ORIGINAL ARTICLE

Orthostatic Hypotension in Middle-Age and Risk of Falls

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BACKGROUND
One-third of older adults fall each year. Orthostatic hypotension (OH) has been hypothesized as an important risk factor for falls, but findings from prior studies have been inconsistent.

METHODS
We conducted a prospective study of the association between baseline OH (1987–1989) and risk of falls in the Atherosclerosis Risk in Communities (ARIC) Study. Falls were ascertained during follow-up *via* ICD-9 hospital discharge codes or Centers for Medicare & Medicaid Services claims data. OH was defined as a drop in systolic blood pressure (SBP) ≥20 mm Hg or diastolic blood pressure (DBP) ≥10 mm Hg within 2 minutes of moving from the supine to standing position. Changes in SBP or DBP during OH assessments were also examined as continuous variables.

RESULTS
During a median follow-up of 23 years, there were 2,384 falls among 12,661 participants (mean age 54 years, 55% women, 26% black). OH was associated with risk of falls even after adjustment for demographic characteristics and other risk factors (hazard ratio (HR): 1.30; 95% confidence interval (CI): 1.10, 1.54; $P = 0.002$). Postural change in DBP was more significantly associated with risk of falls (HR 1.09 per −5 mm Hg change in DBP; 95% CI: 1.05, 1.13; $P < 0.001$) than postural change in SBP (HR 1.03 per −5 mm Hg change in SBP; 95% CI: 1.01, 1.05; $P = 0.002$).

CONCLUSIONS
In a community-based, middle-aged population, OH, and in particular, postural change in DBP, were independent risk factors for falls over 2 decades of follow-up. Future studies are needed to examine OH thresholds associated with increased risk of falls.

Keywords: ARIC; blood pressure; epidemiology; fall; hypertension; orthostatic hypotension; prospective cohort.

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Falls are a major cause of morbidity and mortality among older adults.[1,2] Nearly, one-third of persons aged 65 or older falls each year and the rate of falls in the United States is rising.[1,2] Moreover, falls are a significant reason for emergency room visits[3] and predispose to the risk of fracture,[4] posing a substantial burden on the US health system, estimated at approximately $23 billion yearly.[5] Given the aging US population, identifying risk factors for falls and tailoring interventions (e.g., physical therapy, prescription medication choices, or environment-based interventions like handrails) to prevent falls are recognized public health priorities.

Orthostatic hypotension (OH) is a controversial risk factor for falls that has important implications for clinical guidelines on blood pressure management. The recently published SPRINT trial suggested that more intensive blood pressure management was associated with a lower risk of OH, but not a decreased risk of injurious falls.[6] OH has been traditionally thought to disproportionately impact older adults. The prevalence of OH increases with age,[7] reaching as high as 20% in adults age 75 years and older.[8] Furthermore, OH is associated with a history of falls as well as greater morbidity from falls in older adults.[8–10] Despite the focus in the literature on older adults, OH is also quite prevalent among middle-aged adults (as high as 15.9% in 1 study[11]), who have a notably lower fall rate. While in the short-term, middle-aged OH may not be a major contributor to risk of serious falls, it is unknown whether it might be associated with risk of falls over time as people age.

Thus, the aims of this prospective study were to: (i) determine whether OH in middle age was associated with risk of falls over the lifespan; (ii) characterize the continuous relationship between postural changes in systolic blood pressure (SBP) or diastolic blood pressure (DBP) and fall risk; and (iii) identify whether participant demographic characteristics or cardiovascular risk factors (obesity, hypertension, or diabetes) modified the association between OH and falls. We hypothesized that OH would be significantly associated with falls and this association would be more pronounced among older persons with cardiovascular risk factors.

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METHODS

Study population

The Atherosclerosis Risk in Communities (ARIC) Study is a community-based prospective cohort of 15,792 adults originally enrolled from 1987 to 1989 from 4 US communities and followed for over 2 decades.[12–14] Participants were ages 45 to 64 at the time of enrollment. Physical examinations, medical interviews, and laboratory tests were conducted as part of the original ARIC protocol. Of the original 15,792 baseline participants, our study population was limited to 12,661 participants, after excluding those who did not have an OH assessment at baseline (1987–1989) ($N = 2,599$) and who were missing relevant covariate data at baseline ($N = 532$).

Written informed consent was obtained from all participants and the study protocol was approved by institutional review boards at all study sites.

