Orthostatic hypotension, dizziness, neurology outcomes, and death in older adults

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Abstract

Objective

To test the hypothesis that orthostatic hypotension (OH) might cause cerebral hypoperfusion and injury, we examined the longitudinal relationship between OH or orthostatic symptoms and incident neurologic outcomes in a community population of older adults.

Methods

Cardiovascular Health Study participants (≥ 65 years) without dementia or stroke had blood pressure (BP) measured after lying down for 20 minutes and after standing 3 for minutes. Participants reported dizziness immediately upon standing and any dizziness in the past 2 weeks. OH was defined as a drop in standing systolic/diastolic BP $\geq 20/\geq 10$ mm Hg. We determined the association between OH or dizziness with (1) MRI brain findings (ventricular size, white matter hyperintensities, brain infarcts) using linear or logistic regression, (2) cognitive function (baseline and over time) using generalized estimating equations, and (3) prospective adjudicated events (dementia, stroke, death) using Cox models. Models were adjusted for demographic characteristics and OH risk factors. We used multiple imputation to account for missing OH or dizziness ($n = 534$).

Results

Prior to imputation, there were 5,007 participants (mean age 72.7 ± 5.5 years, 57.6% women, 10.9% Black, 16% with OH). OH was modestly associated with death (hazard ratio [HR] 1.11; 95% confidence interval 1.02–1.20), but not MRI findings, cognition, dementia, or stroke. In contrast, dizziness upon standing was associated with lower baseline cognition ($\beta = -1.20$; -1.94 to -0.47), incident dementia (HR 1.32; 1.04–1.62), incident stroke (HR 1.22; 1.06–1.41), and death (HR 1.13; 1.06–1.21). Similarly, dizziness over the past 2 weeks was associated with higher white matter grade ($\beta = 0.16$; 0.03–0.30), brain infarcts (OR 1.31; 1.06–1.63), lower baseline cognition ($\beta = -1.18$; -2.01 to -0.34), and death (HR 1.13; 1.04–1.22).

Conclusions

Dizziness was more consistently associated with neurologic outcomes than OH 3 minutes after standing. Delayed OH assessments may miss pathologic information related to cerebral injury.

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Glossary

3MSE = modified Mini-Mental State Examination; **ARIC** = Atherosclerosis Risk in Communities; **BMI** = body mass index; **BP** = blood pressure; **CHS** = Cardiovascular Health Study; **CVD** = cardiovascular disease; **CI** = confidence interval; **DBP** = diastolic blood pressure; **HDL** = high-density lipoprotein; **HR** = hazard ratio; **OH** = orthostatic hypotension; **OR** = odds ratio; **SBP** = systolic blood pressure.

Dementia and stroke contribute to over \$170 billion in US health care costs per year,^{1–3} such that identifying causes of vascular brain injury represents a major public health priority. Orthostatic hypotension (OH), a drop in blood pressure (BP) upon standing, is highly prevalent among older adults⁴ and represents an important predictor of both incident dementia⁵ and stroke.⁶ It is hypothesized that OH causes brain injury⁷ via the accumulation of small ischemic events from recurrent hypoperfusion.⁸

The Cardiovascular Health Study (CHS) study is a community-based cohort, examining risk factors of stroke and cognitive decline in older adults.⁹ The CHS previously demonstrated that OH measured 3 minutes after standing was associated with white matter lesions,¹⁰ but not incident stroke.¹¹ Whether OH was associated with change in white matter lesions over time or additional clinical events such as cognitive decline or dementia was not reported. Notably, while BP was not assessed immediately after standing, participants were asked about dizziness with standing, a symptom that is known to reflect short-term postural changes in BP¹²; however, its association with neurologic outcomes was not examined.

In this study, we determined the relationship between OH or self-reported dizziness and (1) cross-sectional structural features and longitudinal change in cranial MRI, (2) cognitive function, and (3) incident dementia, incident stroke, or death. We hypothesized that both OH and dizziness would associate with MRI findings suggestive of atrophy and vascular disease, more rapid cognitive decline, and higher risk of dementia, stroke, and death.

Methods

Study population

The CHS began in 1989–1990 as a prospective cohort of 5,201 adults, age 65 years and older, from 4 US communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. In 1992–1993, 687 African Americans were recruited for participation in the study (total 5,888). Surviving participants (n~250) continue to be followed. During baseline visits, all participants underwent an OH assessment along with medical interviews, serum collections, and physical examinations.

