, after visit 1 through December 31, 2019 (for all clinical events; follow-up was not available for the Jackson site after December 31, 2017). Falls and syncope were defined as the first occurrence of any related hospitalization or claim for inpatient or outpatient services after the baseline visit. These outcomes were identified from active surveillance of all hospitalizations for all ARIC participants and linkage to Centers for Medicare and Medicaid Services (CMS) claims data from 1985 to 2018 for Medicare fee-for-service beneficiaries (see Supplementary Methods SM1).[7,12] Fall and syncope claims corresponded to *International Classification of Diseases, Ninth Revision* (ICD-9) and *Tenth Revision* (ICD-10) codes (see Supplementary Methods SM1 for ICD codes). The sensitivity and specificity of this community surveillance approach has been described previously.[10,12]

Incident CHD events and death were adjudicated by an expert panel based on hospital discharge documents or death certificates through procedures described previously.[7,10] Adjudicated CHD events were determined by a composite definition of fatal CHD, cardiac procedure, or silent myocardial infarction based on electrocardiogram (ECG) changes.[10] Death was determined by surveillance of hospital discharge records, coroner reports, the National Death Index, and next-of-kin interviews.

Covariates of interest

Baseline data from visit 1 was collected by trained study personnel using standardized protocols with quality control measures. Covariates of interest were selected to examine the independent association between standing SBP and falls, syncope, CHD, and all-cause mortality (see Supplementary Methods SM2 for covariate definitions).

Statistical analyses

Baseline study population characteristics were described using means and proportions overall and according to hypertension stage.

We used Cox regression to evaluate the association between standing hypotension (standing SBP < 110 mm Hg vs. ≥110 mm Hg) or standing SBP (continuous variable) and falls, syncope, CHD, and all-cause mortality. In all models, we included covariates related to falls, syncope, and CHD disease, namely, age, sex, race-center, estimated glomerular filtration rate, body mass index, resting heart rate, high density lipoprotein cholesterol, total cholesterol, prevalent CHD, prior stroke, prior heart failure, diabetes, hypertension status, dizziness, alcohol use, education, leisure index, smoking status, and use of antihypertension medications in the last 2 weeks, and use of diuretics, cholesterol-lowering medications, antidepressants, sedatives, hypnotics, antipsychotics, or anticholinergics. We used log–log plots to assess the Cox proportionality assumption for standing hypotension. We also examined the occurrence of the four clinical outcomes according to standing hypotension (<110 mm Hg vs. ≥110 mm Hg) with cumulative incidence plots. To more flexibly model the continuous association of standing SBP with the four clinical outcomes, we also modeled standing SBP as a fully adjusted restricted cubic spline (4 knots, locations selected via Harrell's method).[13]

In stratified analyses, we assessed for effect modification by baseline hypertension stage (3 strata: Normotension, stage 1, and stage 2 or treated hypertension), baseline 10-year atherosclerotic cardiovascular disease (ASCVD) risk calculated with the US-derived pooled cohort equations[14] (2 strata: ASCVD < 10% and ASCVD ≥ 10% or prior CHD history), age (3 strata: <50 years, 50–59 years, and 60–66 years), sex (2 strata: male and female), change in BP upon standing (2 strata: postural change ≤ –20 mm Hg and postural change ≥ –20 mm Hg), baseline hypertension status (2 strata: no hypertension or any hypertension [stage 1, stage 2, or treated]), and antihypertensive medication use at baseline (2 strata: no antihypertensive medication use in the last two weeks and antihypertensive medication use in the last 2 weeks).

All analyses were conducted using Stata 15.0 (StataCorp LP, College Station, TX). A two-tailed *P*-value < 0.05 was considered statistically significant.

RESULTS

Population characteristics

Overall, the mean age of participants was 54.1 ± 5.8 years (range 44–66 years); 55% were female, and 26% were Black. At baseline, 24% of participants had standing hypotension and 4% had orthostatic hypotension (Table 1). Standing hypotension was identified among 38% with normotension, 4% with stage 1 hypertension, and 14% of those with stage 2 or treated hypertension (Supplementary Table ST1).