Exposure: orthostatic hypotension

During the baseline visit, supine SBPs and DBPs were measured with a Dinamap 1846 SX oscillometric device in participants, who had been lying for 20 minutes.[15,16] Measurements were taken approximately every 30 seconds for 2 minutes (range of 2–5 supine measurements with at least 4 measurements obtained for 90% of participants). Participants were subsequently asked to stand and once both their feet were planted on the ground, standing SBP and DBP were measured approximately every 30 seconds for 2 minutes (range of 2–5 standing measurements with at least 4 measurements recorded for 91% of participants). Change in SBP or DBP was defined as the difference between the average of the standing and the supine blood pressure measurements, excluding the first standing measurement to avoid restabilization effects that occur immediately after standing.[17] OH was defined using the consensus definition as a decrease in either SBP or DBP of at least 20 or 10 mm Hg, respectively.[18,19]

Outcome: falls resulting in hospitalization or a physician visit

A fall was defined as the first occurrence of any fall-related hospitalization or claim for inpatient or outpatient services after the baseline visit. Falls were identified *via* 2 sources: (i) active surveillance of all hospitalizations for all ARIC participants and (ii) linkage to Centers for Medicare and Medicaid Services (CMS) claims data from 1991 to 2013. Details related to falls ascertainment may be found in the Supplement (Supplementary Methods). Falls were grouped in the following categories using ICD-9 codes: (i) falls unspecified, defined using codes E888.0, E888.1, E888.8, and E888.9; (ii) falls on the same level (including slipping and collision), defined using codes E885.0–E885.4, E885.9, E886.0, and E886.9; and (iii) falls from a different level (including stairs/steps from both slipping and collision), defined using codes E880.0, E880.1, E880.9, E881.0, E881.1, E882.0, E883.0–E883.2, E883.9, E884.0–E884.6, and E884.9.

In 2013–2014, 6,192 ARIC participants of our analytic dataset were asked whether they had a fall in the preceding 6 months. While these falls events were not included in our primary analysis given the restricted time window embedded in this question, we compared self-reported falls to falls using CMS ICD-9 codes that were identified in the corresponding 6-month period as a validation analysis.

Baseline covariates of interest

Data were collected at baseline by trained study personnel using standardized protocols, including extensive quality control measures.[12–14] Covariates were selected *a priori* based on hypothesized relationships between OH, assessed at the baseline clinical examination and subsequent risk of falls. Age, sex, race, alcohol use (never, former, current), education level (less than high school, high school degree, or vocational school, at least some college or professional school), smoking status (never, former, current), history of stroke, hypertension medication use in last 2 weeks, diuretic medication use, antidepressant medication use, sedative medication use, hypnotic medication use, antipsychotic medication use, and anticholinergic medication use were self-reported. Participants' leisure time physical activity was assessed *via* the ARIC/Baecke Physical Activity questionnaire.[20]

Diabetes status was defined based on a fasting blood glucose ≥126 mg/dl, a nonfasting blood glucose ≥200 mg/dl, a self-reported diagnosis of diabetes, or self-reported diabetes medication use. Hypertension was defined as a SBP ≥140 mm Hg or DBP ≥90 mm Hg or self-report of antihypertensive medication use. Congestive heart failure at baseline was defined as active use of medications to treat heart failure or self-reported symptoms associated with heart failure based on the Gothenburg criteria.[21] Coronary heart disease at baseline was based on electrocardiograms (silent myocardial infarction), self-report, or self-reported history of previous coronary procedures.

Resting SBP and DBP was estimated from a mean of the second and third of 3 measurements obtained with a random-zero mercury sphygmomanometer. Heart rate was determined from a baseline electrocardiogram taken at rest. Body mass index was calculated using height and weight measurements. Serum creatinine was measured by the modified kinetic Jaffé method. Estimated glomerular filtration rate was determined from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[22]