In this analysis, we excluded participants with a self-reported history of stroke (n = 249), a self-reported history of dementia

(n = 9), and those missing relevant covariate data (n = 239). A number of participants met more than 1 exclusion criterion. Participants missing OH assessments (n = 470), self-reported dizziness with standing (n = 43), and self-reported dizziness in the past 2 weeks (n = 35) were ultimately included in our multiple imputation sample. Our final analytic sample prior to imputation was 5,007 participants.

Standard protocol approvals, registrations, and patient consents

Institutional review boards approved the study protocol at all sites, and all participants provided written informed consent. A STROND (Standards of Reporting of Neurological Disorders) checklist is available from Dryad (doi.org/10.5061/dryad.qbzkh18dt).

Exposure: OH

OH was assessed at baseline with a mercury sphygmomanometer (Baumanometer; W.A. Baum Company, Copiague, NY) following 20–30 minutes of supine rest.^{9,13} After recording systolic BP (SBP) and diastolic BP (DBP), participants assumed seated and then standing positions. Participants were allowed up to 30 seconds in the seated position if needed. Once standing, participants' arms were rested on a bedside table with height at heart level. Participants were asked "Are you feeling any dizziness, light-headedness, or faintness?" Anyone answering yes was immediately seated. If symptoms precluded the participant from standing again, the procedure ended. If symptoms resolved or were mild, participants resumed standing and a second SBP and DBP was recorded after 3 minutes of standing.

As part of their baseline medical history interview, participants were also asked, "Have you been dizzy during the past 2 weeks?"

Change in SBP or DBP was determined by subtracting supine from standing measurements. Systolic OH was defined as a drop in SBP of at least 20 mm Hg; diastolic OH, as a drop in DBP of at least 10 mm Hg; and consensus OH, as meeting at least one of the thresholds for systolic or diastolic OH.^{14,15}

Outcomes: MRI structure, cognition, dementia, stroke, and death

Details of outcome ascertainment are provided in supplemental methods SM1 (available from Dryad at doi.org/10.5061/dryad.qbzkh18dt). In brief, we examined 4 features of MRI structure: ventricular size, white matter lesions, change

in white matter lesions (over a 5-year period), and brain infarcts. The first MRI was performed in 3,660 participants in 1991–1994. The second MRI was measured in 2,116 participants about 5 years later (1997–1999). There were 3,147 who met other inclusion criteria with MRI assessments for ventricular size, white matter lesions, and brain infarcts. Among these, 1,858 underwent a second MRI for assessing change in white matter lesions.

We also measured cognitive function using a combination of cognitive tests (primarily the modified Mini-Mental State Examination score [3MSE]) in 1990–1991 to 1998–1999 and again in 2005–2006. In later years, CHS administered the Telephone Instrument of Cognitive Status and the Informant Questionnaire on Cognitive Decline to accommodate telephone-based interviews as well as care proxies that might answer on behalf of participants. Of participants who underwent cognitive testing, 4,864 were available for these analyses.

Dementia, stroke, and mortality were ascertained during follow-up and adjudicated by a panel of investigators. Dementia was assessed between 1991–1994 and 1998–1999 and excluded 227 prevalent cases. There were 2,979 participants followed for dementia. All 5,007 eligible participants were followed for stroke and death from baseline through 2015.

Other covariates

Additional participant data were collected by trained study personnel, following standardized protocols.⁹ Covariates were selected a priori based on the existing literature for OH.^{5,16} Age, sex (male or female), race (non-Black or Black), education (number of years), current drinking status (yes or no), and smoking status (never, former, current) were self-reported. Diabetes status and use of hypertension medications, diuretics, or beta-blockers were also based on self-report.

Both high-density lipoprotein (HDL) cholesterol and triglycerides were measured in fasted serum using standard assays. Seated SBP and DBP were calculated from a mean of 2 measurements obtained after 5 minutes of seated rest with a Hawksley random zero sphygmomanometer, model 7076 (Hawksley and Sons Limited, Sussex, England). Hypertension status was defined by a SBP ≥ 140 mm Hg or a DBP ≥ 90 mm Hg, or active use of antihypertension medication. Body mass index (BMI) was calculated using height and weight measurements.

Statistical analysis

We compared baseline characteristics by OH status with means and proportions. Given the 470 missing OH assessments and the association of dizziness as well as demographic characteristics with missing standing BP (see Dryad, Supplement Table ST1, doi.org/10.5061/dryad.qbzk18dt), we used multiple imputation chained equations to impute values of missing OH measurements as well as missing self-reported dizziness.