Clinical outcomes: falls, syncope, CHD, and death

Participants were followed a median of about 24 years (median follow-up was 28 years for death) and there were a total of 3,526 (28%) incident falls, 3,161 (25%) incident syncopal events, 2,972

Table 1. Baseline study population characteristics by standing SBP < 110 mm Hg vs. standing SBP ≥ 110 mm Hg, mean (SD) or %

Characteristics	Standing SBP < 110 mm Hg (N = 3,000)	Standing SBP ≥ 110 mm Hg (N = 9,467)	Overall (N = 12,467)
Age, years	53.4 (5.7)	54.4 (5.7)	54.1 (5.8)
Female, %	69	51	55
Race-study center, %			
Washington County (White)	27	24	25
Jackson (Black)	9	27	23
Minneapolis (White)	28	25	26
Forsyth County (Black)	2	4	3
Forsyth County (White)	34	20	23
Body mass index, kg/m^2	25.6 (4.5)	28.3 (5.4)	27.6 (5.3)
Seated SBP, mm Hg	105.0 (11.3)	126.2 (18.0)	121.1 (18.9)
Seated DBP, mm Hg	65.5 (8.1)	75.9 (10.8)	73.4 (11.2)
Supine SBP, mm Hg	106.6 (9.3)	130.9 (18.8)	125.1 (19.9)
Supine DBP, mm Hg	64.8 (6.9)	74.8 (9.3)	72.4 (9.8)
Hypertension stage, %			
Normotension	75	40	48
Stage 1 hypertension	3	16	13
Stage 2 (or treated) hypertension	22	44	39
Resting heart rate, beats per minute	65.2 (9.5)	67.2 (10.4)	66.7 (10.2)
Standing SBP < 110 mm Hg, %	100	0	24
Orthostatic hypotension, %	6	4	4
History of coronary heart disease, %	5	5	5
History of heart failure, %	4	5	5
History of stroke, %	2	2	2
Diabetes mellitus, %	6	14	12
eGFR, mL/min per 1.73 m^2	102.7 (12.5)	101.1 (13.4)	101.5 (13.2)
HDL cholesterol, mg/dL	54.3 (17.7)	50.8 (17.0)	51.6 (17.3)
Total cholesterol, mg/dL	211.7 (40.1)	215.2 (42.1)	214.4 (41.6)
Baseline ASCVD risk ≥ 10% or prior CHD*, %	13	32	27
Leisure index, U	2.4 (0.6)	2.3 (0.6)	2.4 (0.6)
Self-reported dizziness, %	12	10	10
Antihypertensive medication use**, %	21	33	30
Diuretic medication use, %	12	19	17
Cholesterol-lowering medication use, %	2	2	2
Antidepressant medication use, %	3	3	3
Sedative medication use, %	2	1	2
Hypnotic medication use, %	2	2	2
Antipsychotic medication use, %	1	1	1
Alcohol use, %			
Never	21	26	25
Former	18	19	19
Current	61	55	57
Education attainment, %			
Less than high school	16	25	23
High school degree or equivalent or vocational school	43	41	41
At least some college or professional school	41	35	36
Smoking status, %			
Never	40	42	41
Former	29	34	33
Current	31	25	26

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; SBP, systolic blood pressure.
*Sample size for ASCVD analysis is smaller (N = 12,463) due to missing low-density lipoprotein data.
**Antihypertensive medication use is within the last 2 weeks. Hypertension stages were defined as normotension SBP < 130 mm Hg/DBP < 80 mm Hg, Stage 1 hypertension SBP 130–139 mm Hg/DBP 80–89 mm Hg, and no antihypertension medication use, and stage 2 hypertension SBP ≥ 140 mm Hg/DBP ≥ 90 mm Hg, or antihypertensive medication use in the past 2 weeks (based on medication review).

(24%) incident CHD events, and 6,713 (54%) deaths. After adjustment, standing hypotension (vs. SBP ≥ 110 mm Hg) was associated with a lower risk of CHD (HR 0.88; 95% CI: 0.80, 0.97) and death (HR 0.91; 95% CI: 0.86, 0.97), but was not significantly associated with falls or syncope (Table 2). Standing SBP (per 10 mm Hg) was associated with a higher risk of CHD events (HR 1.07; 95% CI: 1.05, 1.09) and mortality (HR 1.06; 95% CI: 1.04, 1.07), but not falls or syncope. Similar findings were seen with cumulative incidence plots (Supplementary Figure SF1). The associations between standing SBP and incident falls, syncope, CHD, and all-cause mortality were nonlinear, with a higher risk for CHD and all-cause mortality at greater standing SBP values, but not with falls or syncope (Figure 1).