Statistical analysis

Baseline characteristics were compared using means and proportions according to the presence of OH as well as according to whether a participant experienced a fall. Absolute risk was determined *via* the cumulative incidences (at 5-year increments) or incidence rates (per 1,000 person-years) for participants with and without OH. Age was used as the time axis in addition to follow-up time, given its importance as a risk factor for falls. Nested Cox proportional hazard models, using follow-up time (not age) as the time axis were used to examine the independent association of OH, postural change in SBP, and postural change in DBP with risk of falls. Follow-up time (not age) was used as the time axis in these analyses to allow for an age-based stratified analysis. To facilitate interpretation and comparison, postural change in SBP and DBP were presented per −5 mm Hg and per −1 SD. Model 1 was adjusted for age, sex, and race–study center. Model 2 was adjusted for all variables in Model 1 plus heart rate, body mass index, estimated glomerular filtration rate, diabetes, hypertension, alcohol use, education level, smoking status, physical activity, coronary heart disease, history of stroke, and congestive heart failure. Model 3 was adjusted for all variables in Model 2 plus hypertension medication

Table 1. Baseline population characteristics by OH, mean (SD), or *N* (%)

	Overall (*N* = 12,661)	No OH (*N* = 12,010)	OH (*N* = 651)
Age, year	54.1 (5.7)	53.9 (5.7)	57.4 (5.3)
Female, *N* (%)	6,961 (55.0)	6,604 (55.0)	357 (54.8)
Race–study center, *N* (%)			
Washington county (White)	3,121 (24.7)	2,935 (24.4)	186 (28.6)
Jackson (Black)	2,920 (23.1)	2,747 (22.9)	173 (26.6)
Minneapolis (White)	3,268 (25.8)	3,161 (26.3)	107 (16.4)
Forsyth (Black)	402 (3.2)	364 (3.0)	38 (5.8)
Forsyth (White)	2,950 (23.3)	2,803 (23.3)	147 (22.6)
Systolic blood pressure, mm Hg	121.2 (19.0)	120.7 (18.6)	130.7 (22.4)
Diastolic blood pressure, mm Hg	73.5 (11.2)	73.4 (11.1)	75.5 (12.7)
Resting heart rate, beats per minute	66.7 (10.3)	66.6 (10.1)	68.9 (12.8)
Estimated glomerular filtration rate, ml/min/1.73 m^2	102.3 (15.8)	102.6 (15.4)	96.3 (20.4)
Body mass index, kg/m^2	27.6 (5.3)	27.6 (5.3)	27.7 (6.1)
Leisure index, units	2.4 (0.6)	2.4 (0.6)	2.3 (0.6)
Diabetes, *N* (%)	1,502 (11.9)	1,356 (11.3)	146 (22.4)
Hypertension, *N* (%)	4,335 (34.2)	3,952 (32.9)	383 (58.8)
Hypertensive medication use in last 2 weeks, *N* (%)	3,810 (30.1)	3,469 (28.9)	341 (52.4)
CHD at baseline, *N* (%)	607 (4.8)	550 (4.6)	57 (8.8)
Prior stroke at baseline, *N* (%)	226 (1.8)	188 (1.6)	38 (5.8)
CHF at baseline, *N* (%)	567 (4.5)	511 (4.3)	56 (8.6)
Diuretic use, *N* (%)	2,196 (17.3)	2,008 (16.7)	188 (28.9)
Antidepressant use, *N* (%)	351 (2.8)	317 (2.6)	34 (5.2)
Sedative use, *N* (%)	186 (1.5)	179 (1.5)	7 (1.1)
Hypnotic medication use, *N* (%)	258 (2.0)	247 (2.1)	11 (1.7)
Antipsychotic medication use, *N* (%)	88 (0.7)	80 (0.7)	8 (1.2)
Anticholinergic use, *N* (%)	247 (2.0)	226 (1.9)	21 (3.2)
Alcohol use, *N* (%)			
Never	3,155 (24.9)	2,962 (24.7)	193 (29.6)
Former	2,371 (18.7)	2,203 (18.3)	168 (25.8)
Current	7,135 (56.4)	6,845 (57.0)	290 (44.5)
Education attainment, *N* (%)			
Low	2,900 (22.9)	2,657 (22.1)	243 (37.3)
Medium	5,192 (41.0)	4,955 (41.3)	237 (36.4)
High	4,569 (36.1)	4,398 (36.6)	171 (26.3)
Smoking status, *N* (%)			
Never	5,228 (41.3)	4,985 (41.5)	243 (37.3)
Former	4,140 (32.7)	3,939 (32.8)	201 (30.9)
Current	3,293 (26.0)	3,086 (25.7)	207 (31.8)

Abbreviation: CHD, coronary heart disease; CHF, congestive heart failure; OH, orthostatic hypotension.