We examined outcomes following the same standard approach: (1) a minimally adjusted model (model 1), adjusted

for age, female sex, Black race, and study site; (2) a fully adjusted model (model 2) adjusted for model 1 covariates and BMI, HDL cholesterol, triglycerides, diabetes status, hypertension status, mean SBP, mean DBP, diuretic use, beta-blocker use, education, current drinking status, and smoking status; and (3) a fully adjusted model (model 2), which included imputed data.

Regression equations differed by outcome examined. Among MRI measures, we used linear regression for ventricular and white matter grades. We used logistic regression for the presence or absence of brain infarct. For cognitive function, we used generalized estimating equations to account for the repeat measurements, specifying a Gaussian distribution, identity link, exchangeable correlation matrix, and robust variance estimation. Models included an OH or dizziness variable (representing the baseline association), time variable, and an interaction term for each OH or dizziness variable as a test for difference in rate of decline over time. For incident dementia, incident stroke, and mortality, we used Poisson regression, adjusted for age, sex, and race, to estimate incidence rates, and Cox proportional hazards models to estimate relative hazards.

We characterized the relationship between postural change in SBP or DBP with clinical events, using restricted cubic splines adjusted for model 2 covariates with 4 knots at locations determined by Harrell's method,¹⁷ centered at the median value.

In sensitivity analyses, we modeled white matter lesions as a grade >3 (yes or no) or any decline in white matter grade between MRIs (yes or no), using logistic regression.¹⁸ In addition, we modeled cognitive function using 3MSE examinations only. Moreover, we examined the association of missing standing SBP and DBP, as a proxy for dizziness upon standing, among those who participated in the OH protocol with study outcomes, using those who had complete supine SBP and DBP measurements. We also repeated all analyses in a “complete case” subpopulation, restricted to participants with all outcome assessments. Finally, we examined the relationship of OH or orthostatic symptoms with cardiovascular disease (CVD) related mortality. Models were adjusted for model 2 covariates.

All analyses were conducted using Stata 15.1 (StataCorp LP, College Station, TX).

Data availability

Individual de-identified participant data are available for proposals approved by CHS investigators.

Results

The study population ($n = 5,007$) was 57.6% women and 10.9% Black with a mean baseline age of 72.7 (SD 5.5) years

(table 1); 800 participants (16%) had OH upon standing based on the consensus definition. Participants with OH were less likely to be Black or to use alcohol. Dizziness during the OH protocol was reported by 941 participants and dizziness in the past 2 weeks was reported by 673 participants (see Dryad, supplemental table ST2, doi.org/10.5061/dryad.qbzkh18dt).

MRI findings

Consensus OH, systolic OH, and diastolic OH were not associated with any of the MRI findings (table 2). Similarly, dizziness with standing was not associated with any of the MRI findings. However, dizziness in the past 2 weeks was

associated with higher white matter grade ($\beta = 0.16$; 95% confidence interval [CI] 0.02–0.30) and higher odds of brain infarcts (odds ratio [OR] 1.31; 95% CI 1.04–1.65). Imputing missing OH measures did not substantially alter these findings. Also, sensitivity analyses examining alternative definitions of white matter lesions did not significantly change our findings (see Dryad, supplemental table ST3, doi.org/10.5061/dryad.qbzkh18dt).

Change in cognitive function over time

We examined the relationship between OH or dizziness questions with cognitive function at baseline and whether change in cognitive function varied by OH or dizziness

Table 1 Baseline characteristics overall and by the presence of orthostatic hypotension (OH)

	Overall (n = 5,007)	No OH (n = 4,207)	OH (n = 800)
Age, y	72.7 (5.5)	72.6 (5.5)	73.2 (5.4)
Female	57.6	57.9	56.5
Black	10.9	11.4	8.5
Study site			
Forsyth County, NC	23.6	25.6	13.3
Sacramento County, CA	25.4	25.6	24.8
Washington County, MD	24.2	21.7	37.5
Pittsburgh, PA	26.7	27.1	24.5
Body mass index, kg/m ²	26.7 (4.7)	26.9 (4.8)	26.0 (4.3)
HDL cholesterol, mg/dL	54.3 (15.6)	54.5 (15.7)	53.2 (15.3)
Triglycerides, mg/dL	138.7 (73.8)	137.9 (73.2)	143.1 (76.7)
Diabetes	16.1	15.7	18.1
Hypertension ^a	64.9	64.6	66.9
Systolic blood pressure, mm Hg	136.1 (21.5)	135.8 (21.2)	137.6 (22.9)
Diastolic blood pressure, mm Hg	70.7 (11.2)	71.0 (11.1)	68.8 (11.7)
Antihypertension medicine use	46.2	46.0	46.9
Diuretic use	25.8	25.5	27.0
Beta-blocker use	12.0	12.0	12.4
Dizziness during standing protocol	18.8	19.4	15.4
Dizziness in the past 2 weeks	13.4	13.6	12.5
Education, years of schooling	13.8 (4.7)	13.8 (4.7)	13.4 (4.6)
Current alcohol use	51.2	52.0	47.4
Smoking status			
Never	46.3	46.7	44.1
Former	42.0	41.7	43.4
Current	11.8	11.6	12.5

Abbreviation: HDL = high-density lipoprotein.