Clinical outcomes by subgroups: hypertension, 10-year ASCVD risk, age, and sex

Standing hypotension was associated with a higher risk of syncope (*P*-trend = 0.035) and CHD (*P*-trend = 0.0008) across hypertension strata (normotension, stage 1, stage 2, or treated), but there was no significant trend observed for falls or all-cause

Table 2. Association of standing hypotension and standing systolic blood pressure with adverse events: The Atherosclerosis Risk in Communities (ARIC) Study (1987–2019)

Outcomes	Standing SBP < 110 mm Hg (*N* = 3,000) vs. SBP ≥ 110 mm Hg (*N* = 9,467)		Standing SBP per 10 mm Hg (*N* = 12,467)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Fall	1.02 (0.94, 1.11)	0.66	1.00 (0.98, 1.02)	0.83
Syncope	1.02 (0.93, 1.11)	0.67	1.01 (0.99, 1.03)	0.30
CHD	0.88 (0.80, 0.97)	0.009	1.07 (1.05, 1.09)	<0.001
Death	0.91 (0.86, 0.97)	0.006	1.06 (1.04, 1.07)	<0.001

Adjusted for age, sex, race-center, estimated glomerular filtration rate, body mass index, resting heart rate, high-density lipoprotein cholesterol, total cholesterol, prevalent CHD, prior stroke, prevalent heart failure, diabetes mellitus status, hypertension status, self-reported dizziness, alcohol consumption, education level, leisure index, smoking status, antihypertensive medication use in the last two weeks, and use of diuretics, antidepressants, sedatives, hypnotics, antipsychotics, and cholesterol-lowering medications. Participants were followed up through December 31, 2019, for a median of 24 years of follow-up. Abbreviations: CHD, coronary heart disease; SBP, systolic blood pressure.

mortality (Table 3). Within each hypertension stage, however, standing hypotension was not significantly associated with risks of falls or syncope. Additionally, standing hypotension was not significantly associated with CHD or all-cause mortality in participants with stage 1 or stage 2/treated hypertension, but was associated with a lower risk of CHD (HR 0.83; 95% CI: 0.73, 0.95) and death (HR 0.90; 95% CI: 0.83, 0.98) in normotensive participants.

The associations between standing SBP and outcomes when stratified by baseline hypertension status (stage 1 or stage 2/treated) were nonlinear, showing a higher risk for CHD and death at greater standing SBP values, but no association with falls or syncope (Supplementary Figure SF2).

Across baseline 10-year ASCVD risk strata (<10% vs. ≥10%), standing hypotension was differentially associated with higher risk of CHD events ($P = 0.015$) and all-cause mortality ($P = 0.019$), but not falls or syncope (Table 4). In stratified analyses, standing hypotension among participants with a baseline 10-year ASCVD risk < 10% was associated with lower rates of CHD (HR 0.84; 95% CI: 0.74, 0.95) and death (HR 0.89; 95% CI 0.82, 0.96), but was not significantly associated with fall or syncope. Standing hypotension among adults with higher baseline 10-year ASCVD risk or prior CHD history was not significantly associated with any outcomes.

Across age strata (<50 years; 50–59 years; 60–66 years), standing hypotension was associated with a higher risk of syncope with increasing age category (P-trend = 0.043), but no trends across age categories were observed with other outcomes (Supplementary Table ST2). Within each age category, however, standing hypotension was not significantly associated with fall or syncope. Although the trend was not significant, in stratified analyses standing hypotension was associated with lower risk of CHD (HR 0.82; 95% CI: 0.71, 0.94) and death (HR 0.90; 95% CI: 0.83, 0.99) among participants aged 50–59 years, but not for other younger or older participants. Lastly, standing hypotension was associated with lower risk of death (HR 0.87; 95% CI: 0.78, 0.97) in patients aged ≥ 60 years, but not for younger patients.

Compared to men, standing hypotension among women was associated with a lower risk of CHD events ($P = 0.009$) and death ($P = 0.015$), but not falls or syncope (Supplementary Table ST3). Standing hypotension among male adults was not significantly associated with any outcomes.

Sensitivity analyses stratified by degree of change in standing SBP, (≤–20 or > –20 mm Hg), no hypertension or any hypertension (stage 1 or 2 combined), or by anytihypertensive medication use in the past 2 weeks did not significantly alter our findings (Supplementary Tables ST4–ST6).