use in last 2 weeks, diuretic use, antidepressant use, sedative use, hypnotic use, antipsychotic medication use, and anticholinergic medication use. Model 4 was adjusted for all the variables in Model 3 plus resting SBP and resting DBP. Finally, Model 5 included all the covariates of Model 4, but also included both postural change in SBP and DBP to allow a direct comparison of these 2 exposures. The continuous associations between postural change in SBP or DBP, and risk of fall, were characterized using restricted cubic splines with 4 knots specified *via* Harrell's method.[23]

We also tested for interactions by demographic characteristics (age, sex, race) or cardiovascular risk factors (obesity, hypertension, and diabetes) in Model 4. In addition, we performed sensitivity analyses examining the independent association of OH using different definitions of falls based on ARIC hospitalization surveillance data alone with follow-up starting from baseline, CMS claims alone among those with continuous enrollment with follow-up starting on the day of enrollment, and fee-for-service claims alone among those with continuous enrollment with follow-up starting on the day of enrollment. Furthermore, we repeated analyses using different ICD-9 groupings to define falls: (i) falls unspecified, (ii) falls on the same level (including slipping and collision), and (iii) falls from a different level (including stairs/steps from both slipping and collision).

All analyses were conducted using Stata 14.0 (StataCorp LP, College Station, TX).

RESULTS

The study population (N = 12,661) included 55% women and 26% Black participants with a mean baseline age of 54 (SD, 6) years (Table 1). Five percent of the study population had OH at baseline. During a median of 23 years of follow-up, there were 2,384 (19%) falls (occurring at 2.6 months to 26.4 years from date of the baseline examination); 22% of falls were identified from ARIC hospital surveillance, while 78% were identified from CMS Medicare claims (Supplementary Table S2). Of the falls identified from claims, 76% represented claims for outpatient services. The median crude time to a fall was 16.9 years (interquartile interval of 12.5–20.8) among participants without OH (number of falls was 2,234 of 12,010 participants) and 14.2 years (interquartile interval of 10.9–18.7) among participants with OH at baseline (number of falls was 150 of 651 participants). The most common ICD-9 code for fall was E885.9, i.e., "accidental fall from other slipping, tripping, or stumbling" (Supplementary Table S1). In our validation study comparing self-reported falls to those identified using CMS ICD-9 codes, we determined the sensitivity and specificity of CMS ICD-9 codes to be 5.3% and 99.6%, respectively (Supplementary Table S3).

The overall incidence rate of falls (identified from all available data sources), using age as the time axis, was 2.6 per 1,000 person-years. This varied significantly by the presence of OH with participants with OH at baseline having an incidence rate of 3.2 per 1,000 person-years vs. 2.5 per 1,000 person-years among those without OH at baseline (P = 0.03) (Supplementary Table S4).

After adjustment for age, sex, and race–study center (Model 1), OH in middle age was significantly associated with risk of falls (hazard ratio (HR): 1.43; 95% confidence interval (CI): 1.21, 1.69) (Table 2). After full adjustment (Model 4), this relationship was attenuated, but still significant (HR: 1.30; 95% CI: 1.10, 1.54). Similarly, both postural change in SBP or DBP were associated with falls, demonstrating adjusted HRs of 1.03 (95% CI: 1.01, 1.05) and 1.09 (95% CI: 1.05, 1.13)

Table 2. Association between orthostatic hypotension and risk of falls[a]

	Falls (*N* = 2,384)[a]	
	HR (95% CI)	***P***
Orthostatic hypotension		
Unadjusted	1.97 (1.67, 2.33)	<0.001
Model 1	1.43 (1.21, 1.69)	<0.001
Model 2	1.33 (1.12, 1.57)	0.001
Model 3	1.31 (1.10, 1.54)	0.002
Model 4	1.30 (1.10, 1.54)	0.002
Postural change in SBP, per −5 mm Hg		
Unadjusted	1.07 (1.05, 1.09)	<0.001
Model 1	1.03 (1.02, 1.05)	<0.001
Model 2	1.03 (1.01, 1.05)	0.001
Model 3	1.03 (1.01, 1.05)	0.002
Model 4	1.03 (1.01, 1.05)	0.002
Postural change in DBP, per −5 mm Hg		
Unadjusted	1.14 (1.10, 1.18)	<0.001
Model 1	1.11 (1.07, 1.16)	<0.001
Model 2	1.09 (1.05, 1.13)	<0.001
Model 3	1.09 (1.05, 1.13)	<0.001
Model 4	1.09 (1.05, 1.13)	<0.001
Postural change in SBP, per −1 SD (Model 4)	1.07 (1.02, 1.11)	0.002
Postural change in DBP, per −1 SD (Model 4)	1.10 (1.05, 1.15)	<0.001
Model 5 both postural changes in SBP and DBP		
SBP per −5 mm Hg	1.01 (0.98, 1.03)	0.53
DBP per −5 mm Hg	1.08 (1.03, 1.13)	0.002