Values are mean (SD) or %.

^a Defined by a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg or active hypertension medication use.

Table 2 Orthostatic hypotension (OH) measures and MRI findings

	Ventricles grade, ^a β (95% CI)	White matter grade, ^a β (95% CI)	Worsening white matter grade, ^b β (95% CI)	Brain infarct, OR (95% CI)
Model 1 (n = 3,147)				
Consensus OH	−0.02 (−0.13 to 0.10)	0.02 (−0.11 to 0.15)	0.06 (−0.08 to 0.20)	1.15 (0.93 to 1.43)
Systolic OH	−0.08 (−0.21 to 0.06)	−0.02 (−0.18 to 0.14)	0.16 (−0.01 to 0.33)	1.03 (0.80 to 1.33)
Diastolic OH	0.02 (−0.13 to 0.17)	0.10 (−0.08 to 0.27)	−0.12 (−0.31 to 0.07)	1.20 (0.91 to 1.58)
Dizziness with standing	0.05 (−0.06 to 0.16)	0.02 (−0.11 to 0.15)	0.00 (−0.14 to 0.14)	1.06 (0.86 to 1.30)
Dizziness in past 2 weeks	0.09 (−0.04 to 0.21)	0.16 (0.02 to 0.31)	−0.04 (−0.20 to 0.12)	1.33 (1.06 to 1.67)
Model 2 (n = 3,147)				
Consensus OH	−0.01 (−0.12 to 0.11)	0.01 (−0.12 to 0.14)	0.04 (−0.10 to 0.19)	1.14 (0.92 to 1.42)
Systolic OH	−0.06 (−0.20 to 0.07)	−0.03 (−0.18 to 0.13)	0.12 (−0.05 to 0.29)	1.03 (0.80 to 1.34)
Diastolic OH	0.03 (−0.12 to 0.18)	0.10 (−0.08 to 0.27)	−0.10 (−0.29 to 0.09)	1.19 (0.90 to 1.58)
Dizziness with standing	0.05 (−0.06 to 0.16)	0.02 (−0.11 to 0.14)	0.01 (−0.12 to 0.15)	1.05 (0.85 to 1.29)
Dizziness in past 2 weeks	0.09 (−0.04 to 0.21)	0.16 (0.01 to 0.30)	−0.02 (−0.18 to 0.13)	1.31 (1.04 to 1.65)
Model 2 with imputed missing data (n = 3,396)				
Consensus OH	0.00 (−0.11 to 0.12)	0.02 (−0.11 to 0.15)	0.03 (−0.11 to 0.18)	1.17 (0.94 to 1.44)
Systolic OH	−0.05 (−0.19 to 0.08)	−0.02 (−0.18 to 0.13)	0.12 (−0.05 to 0.30)	1.06 (0.82 to 1.38)
Diastolic OH	0.03 (−0.12 to 0.18)	0.11 (−0.06 to 0.28)	−0.09 (−0.28 to 0.10)	1.20 (0.90 to 1.58)
Dizziness with standing	0.08 (−0.03 to 0.18)	0.01 (−0.11 to 0.13)	−0.03 (−0.17 to 0.10)	1.06 (0.87 to 1.29)
Dizziness in past 2 weeks	0.11 (−0.01 to 0.23)	0.17 (0.03 to 0.30)	−0.03 (−0.18 to 0.12)	1.31 (1.06 to 1.63)

Abbreviations: CI = confidence interval; OR = odds ratio.

Model 1 adjusted for age, female sex, Black race, and research clinic. Model 2 adjusted for age, female sex, Black race, research clinic, body mass index, HDL cholesterol, triglycerides, diabetes status, hypertension status, mean systolic blood pressure, mean diastolic blood pressure, diuretic use, beta-blocker use, education, current drinking status, and smoking status.

^a Grades 0 to 9, with higher grades indicating more abnormal.