DISCUSSION

In this middle-aged, community-dwelling adult population, we found that the prevalence of standing hypotension was common overall (24%) and among adults with stage 2 (or treated) hypertension (14%). Standing hypotension was not significantly associated with falls or syncope. Furthermore, standing hypotension was associated with a lower risk for CHD and death, and higher standing SBP was associated with increased risk of these outcomes. While there was a nominally greater risk of syncope among higher hypertension stages and older age groups with standing hypotension, standing hypotension was not significantly associated with adverse events overall or in any hypertension stage. These findings do not provide compelling support to screen for standing hypotension among adults with stage 1 or stage 2 hypertension.

Clinical trials of hypertension treatment have repeatedly demonstrated reduced risk for CHD events and mortality from more intensive BP treatment goals.[2,15–19] However, a critique of trials with more intensive BP goals, like SPRINT, has been their exclusion of adults with standing hypotension, causing many to question SPRINT's generalizability in ambulatory populations where standing BP is not routinely assessed.[3,4] Indeed, hypotensive events and syncope were among the most common complications of intensive BP treatment in SPRINT, generating speculation as to whether these complications could be greater in general populations of adults with standing hypotension.[2] In response to these concerns, the 2017 ACC/AHA BP management guidelines caution that initiation of pharmacologic hypertension treatment or uptitration of existing therapy may portend adverse events for patients with low standing BP. However, it was unclear how common standing hypotension was in the general population or among adults with hypertension. Our study demonstrates that standing hypotension is common among a quarter of the general population and about 14% of the adults with stage 2 (or treated) hypertension.

The prognostic significance of standing hypotension has not been a focus of prior research. However, prior studies have demonstrated strong associations between orthostatic hypotension (a form of standing hypotension) and CHD events.[7,20] Many have postulated that this is secondary to cumulative micro-ischemia and end-organ injury due to transient hypoperfusion injuries.[7,21–23] Our study is among the first to characterize adverse clinical outcomes associated with standing hypotension among community-dwelling, middle-aged adults. Contrary to our hypothesis, we found that standing hypotension was inversely

