Orthostatic Hypotension Predicts Mortality in Middle-Aged Adults

The Atherosclerosis Risk in Communities (ARIC) Study

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Background—An association between orthostatic hypotension (OH) and mortality has been reported, but studies are limited to older adults or high-risk populations.

Methods and Results—We investigated the association between OH (a decrease of 20 mm Hg in systolic blood pressure or a decrease of 10 mm Hg in diastolic blood pressure on standing) and 13-year mortality among middle-aged black and white men and women from the Atherosclerosis Risk in Communities Study (1987–1989). At baseline, 674 participants (5%) had OH. All-cause mortality was higher among those with (13.7%) than without (4.2%) OH. After we controlled for ethnicity, gender, and age, the hazard ratio (HR) for OH was 2.4 (95% confidence interval [CI], 1.7 to 3.1). Adjustment for risk factors for cardiovascular disease and mortality and selected health conditions at baseline attenuated but did not completely explain this association (HR=1.7; 95% CI, 1.4 to 2.0). This association persisted among subsets that (1) excluded those who died within the first 2 years of follow-up and (2) were limited to those without coronary heart disease, cancer, stroke, diabetes, hypertension, or fair/poor perceived health status at baseline. In analyses by causes of death, a significant increased hazard of death among those with versus without OH persisted after adjustment for risk factors for cardiovascular disease (HR=2.0; 95% CI, 1.6 to 2.7) and other deaths (HR=2.1; 95% CI, 1.6 to 2.8) but not for cancer (odds ratio=1.1; 95% CI, 0.8 to 1.6).

Conclusions—OH predicts mortality in middle-aged adults. This association is only partly explained by traditional risk factors for cardiovascular disease and overall mortality. (Circulation. 2006;114:630-636.)

Key Words: hypotension, orthostatic • middle aged • mortality • cardiovascular diseases

Central blood volume is abruptly reduced when one stands up. A complex set of compensatory physiological mechanisms then occur to maintain the upright posture. These include reflex responses in the cardiovascular and autonomic nervous systems as well as activation of the skeletal muscle and respiratory pumps. As a result, rapid changes in arterial blood pressure occur. In population studies, the systolic blood pressure (SBP) response to a change in posture is approximately normally distributed with a mean close to 0 mm Hg, but the range includes SBP decreases and increases of considerable magnitude. Orthostatic hypotension (OH) occurs when there is a marked decrease in blood pressure after the upright posture is assumed. Although previously not consistently defined, guidelines established in the 1990s suggested defining OH as a decrease in SBP ≥20 mm Hg and/or a decrease in diastolic blood pressure (DBP) ≥10 mm Hg.6

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Most research on OH is based on elderly, frail populations in which OH is accompanied by symptoms of dizziness and syncope and is associated with falls, fractures, and potential serious morbidity. Recent evidence suggests that OH in the elderly is associated with decreases in vestibular function.7 OH is consistently associated with older age, elevated blood pressure,8-12 and thicker carotid arterial walls.8,11 Inconsistent associations are noted between OH and body mass index (BMI),8,10-13 diabetes,8,11,12 and cigarette smoking.8,11 Few prospective studies have investigated the association between OH and cardiovascular disease (CVD) outcomes. A recent study reported a link between diastolic but not systolic OH and the occurrence of myocardial infarction.14 In middle-aged persons in the Atherosclerosis Risk in Communities (ARIC) Study, OH has been associated with incident hypertension.15

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coronary heart disease (CHD),8 and stroke.18 Several studies have examined the association between OH and mortality in the elderly or other high-risk populations. Some have reported a modest increased risk of mortality among those with OH,17–20 whereas others have reported no association.21

The present study investigated the association between OH and mortality in a population-based, middle-aged cohort of men and women. Questions addressed included the following: (1) Is OH associated with an increased risk of mortality in a middle-aged sample? (2) Do associations vary by cause of death (cardiovascular, cancer, other)? (3) Do associations persist after controlling for comorbidities and chronic disease risk factors?