^b There were fewer participants with a repeat MRI: these numbers were 1,858 for models 1 and 2 and 2,002 for model 2 with imputed missing data.

status over time (table 3). After adjustment, only self-reported dizziness during the past 2 weeks was associated with lower cognitive function at baseline ($\beta = -1.20$; 95% CI -2.11 to -0.29). Only diastolic OH was associated with a greater decline in cognitive function over time. Notably, imputation of missing covariates did impact the association of dizziness upon standing, which became associated with a lower cognitive score at baseline ($\beta = -0.68$; 95% CI -1.44 to -0.07 without imputation vs $\beta = -1.20$; 95% CI -1.94 to 0.47 with imputation). In our sensitivity analysis restricted to 3MSE only, results were generally attenuated. However, both dizziness upon standing and dizziness in the past 2 weeks continued to be associated with lower cognitive scores at baseline. Also, in this sensitivity analysis, dizziness upon standing was associated with faster decline in score over time with imputation (see Dryad, supplemental table ST4, doi.org/10.5061/dryad.qbzkh18dt).

Dementia, stroke, and mortality

Over a median of 6.0 years of follow-up, we confirmed 417 cases of dementia. The overall adjusted incidence rate of

dementia was 21.9 per 1,000 person-years (see Dryad, supplemental table ST5, doi.org/10.5061/dryad.qbzkh18dt). Change in SBP or DBP across the range of postural changes were not associated with incident dementia (figure, A and D). After adjustment for model 2 covariates, only dizziness reported during the process of standing (hazard ratio [HR] 1.34; 95% CI 1.06–1.71) and dizziness in the last 2 weeks (HR 1.31; 95% CI 1.01–1.70) were associated with incident dementia (table 4). The association of dizziness in the last 2 weeks with incident dementia was attenuated after imputation (HR 1.25; 95% CI 0.98–1.59).

Stroke was identified in 1,020 cases over a median of 12.6 years of follow-up at an overall adjusted incidence rate of 16.0 per 1,000 person-years (see Dryad, supplemental table ST5, doi.org/10.5061/dryad.qbzkh18dt). Risk varied across the range of postural change in BP, with a lower risk of stroke being associated with increases in SBP upon standing (figure, B) and a higher risk of stroke being associated with decreases in DBP upon standing (figure, E). None of the OH metrics or

Table 3 Association of orthostatic hypotension (OH) measures with cognitive function

	Cognitive score ^a		
	N	Baseline cognition, β (95% CI)	Difference in cognition per year of follow-up, β (95% CI)
Model 1			
Consensus OH	4,864	0.10 (−0.74 to 0.94)	−0.09 (−0.21 to 0.02)
Systolic OH	4,864	0.11 (−0.89 to 1.12)	−0.09 (−0.23 to 0.05)
Diastolic OH	4,864	0.27 (−0.86 to 1.40)	−0.19 (−0.35 to −0.04)
Dizziness with standing	4,864	−1.68 (−2.48 to −0.87)	−0.03 (−0.14 to 0.07)
Dizziness in past 2 weeks	4,864	−1.68 (−2.66 to −0.70)	−0.04 (−0.15 to 0.08)
Model 2			
Consensus OH	4,864	0.51 (−0.28 to 1.31)	−0.10 (−0.21 to 0.02)
Systolic OH	4,864	0.54 (−0.42 to 1.50)	−0.09 (−0.23 to 0.05)
Diastolic OH	4,864	0.74 (−0.32 to 1.80)	−0.19 (−0.35 to −0.04)
Dizziness with standing	4,864	−0.68 (−1.44 to 0.07)	−0.03 (−0.14 to 0.08)
Dizziness in past 2 weeks	4,864	−1.20 (−2.11 to −0.29)	−0.04 (−0.15 to 0.08)
Model 2 with imputed missing data			
Consensus OH	5,536	0.48 (−0.30 to 1.26)	−0.10 (−0.21 to 0.01)
Systolic OH	5,536	0.44 (−0.53 to 1.40)	−0.10 (−0.23 to 0.03)
Diastolic OH	5,536	0.71 (−0.32 to 1.73)	−0.19 (−0.34 to −0.03)
Dizziness with standing	5,536	−1.20 (−1.94 to −0.47)	−0.02 (−0.12 to 0.08)
Dizziness in past 2 weeks	5,536	−1.18 (−2.01 to −0.34)	−0.06 (−0.17 to 0.05)

Abbreviation: CI = confidence interval.