Model 1: adjusted for age, sex, race–study center. Model 2: Model 1 + heart rate, body mass index, estimated glomerular filtration rate, diabetes, hypertension, alcohol use, education level, smoking status, leisure index, prior CHD, prior CHD, prior stroke. Model 3: Model 2 + hypertension medication use in last 2 weeks, diuretic use, antidepressant use, sedative use, hypnotic use, antipsychotic medication use, anticholinergic medication use. Model 4: Model 3 + resting systolic blood pressure, resting diastolic blood pressure. Model 5: Model 4 including both postural change in SBP (per −5 mmHg) and postural change in DBP (per −5 mm Hg). Abbreviations: ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

[a] Falls were ascertained from diagnostic codes from either ARIC or CMS sources.

per −5 mm Hg, respectively. Interestingly, postural changes in DBP were more significantly associated with falls than postural changes in SBP (Model 5). The relationship between postural change in SBP and DBP appeared linear with no obvious threshold at the standard cut points (Figure 1). There was no evidence of effect modification across strata of age, sex, race, obesity, hypertension, or diabetes (Table 3).

Sensitivity analyses were performed, restricting our definition of falls to either ARIC cohort surveillance of hospitalized events, and CMS Medicare claims, or continuous FFS alone. Despite notable attenuation, we observed similar patterns of association regardless of the source of falls (Supplementary Table S5). Similarly, defining falls by more specific categories of ICD-9 codes merely attenuated our findings (Supplementary Table S6).

DISCUSSION

We found that baseline OH assessed in a middle-aged, community-based population was associated with risk of hospital- or health care-related falls over a substantial time period. Postural reductions in either SBP or DBP both showed inverse associations with falls; although, changes in DBP were more strongly and significantly associated with risk of falls. Furthermore, similar associations between OH and fall risk were observed in demographic subgroups and in persons with and without cardiovascular risk factors. Overall, our study suggests that OH and, more specifically, postural changes in DBP are important risk factors for falls over a long period of time.

Our finding that OH precedes falls in a community-based, middle-aged population represents an important contribution to the literature. Prior cross-sectional studies have shown that OH is associated with history of falls among older adults[8,10,24] with few exceptions.[25] However, prospective studies examining this relationship are small, of short duration, and inconsistent with some showing OH to be associated with risk of falls[26–30] and others showing no association.[31–38] One of the larger prospective studies, conducted in 844 nursing home residents, reported that OH was associated with a higher risk of falls (relative risk: 2.1, 95% CI: 1.4, 3.1) during 1.2 years of follow-up.[26] In contrast, a larger prospective study of 1,517 ambulatory Chinese patients, showed that OH was not associated with falls after adjustment for other risk factors.[31] These inconsistencies have led to the conclusion that OH is an important predictor of falls in institutionalized, but not ambulatory adults.[39] In contrast, our study of 12,661 ambulatory middle-aged adults, showed that OH was not only associated with falls, but also that the association was independent of other risk factors well in advance of a fall event.

The hypothesis that OH is causal in the pathogenesis of falls is biologically plausible. In healthy persons, change from a recumbent to standing position causes venous pooling, decreased venous return, and reduced stroke volume.[40] The cardiovascular system responds with increased heart rate and vasoconstriction to maintain cerebral perfusion.[40] As 1 ages, these responses become blunted—heart rate is more fixed, blood vessels are less responsive to changes in pressure and hormonal signaling pathways, and often there is reduced blood volume due to dehydration or reduced endogenous blood production.[40] Many of these acquired conditions are irreversible and worsen over time. Furthermore, adults are