Methods

Participants

Participants were black and white middle-aged men and women from the baseline examination of the ARIC Study (1987–1989), designed to investigate the causes and natural history of atherosclerosis and its sequelae. Participants were sampled from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; the suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Blacks were sampled exclusively in Jackson and sampled proportionately in Forsyth County to ensure race-specific estimates. The Minneapolis and Washington County sites were predominantly white. Response rates were 46% in Jackson and 65% to 67% in the other sites. A comparison of respondents with nonrespondents22 and details about the study design and procedures have been published.23

Of the 15 792 baseline examinees, we excluded those with an ethnicity other than black or white and blacks in Minneapolis and Washington County (n=89). We also excluded those with missing data for seated blood pressure (n=3) and those with missing data that precluded the computation of baseline postural change in blood pressure (n=2376). Most of these participants underwent their baseline examination during the first 6 months of the study, which occurred before implementation of the postural blood pressure measurement protocol. The 13 152 remaining participants were included in this study.

Measurement and Classification of Blood Pressure Response to a Change in Posture

Supine and standing blood pressure measurements were ascertained with the use of a Dinamap 1846 SX oscillometric device, which has high within-subject reliability and is comparable to Doppler ultrasound blood pressure measurement.24 After a 20-minute ultrasound examination with the participant lying supine, a trained and certified ARIC sonographer instructed the participant on how to change position. Automated supine blood pressure measurements were taken approximately every 30 seconds for 2 minutes (range of 2 to 5 measurements; 90% had at least 4 measurements). Participants were then asked to stand, and as their feet touched the ground, a standing blood pressure measurement was taken. Measurements were repeated during the first 2 minutes after standing (range of 2 to 5 measurements; 91% had at least 4 measurements).

Because blood pressure restabilization is still occurring during the first 30 seconds after standing,2 blood pressure change was defined as the difference between the average of the standing and the supine blood pressure measurements, excluding the first standing measurement. With the use of established guidelines,6 participants were classified by the presence (a decrease of at least 20 mm Hg SBP or a decrease of at least 10 mm Hg DBP) or absence of OH.

Identification of Deaths

Participants were contacted annually to ascertain vital status after baseline through December 2001. If a participant was reported deceased by the next of kin or other designated contact person, then the date of death, as well as hospitalizations before death, was ascertained. If the participant was not located during annual follow-up, an attempt was made to determine vital status via search of obituaries, funeral and hospital records, and the National Death Index. On the basis of nosological coding, fatal events were further classified into 3 categories (CVD, cancer, and all other causes of death). Deaths occurring through 1998 were classified with the use of International Classification of Diseases, 9th Revision (ICD-9) codes as neoplasms (ICD-9 140 to 239), diseases of the circulatory system (ICD-9 390 to 459), and all other causes of death. Deaths occurring during the 1999 to 2001 period were converted from analogous codes assigned with the use of the International Statistical Classification of Diseases, 10th Revision (ICD-10) codes. ICD codes were available for 98% of the decedents.

Covariates

At baseline, standardized interviews were conducted to obtain participants’ self-reported sociodemographic and behavioral risk factors. Education was classified as less than high school diploma, high school diploma, or at least some college. Smoking status was categorized as former smoker, current smoker, and never smoked. Alcohol use was categorized as current, former, and never. A sports index estimated physical activity.25 Use of medications to control blood pressure and high blood sugar were based on participants’ self-reported use during the previous 2 weeks. Participants were also asked to bring current medications to their examination. This information was recorded, and investigators measured use of specific agents (eg, β-blockers, tricyclic antidepressants). Participants were queried about their perception of their general health compared with their peers and were categorized as fair/poor and excellent/good. In addition, before the postural blood pressure examination, participants were queried about whether they had a history of experiencing dizziness on standing.