Model 1 adjusted for age, female sex, Black race, and research clinic. Model 2 adjusted for age, female sex, Black race, research clinic, body mass index, high-density lipoprotein cholesterol, triglycerides, diabetes status, hypertension status, mean systolic blood pressure, mean diastolic blood pressure, diuretic use, beta-blocker use, education, current drinking status, and smoking status.

^a Cognitive score was based on the modified Mini-Mental State Examination if observed; if not, it was estimated from the Telephone Instrument of Cognitive Status and/or Informant Questionnaire on Cognitive Decline (IQCODE) using both the original and short forms of the IQCODE. Modeling performed using generalized estimating equations.

self-reported dizziness were associated with incident stroke (table 4). However, after imputation, dizziness with standing was associated with incident stroke (HR 1.22; 95% CI 1.06–1.41).

A total of 4,372 participants died during the follow-up period; the median follow-up duration was 13.7 years. The overall adjusted mortality rate was 64.7 per 1,000 person-years (see Dryad, supplemental table ST5, doi.org/10.5061/dryad.qbzkh18dt). Greater drops in SBP and DBP were associated with a higher risk of death (figure, C and F). Furthermore, both consensus OH (HR 1.09; 95% CI 1.00–1.18) and systolic OH (HR 1.13; 95% CI 1.03–1.25) were associated with mortality (model 2, table 4). After imputation, both dizziness with standing (HR 1.13; 95% CI 1.06–1.21) and dizziness in the past 2 weeks (HR 1.13; 95% CI 1.04–1.22) were also associated with mortality.

In a sensitivity analysis, early termination of the OH protocol was associated with higher risk of brain infarct (OR 1.86; 95% CI 1.36–2.56) and death (HR 1.22; 95% CI 1.09–1.37) compared with those who were able to complete the OH protocol (see Dryad, supplemental table ST6, doi.org/10.5061/dryad.qbzkh18dt). Analyses restricted to complete outcome ascertainment were similar, with the following exceptions: attenuation of the association between dizziness in the past 2 weeks and white matter grade, attenuation of the association of dizziness in the past 2 weeks with baseline cognition, strengthening of the association between diastolic OH and baseline cognition, and attenuation of the association between dizziness in the past 2 weeks with incident dementia (see Dryad, supplemental tables ST7–9, doi.org/10.5061/dryad.qbzkh18dt). Associations between OH and mortality were greater when the cause of death was related to CVD (see Dryad, supplemental table ST10, doi.org/10.5061/dryad.qbzkh18dt).

Figure Change in blood pressure and incident dementia, incident stroke, and death

Adjusted hazard ratios (solid line) for (A) incident dementia, (B) incident stroke, and (C) death according to difference in systolic blood pressure (SBP) per 1 mm Hg and (D) incident dementia, (E) incident stroke, and (F) death according to difference in diastolic blood pressure (DBP) per 1 mm Hg, using a restricted cubic spline with 4 knots determined by Harrell's method. Gray shade represents 95% confidence intervals. Both models were expressed relative to the median value and were truncated at the 2.5th and 97.5th percentiles. Models were adjusted for age, female sex, Black race, research clinic, body mass index, high-density lipoprotein cholesterol, triglycerides, diabetes status, hypertension status, mean SBP, mean DBP, diuretic use, beta-blocker use, education, current drinking status, and smoking status. The hazard ratios are shown on a natural log scale. Kernel density plots of difference in blood pressure are presented by presence (dashed line) or absence (solid line) of each clinical outcome (axis 2). These models did not include imputed data.

Discussion

In this older-aged, community-dwelling population without baseline dementia or stroke, OH measured after 3 minutes of standing was not consistently associated with neurologic outcomes. In contrast, dizziness upon standing or in the preceding 2 weeks was associated with worse white matter grade, more brain infarcts, lower baseline cognitive function, incident dementia, incident stroke, and mortality. These findings suggest that delayed standing BP assessments in older adults may miss a critical and informative phase of BP dysregulation after standing.

OH is associated with MRI lesions^{19–21} and stroke^{22,23} in some studies, but not others.^{24–26} In fact, one cross-sectional study of CHS reported a positive association between OH and MRI lesions.¹⁰ In contrast, the present study found that 3-minute OH assessments were not associated with MRI findings or stroke. Rather, dizziness with standing was

associated with stroke and dizziness in the prior 2 weeks was associated with white matter grade and brain infarcts. Unlike the previous CHS study, we excluded participants with baseline stroke and dementia. Furthermore, we did not include dizziness in the same definition as OH based on measured SBP or DBP. Notably, the Atherosclerosis Risk in Communities (ARIC) study, which found OH to be associated with stroke, measured OH within the first 2 minutes of standing. Given the strong association between early OH and dizziness,^{12,27} dizziness in CHS, like in ARIC, likely reflects BP dysfunction soon after standing. However, dizziness may more broadly represent poor cerebral tolerance to any change in BP or to global heart dysfunction.²⁸ It is also possible that vascular disease underlies both the sensation of dizziness and subsequent stroke independent of BP. Further work is needed to understand the physiologic pathways underlying the manifestation of dizziness and cerebral injury.