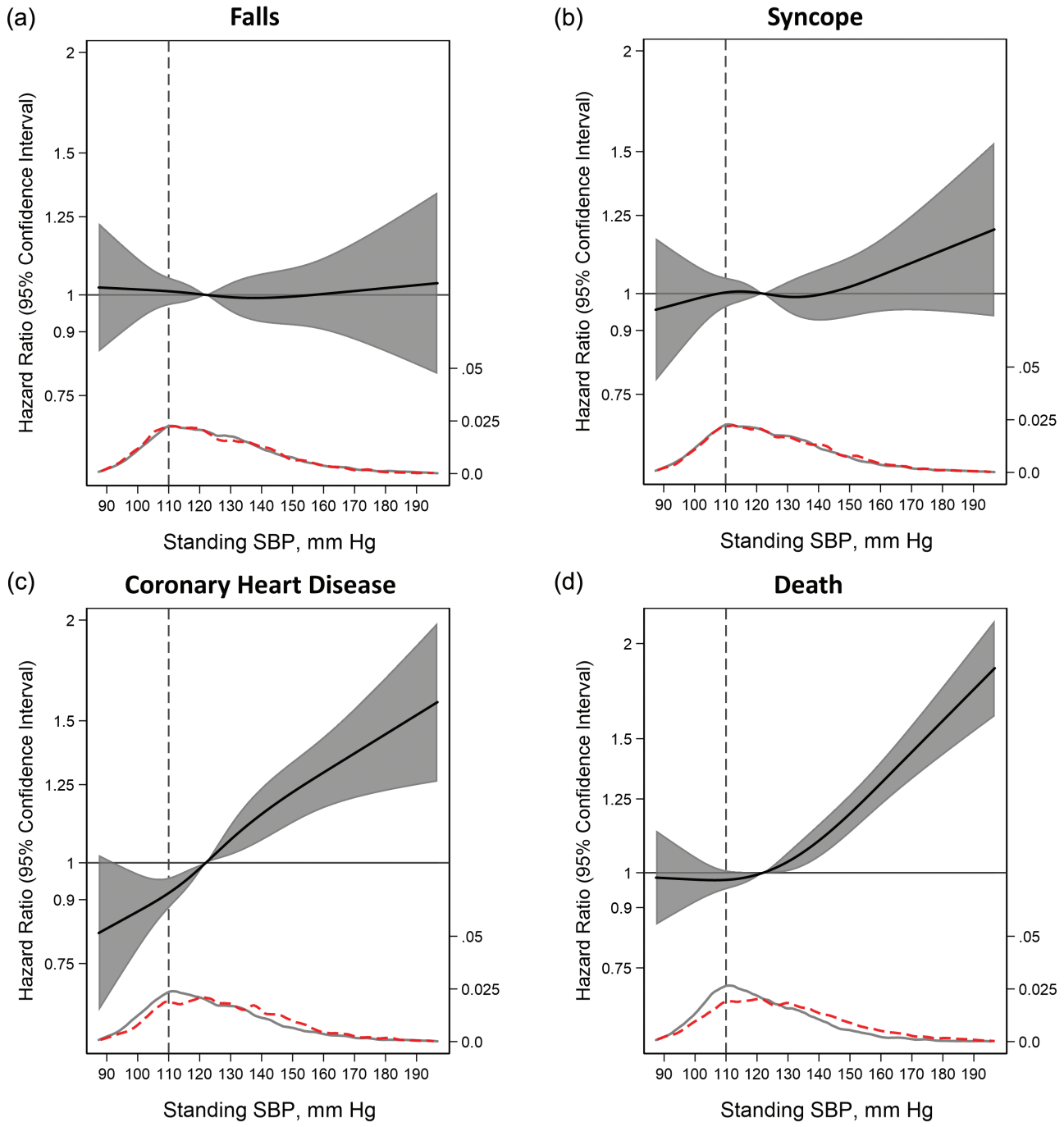


Figure 1. Adjusted association of standing SBP (mm Hg) modeled as a restricted cubic splines (solid line) with (**a**) fall (N = 2,366), (**b**) syncope (*N* = 2,634), (**c**) CHD (*N* = 2,767), and (**d**) death (*N* = 5,358). Hazards are presented relative to the 50th percentile of standing SBP with 4 knots via Harrell's method (SBP < 110 mm Hg; vertical dotted line). All models used Cox proportional hazards models to determine hazard ratios shown on a natural log scale. Model included age, sex, race-center, estimated glomerular filtration rate, body mass index, resting heart rate, high-density lipoprotein cholesterol, total cholesterol, prevalent coronary heart disease, prior stroke, prevalent heart failure, diabetes mellitus status, hypertension status, self-reported dizziness, alcohol consumption, education level, leisure index, smoking status, antihypertensive medication use in the last 2 weeks, and use of diuretics, antidepressants, sedatives, hypnotics, antipsychotics, and cholesterol-lowering medications. The figure display was truncated at the 0.5th and 99.5th percentiles of standing SBP. Kernel density plots depict the distribution of standing SBP by participants who had the outcome of interest (dashed) vs. those who did not have the outcome of interest (gray solid). Vertical dash line represents SBP < 110 mm Hg. SBP indicates systolic blood pressure.

associated with risk of CHD and death. Although there was a higher risk of CHD with standing hypotension across hypertension strata, ASCVD risk, and antihypertensive medication use, standing hypotension was not itself significantly associated with increased risk of CHD. Rather, the associations across hypertension strata suggested that standing hypotension was a healthy phenotype among middle-aged, normotensive participants with no association with CHD even among participants with stage 2 (or treated) hypertension. Similarly, standing hypotension was inversely associated with CHD among participants at low risk for ASCVD and women with no association observed among those at higher risk of ASCVD or men.

Table 3. Association of standing hypotension (<110 mm Hg vs. ≥ 110 mm Hg) with adverse events stratified by hypertension category: The ARIC Study (1987–2019)

Outcomes	Normotensive (*N* = 6,024)	Stage 1 Hypertension (*N* = 1,600)	Stage 2 (or treated) Hypertension (*N* = 4,843)	*P*-trend
Fall	1.00 (0.90, 1.11)	1.22 (0.81, 1.83)	1.03 (0.88, 1.21)	0.42
Syncope	0.97 (0.87, 1.09)	1.17 (0.76, 1.79)	1.14 (0.97, 1.34)	0.035
CHD	0.83 (0.73, 0.95)	1.06 (0.65, 1.72)	1.03 (0.88, 1.21)	0.0008
Death	0.90 (0.83, 0.98)	1.20 (0.89, 1.62)	0.93 (0.83, 1.04)	0.33