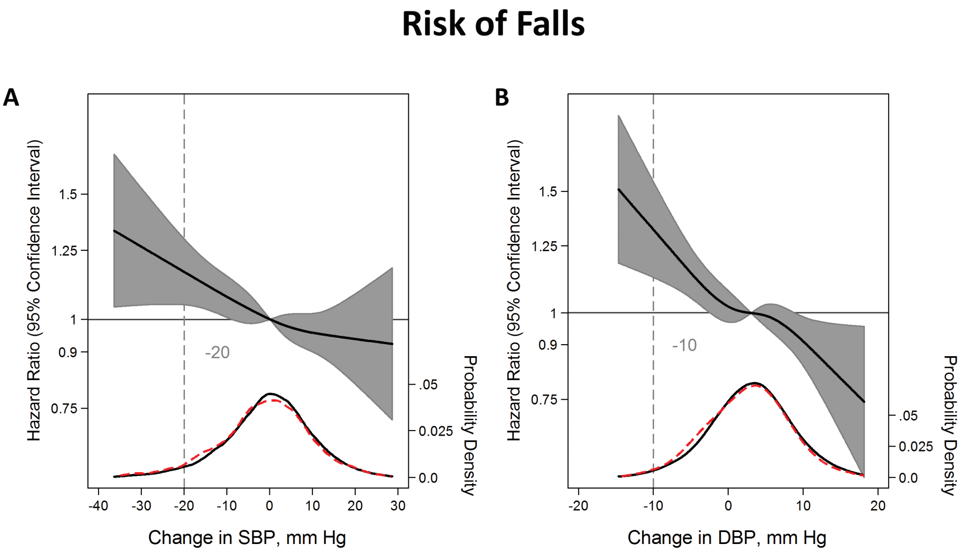

Figure 1. Adjusted hazard ratios (solid line) for falls between baseline and 1 January 2012, according to postural change in (**A**) SBP or (**B**) DBP, using a restricted cubic spline model. Gray shade represents 95% confidence intervals. Vertical lines represent orthostatic hypotension thresholds (−20 mm Hg for SBP; −10 mm Hg for DBP). The models were expressed relative to the 50th percentile of postural change in SBP or DBP with 4 knots specified using Harrell's method.[23] Models were adjusted for age, sex, race–study center, heart rate, body mass index, estimated glomerular filtration rate, diabetes, hypertension, alcohol use, education level, smoking status, leisure index, prior coronary heart disease, prior stroke, prior congestive heart failure, hypertension medication use in last 2 weeks, diuretic use, antidepressant use, sedative use, hypnotic use, antipsychotic medication use, anticholinergic medication use, resting SBP, and resting DBP. The plot was truncated at the 0.5st and 99.5th percentiles of postural change in SBP or DBP (standing blood pressure minus supine blood pressure; note that a negative value represents a drop in blood pressure with standing). The hazard ratios are shown on a natural log scale. In addition, overlaid are kernel density plots depicting the distribution of postural change in SBP or DBP by participants who fell (dash) vs. those who did not fall (solid). Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 3. Stratified analysis of the association between orthostatic hypotension and risk of falls[a]

	N	HR (95% CI)	*P* interaction
Age (years)[b]			
<50	3,408	1.60 (0.85, 3.02)	0.72
50–60	6,952	1.23 (0.97, 1.58)	
>60	2,294	1.35 (1.04, 1.75)	
Sex			
Male	5,694	1.61 (1.23, 2.11)	0.11
Female	6,960	1.18 (0.95, 1.46)	
Race[c]			
White	9,336	1.27 (1.04, 1.54)	0.40
Black	3,318	1.51 (1.08, 2.13)	
Obese (body mass index ≥30 kg/m^2)			
No	9,242	1.28 (1.04, 1.57)	0.76
Yes	3,412	1.36 (1.01, 1.84)	
Hypertension			
No	8,323	1.29 (1.00, 1.66)	0.72
Yes	4,331	1.25 (0.99, 1.56)	
Diabetes			
No	11,152	1.28 (1.06, 1.55)	0.87
Yes	1,502	1.35 (0.93, 1.96)	

Models adjusted for all covariates with exception of covariate related to associated strata. Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; HR, hazard ratio.

[a] Falls were ascertained from diagnostic codes from either ARIC or CMS sources.

[b] When evaluating an interaction between strata of age, the age variable was replaced with a simplified variable (<50, 50–60, >60).