Table 4 Orthostatic hypotension (OH) measures and incident dementia, stroke, or mortality

	Dementia		Stroke		Death	
	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)
Model 1						
Consensus OH	2,979	0.91 (0.69–1.18)	5,007	1.15 (0.97–1.35)	5,007	1.12 (1.03–1.22)
Systolic OH	2,979	1.04 (0.77–1.40)	5,007	1.07 (0.88–1.31)	5,007	1.15 (1.05–1.27)
Diastolic OH	2,979	0.78 (0.53–1.13)	5,007	1.20 (0.97–1.49)	5,007	1.10 (0.99–1.23)
Dizziness with standing	2,979	1.39 (1.10–1.77)	5,007	1.18 (1.01–1.38)	5,007	1.12 (1.04–1.21)
Dizziness in past 2 weeks	2,979	1.33 (1.03–1.72)	5,007	1.02 (0.85–1.22)	5,007	1.15 (1.05–1.25)
Model 2						
Consensus OH	2,979	0.89 (0.68–1.16)	5,007	1.09 (0.92–1.29)	5,007	1.09 (1.00–1.18)
Systolic OH	2,979	1.02 (0.75–1.38)	5,007	1.02 (0.83–1.24)	5,007	1.13 (1.03–1.25)
Diastolic OH	2,979	0.75 (0.51–1.09)	5,007	1.16 (0.94–1.44)	5,007	1.05 (0.95–1.17)
Dizziness with standing	2,979	1.34 (1.06–1.71)	5,007	1.15 (0.98–1.35)	5,007	1.06 (0.98–1.15)
Dizziness in past 2 weeks	2,979	1.31 (1.01–1.70)	5,007	1.00 (0.83–1.19)	5,007	1.09 (0.99–1.18)
Model 2 with imputed missing data						
Consensus OH	3,303	0.85 (0.65–1.11)	5,481	1.08 (0.91–1.28)	5,719	1.11 (1.02–1.20)
Systolic OH	3,303	0.98 (0.73–1.32)	5,481	1.03 (0.85–1.25)	5,719	1.15 (1.05–1.27)
Diastolic OH	3,303	0.77 (0.53–1.11)	5,481	1.13 (0.91–1.41)	5,719	1.07 (0.97–1.19)
Dizziness with standing	3,303	1.32 (1.06–1.65)	5,481	1.22 (1.06–1.41)	5,719	1.13 (1.06–1.21)
Dizziness in past 2 weeks	3,303	1.25 (0.98–1.59)	5,481	1.04 (0.88–1.23)	5,719	1.13 (1.04–1.22)

Abbreviations: CI = confidence interval; HR = hazard ratio.

Model 1 adjusted for age, female sex, Black race, and research clinic. Model 2 adjusted for age, female sex, Black race, research clinic, body mass index, high-density lipoprotein cholesterol, triglycerides, diabetes status, hypertension status, mean systolic blood pressure, mean diastolic blood pressure, diuretic use, beta-blocker use, education, current drinking status, and smoking status.

The relationships between OH and cognitive decline or dementia have conflicted in the literature.^{5,20,24,29,30} In our study, dizziness with standing and dizziness in the past 2 weeks were associated with lower baseline cognitive function. Further, dizziness with standing was associated with incident dementia. None of the OH measurements were associated with cognitive function or dementia aside from diastolic OH. In ARIC, OH measured within 2 minutes of standing was strongly associated with dementia and a greater rate of decline in cognitive function. However, the DANTE Study Leiden (Discontinuation of Antihypertensive Treatment in Elderly People), which included 420 older adults (mean age 81 years) and measurements within 3 minutes of standing, did not observe an association between measured OH and cognitive decline.²⁴ Given the potential role of early BP dysregulation in cognitive damage and ongoing cognitive decline, future studies should study BP fluctuation within 1 minute of standing in relation to cognitive function over time.

Our study demonstrated that both measured OH (consensus and systolic definitions) as well as dizziness with standing and dizziness in the last 2 weeks were associated with mortality.