Hypertension stages were defined as normotension SBP < 130 mm Hg/DBP < 80 mm Hg, Stage 1 hypertension SBP 130–139 mm Hg/DBP 80–89 mm Hg, and no antihypertension medication use, and stage 2 hypertension SBP ≥ 140 mm Hg/DBP ≥ 90 mm Hg, or antihypertensive medication use in the past 2 weeks (based on medication review). Values are given as hazards ratio (95% confidence interval). Adjusted for age, sex, race-center, estimated glomerular filtration rate, body mass index, resting heart rate, high-density lipoprotein cholesterol, total cholesterol, prevalent CHD, prior stroke, prevalent heart failure, diabetes mellitus status, hypertension status, self-reported dizziness, alcohol consumption, education level, leisure index, smoking status, antihypertensive medication use in the last 2 weeks, and use of diuretics, antidepressants, sedatives, hypnotics, antipsychotics, and cholesterol-lowering medications. Participants were followed up through December 31, 2019, for a median of 24 years of follow-up. Abbreviations: CHD, coronary heart disease; SBP, systolic blood pressure.

Table 4. Association of standing hypotension (<110 mm Hg vs. ≥ 110 mm Hg) with adverse events stratified by baseline 10-year atherosclerotic cardiovascular disease risk: The ARIC Study (1987–2019)

Outcomes	ASCVD < 10% (*N* = 9,079)	ASCVD ≥ 10% or prior CHD (*N* = 3,384)	*P*-value
Fall	1.01 (0.92, 1.11)	1.05 (0.84, 1.31)	0.79
Syncope	1.00 (0.90, 1.10)	1.10 (0.88, 1.38)	0.40
CHD	0.84 (0.74, 0.95)	0.99 (0.84, 1.17)	0.015
Death	0.89 (0.82, 0.96)	1.03 (0.91, 1.17)	0.019

Values are given as hazards ratio (95% confidence interval). Reduced sample size (*N* = 12,463) for ASCVD analysis due to missing low-density lipoprotein cholesterol data. Models are adjusted for age, sex, race-center, estimated glomerular filtration rate, body mass index, resting heart rate, high-density lipoprotein cholesterol, total cholesterol, prevalent CHD, prior stroke, prevalent heart failure, diabetes mellitus status, hypertension status, self-reported dizziness, alcohol consumption, education level, leisure index, smoking status, antihypertensive medication use in the last two weeks, and use of diuretics, antidepressants, sedatives, hypnotics, antipsychotics, and cholesterol-lowering medications. Participants were followed up through December 31, 2019, for a median of 24 years of follow-up. Abbreviations: ASCVD, baseline 10-year atherosclerotic cardiovascular disease risk; CHD, coronary heart disease; SBP, systolic blood pressure.

Our study found no association between standing hypotension or standing SBP overall with falls or syncope. In the literature, there are mixed associations between standing SBP with falls or syncope in the setting of orthostatic hypotension. While previous observational studies demonstrated that orthostatic hypotension is a risk factor for falls[5,24,25] and syncope,[6,26,27] in SPRINT there was no association between orthostatic hypotension with falls or syncope among adults with a standing SBP > 110 mm Hg.[28] Although the SPRINT population excluded adults with standing hypotension, our study suggests that neither standing SBP nor standing hypotension are significantly associated with falls or syncope. Nevertheless, there was nominally greater risk of syncope across higher hypertension and age strata. As standing hypotension was not significantly associated with increased syncope within any category of hypertension or age strata, the clinical implications of these trends are unclear. We can speculate that the higher risk of syncope from standing hypotension among adults with hypertension is due to orthostatic hypotension as drops in BP upon standing are thought to contribute to cerebral hypoperfusion and may be exacerbated by poor cardiac and vascular compliance or autonomic dysfunction.[29,30] It is also possible that the trend toward higher syncope among this group is secondary to the effects of hypertension treatment, particularly among adults where the standing hypotension was not identified prior to treatment intensification. However, despite a trend towards increased risk of syncope among adults who used antihypertensive medications at baseline evaluation, confirmation of these mechanisms is beyond the scope of the current study, particularly given our lack of standing BP measurements longitudinally or at the time of clinically-driven medication changes.