[c] In analysis of strata by race, the race–ARIC center variable was replaced by a dichotomous Black vs. White variable to reflect the strata presented in this table and assess for an interaction.

commonly introduced to medications as they age, e.g., diuretics, beta-blockers, that may attenuate the normal physiologic response to standing. This contributes to a number of symptoms—lightheadedness, vision problems, weakness, fatigue, trouble concentrating, and head or neck discomfort,[41] which can increase the risk of falling.

In this study, for the first time, we characterized the continuous association between postural changes in SBP or DBP and falls. Not only were they both associated with falls, but the inverse relationships between postural change in SBP or DBP extended above and below the cut points used in the consensus definition of OH with no threshold effect. These findings highlight a need for further research to establish a definition of OH based on more objective evidence, such as clinically relevant outcomes (e.g., fall vs. fracture vs. mortality).

We found postural change in DBP to be a stronger predictor of falls than postural changes in SBP. While prior studies have shown postural changes in DBP to be associated with an increased risk of coronary events,[42] myocardial infarction,[43] and mortality,[44] its role in the development of falls is unclear. In 1 study of 446 diabetic participants with mean follow-up of 5 years, postural change in DBP (not SBP), was associated with more frequent falls.[45] However, the mechanism behind this association is beyond the scope of this study.

Given the public health burden of falls, this study has important implications. Not only was OH associated with subsequent fall, but it was associated with falls many years after the assessment of OH. This latency period between middle age OH and falls supports the notion that the pathogenesis of a fall is a multifactorial process. Prior research studies have identified multiple factors that contribute to falls—age, muscle strength, gait speed, etc.[31,39] It is possible that when OH is developed at a younger age, a person can compensate for this destabilizing factor, but with age the ability to compensate for OH is lost, which we speculate could be related to the acquisition of additional functional and neurologic deficits. However, further research is needed to confirm this hypothesis. At the very least, adults identified as having OH should receive special consideration when prescribed medications known to worsen alertness, affect balance, or increase the risk of falls.[34,37,39] Moreover, interventions useful in preventing falls may be worth implementing in adults with OH such as physical therapy.[46]

This study has a number of important limitations. First, fall history was not assessed at baseline. As a result, we are unable to differentiate between participants with falls prior to baseline vs. participants who never had a fall. Falls are estimated to occur in about 1% of middle-aged adults each year.[47] Second, while external cause of injury codes are reportedly valid,[48] there is likely substantial under-ascertainment of falls given the fact that we only capture falls reported to health care providers, not the large number of falls that are not reported and do not result in significant injury. This is supported by the low sensitivity we observed from CMS claims data (for further elaboration on CMS limitations see Supplementary Methods). Third, OH was measured in a subgroup of ARIC participants due to late implementation of this protocol and was not re-measured at a later time. As a result, our sample size was smaller than the original ARIC cohort; furthermore, we could not evaluate change in OH over time. Fourth, the OH assessment reflected the first 1–2 minutes after standing, but not 3 minutes or more, as suggested by the consensus definition. As a result, it is possible the OH status of some participants was misclassified. Fifth, our analyses of types of falls according to broader groupings of ICD-9 codes, namely, falls from the same level and falls from a different level had fewer events. As a result, these results may be underpowered to show an association between OH and falls. Finally, residual confounding is always a concern with observational studies. In particular, we lack data on important contributing factors such as vision, neuropathy, long-term glucose-lowering medication use, vitamin D deficiency, vitamin B12 deficiency, osteoarthritis, and strength.

This study also has a number of strengths. Its biracial, large sample is representative of a general US population. Further, participants were followed for a substantial time period.

Hospitalization records were reviewed in a detailed fashion by trained ARIC staff following a rigorous protocol. Use of ICD-9 codes to ascertain falls ensures that these events had some degree of clinical relevance. Finally, OH was assessed *via* a standardized protocol. This along with other covariate measures afforded the opportunity to account for multiple potential confounders in our models.

In conclusion, the traditional definition of OH was associated with risk of fall irrespective of participant characteristics or comorbid conditions. Postural change in SBP and DBP were associated with fall above and below traditional cut points with DBP being more strongly associated with risk of falls. Future studies should examine alternative definitions of OH as well as exposures and outcomes associated with change in OH over time. Finally, future studies should determine whether targeted therapies can reduce falls in persons with OH.

SUPPLEMENTARY MATERIAL

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

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DISCLOSURE

The authors declared no conflict of interest.

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