This observation is consistent with a number of other studies on this topic where timing among early measurements did not differentiate risk²⁷ with potential improvements in prediction using later measurements.¹² Sustained OH after 3 minutes of changing position may represent severity of OH or could also reflect distinct underlying pathophysiology.

This study has limitations. First, as stated previously, CHS did not measure OH within 1 minute of standing. Nevertheless, participants were asked about dizziness after standing, and OH is highly specific for dizziness symptoms.³¹ Second, the most symptomatic persons did not provide standing BP measurements and early termination of the study was associated with brain infarct and death. This could bias OH assessments, albeit less so in imputed analyses. Third, MRI was only available in a subset of participants and even fewer had a repeated assessment over time, limiting the power of these analyses. While CHS did examine additional regions and measures (e.g., deep brain structures, hippocampus, total brain volume), these measures occurred 5 years after the OH assessment and were only available in a subpopulation (<1,000 participants). Furthermore, prior analyses have shown that those with an initial MRI were

healthier than those without an initial MRI.¹⁸ Fourth, the 3MSE did not distinguish between cognitive decline early in the study. While the transition to telephone-based interviews facilitated home-based cognitive assessments, this change in measurement tool introduced some variability into cognitive function assessments, reducing study power. Fifth, 3-minute standing BP measurements were missing on symptomatic people, requiring imputation. Sixth, while dizziness was assessed in 2 different ways in our study (acute symptoms and historic), the definitions used in this study did not differentiate between symptoms often construed as dizziness, such as vertigo. Furthermore, dizziness is often a nonspecific finding resulting from multiple etiologies (e.g., transient ischemia accident, vestibular disorders, orthostatic hypotension). Seventh, OH assessments were not accompanied by assessments of the autonomic reflex. As a result, we are unable to confirm autonomic dysfunction as the cause of OH. Finally, despite rigorous adjustment for relevant covariates, residual confounding is always a concern with observational studies. Furthermore, we examined multiple exposures and outcomes, which increases the possibility of falsely positive associations.

Our study also has strengths. First, the CHS study was comprised of a relatively large, biracial population of community-dwelling older adults. As a result, our findings are applicable to the broader ambulatory population among whom OH is routinely detected in clinical practice. Second, staff underwent extensive training to perform CHS's standardized protocol and assessments were comprehensive, allowing us to account for multiple factors in models. Third, we examined a range of outcomes associated with neurologic hypoperfusion injuries including MRI, long-term cognitive scores, and relevant clinical events.

This study has implications for clinical assessment of OH. Dizziness was more strongly associated with adverse outcomes than delayed measurements of OH. Despite the recognition of OH as a predictor of adverse health events, disagreement is widespread on how best to screen for OH, with guidelines variably recommending measurements at 1, 2, or 3 minutes after standing and some even calling for multiple assessments.^{32–35} Up to this point, consensus as to the right approach has been elusive. Our findings regarding self-reported dizziness, like others with early OH assessments,²⁷ imply a potentially important role for early changes in BP regulation soon after standing. Further, our study highlights the complexity of BP regulation after standing with implications for causal effects from hypotension soon after standing.

OH measurements, 3 minutes after standing, were not associated with MRI findings, cognitive decline, dementia, or stroke. However, dizziness with standing or in the preceding 2 weeks were more consistently associated with adverse events. Subsequent research should comprehensively evaluate patterns of BP regulation upon standing in association with clinical outcomes.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Stephen P. Juraschek, MD, PhD	Beth Israel Deaconess Medical Center, Boston	Designed and conceptualized study, analyzed the data, drafted the manuscript for intellectual content
W.T. Longstreth Jr, MD, MPH	University of Washington, Seattle	Major role in acquisition of data, interpreted the data, revised the manuscript for intellectual content
Oscar L. Lopez, MD	University of Pittsburgh	Major role in acquisition of data, interpreted the data, revised the manuscript for intellectual content
John S. Gottdiener, MD	University of Maryland, Baltimore	Major role in acquisition of data, interpreted the data, revised the manuscript for intellectual content
Lewis A. Lipsitz, MD	Hinda and Arthur Marcus Institute for Aging Research, Roslindale	Interpreted the data, revised the manuscript for intellectual content
Lewis H. Kuller, MD, DrPH	University of Pittsburgh	Major role in acquisition of data, interpreted the data, revised the manuscript for intellectual content
Kenneth J. Mukamal, MD, MPH, MA	Beth Israel Deaconess Medical Center, Boston	Major role in acquisition of data, interpreted the data, revised the manuscript for intellectual content

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