It is important to note that our study included a large number of adults with BPs in a range that would not have been included in hypertension trials like SPRINT. Because of the SPRINT requirement to have an elevated seated BP ≥ 130 mm Hg, participants with a standing SBP < 110 mm Hg would have had orthostatic hypotension. However, sensitivity analyses by change in SBP upon standing did not demonstrate a significant difference between those with a change in SBP upon standing of > –20 mm Hg (no orthostatic hypotension) vs. ≤ –20 mm Hg (orthostatic hypotension). In contrast to SPRINT, about a fourth of adults were found to have baseline hypertension and standing hypotension in our study. Moreover, stratifying by hypertension stage allowed us to examine standing hypotension more thoroughly and how associations with outcomes differed by baseline hypertension status.

Our study has some limitations. First, baseline assessments did not include fall history, thus we are unable to differentiate participants with falls prior to baseline vs. participants without any fall history. About 1% of middle-aged adults are estimated to have a fall each year.[31] Second, although ICD injury codes are reportedly valid,[32] falls and syncope are likely under-ascertained since only those reported to health care providers are recorded, missing the falls or syncopal events that do not result in serious injury. Further elaboration on the limitations from CMS claims data are discussed in the Supplementary Methods. Third, while we account for hypertension treatment at the time of standing BP measurement, we did not have standing BP measured over time or coupled with changes in BP management. Thus, while one might assume that participants with stage 1 or stage 2 hypertension were more likely to undergo hypertension treatment, our findings should not be used to infer causality related to BP

treatment, but are more informative with respect to risks related to the identification of standing hypotension. Fourth, our study population focused on middle-aged adults with and without hypertension. These findings should be replicated in a population of older adults with a greater prevalence of stage 1 and stage 2 hypertension. Fifth, participants were not asked about hydration status, which may have implications for standing blood pressure measurements. Finally, residual confounding is always a concern with observational studies.

Our study also has several strengths. Our study population included a large sample of middle-aged, community-dwelling Black or White adults, who experienced a substantial number of events during follow-up. Blood pressure and other covariates were measured using a standardized protocol to enhance precision and accuracy. Hospitalization records were reviewed carefully by trained ARIC staff to adjudicate CHD outcomes using a rigorous protocol. Finally, falls and syncope were ascertained by ICD-9 and 10 codes, increasing the likelihood that these events were clinically relevant.

Our findings have clinical implications. Somewhat unexpectedly, we found that standing hypotension was present in about one of seven middle-aged adults with stage 2 hypertension. Thus, if patients are screened for low standing SBP, a sizeable number of patients may be considered inappropriate for hypertension treatment based on the standing hypotension threshold used in SPRINT. Alternatively, clinicians could initiate antihypertensive therapy after reviewing additional BP assessments (ambulatory or in clinic) or use lower doses of medications. However, our study also showed that standing hypotension was not significantly associated with non-cardiovascular or cardiovascular events and that only standing hypertension was associated with a higher risk of all-cause mortality. These findings suggest that standing BP assessments may not be an informative screening modality for determining middle-aged adults at risk for falls or syncope even among those with hypertension. While further work is needed, particularly research examining the impacts of BP treatment intensification on syncope among adults with standing hypotension, our study does not support current guideline recommendations that standing hypotension be viewed as a reason to avoid BP intensification.

In conclusion, in this middle-aged population with and without hypertension, low standing SBP < 110 mm Hg (i.e., standing hypotension) was not significantly associated with increased risk of falls, syncope, CHD events, or death. There was no clinically meaningful difference when stratified by hypertension stage, baseline 10-year ASCVD risk, age, or sex. These findings do not support screening for standing SBP < 110 mm Hg. Additional studies on treatment initiation are needed to determine if antihypertensive therapy intensification impacts syncope risk among hypertensive adults with standing hypotension.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

ACKNOWLEDGMENTS

The authors thank the staff and participants of the ARIC study for their important contributions. For a full list of contributors to ARIC, please visit sites.cscc.unc.edu/aric/. An abstract of this work was presented at the AHA Hypertension Conference in San Diego, CA in September 2022.

FUNDING

The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (75N92022D00001, 75N92022D00002, 75N92022D00003, 75N92022D00004, 75N92022D00005). Kondo is supported by an Amazon Web Services (AWS) Cloud Credit for Research grant. Juraschek is supported by the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) grant R01 HL153191. Selvin is supported by NIH/NHLBI grant K24 HL152440. Lutsey is supported by NIH/NHLBI grant K24 HL159246.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data underlying this article may be obtained with an approved ARIC proposal. Please visit sites.cscc.unc.edu/aric/.

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