Standard protocols measured height and weight. Body mass index (BMI) was calculated as weight (kg)/height (m2). High-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels (mmol/L) were determined at the ARIC Central Lipid Laboratory by standardized methods.26 Two noninvasive measures of atherosclerosis were included. The ankle-brachial index (ABI), a ratio of ankle to brachial systolic blood pressure, was dichotomized (<0.90, >0.90), with a value of <0.90 used as an indicator of peripheral artery disease. Carotid artery intima-media thickness (IMT) was determined by B-mode ultrasound, as previously described.26

Diabetes was defined as nonfasting plasma glucose >11.1 mmol/L (200 mg/dL, hexokinase method), fasting glucose ≥7 mmol/L (126 mg/dL), and/or a self-reported history of diabetes, and/or current pharmacological treatment of diabetes. Three seated blood pressure measurements were taken on the right arm with a random-zero sphygmomanometer after 5 minutes of rest. With the use of techniques previously described,27 resting heart rate was determined from a standard supine 12-lead ECG. Blood pressure values were based on the average of the second and third measurements. Hypertension was defined as an SBP ≥140 mm Hg and/or DBP ≥90 mm Hg and/or current use of medications to control hypertension. Prevalence of cancer, CHD, and stroke was based on self-report.

Statistical Methods

A procedure for the adjustment of proportions in logistic regression28 was used to calculate age-, race-, and gender-adjusted proportions of risk factors and selected conditions at baseline by OH status. Similarly, ANCOVA was used to produce age-, race-, and gender-adjusted means of risk factors by OH status. Proportional hazards regression analysis was used to model the hazards of all-cause mortality among those with compared with those without OH. We assessed for violation of the proportional hazards assumption by examining the ln (−ln) survival curves for the 2 OH groups, and the curves were roughly parallel. A formal test also did not indicate an interaction between OH and mortality by time (P>0.86). Four sets of models were run: (1) unadjusted; (2) models controlling for age, gender, and ethnicity; (3) models additionally controlling for behav-
oral and chronic disease risk factors (SBP, BMI, HDL and LDL cholesterol, carotid IMT, diabetes, educational attainment, low ABI, current smoking, physical activity, current alcohol intake) and use of medications potentially associated with OH (eg, antihypertensive agents, anti-Parkinsonian drugs, tricyclic antidepressants, benzodiazepines, phenothiazines); and (4) models additionally controlling for selected baseline health conditions (cancer, stroke, hypertension, CHD, fair/poor perceived health status). An assessment of effect modification of the main effect by covariates was included with a significance level of 0.10.29

To address whether frail or poor health contributed to associations, we repeated all analyses excluding those who died within the first 2 years of follow-up. Alternatively, we repeated analyses excluding those with selected baseline morbidities (CHD, stroke, cancer, hypertension, diabetes, or a self-reported fair/poor health status). Models were also run by causes of death (CVD, cancer, all other causes). In these analyses, those who died from other causes of death were censored at the date of death. All analyses used Statistical Analysis Software, version 8.2 (SAS Institute, Inc, Cary, NC).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Participants averaged 54 years of age. Twenty-seven percent were black, 55% were female, and 23% had less than a high school education. At baseline, 35% were classified as having hypertension and 12% with diabetes. Five percent reported a history of CHD, 6% a history of cancer, and 2% a history of stroke.

Table 1 presents age-, race-, and gender-adjusted means and percentages of risk factors and conditions by OH status. Five percent of participants had OH at baseline. Those with OH were older, more likely to be black, and more likely to have less than a high school education than those without OH. They were also more likely to be diabetic; to currently smoke; to have higher resting heart rates, higher LDL and lower HDL cholesterol, and greater carotid IMT; and to have low ABI. Those with OH were less likely to currently drink and slightly more likely to report a history of dizziness on standing.

Table 2 presents age-, race-, and gender-adjusted means and percentages of arterial blood pressure and related factors by OH status. Those with OH had higher resting mean SBP and DBP levels and higher rates of hypertension than those without OH. Among hypertensives, use of β-blockers, diuretics, and angiotensin-converting enzyme inhibitors did not vary by OH status, whereas those with OH were slightly more likely to use calcium channel blockers. Among hypertensives using medications, those with OH achieved poorer control, being more likely to have blood pressure values in the prehypertension to stage II hypertension ranges as defined by the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VII guidelines.30

From baseline (1987–1989) through December 2001, 1693 participants (13%) died. Among the coded causes of death (n=1666), the most common causes of death were CVD (n=593, 36%) and cancer (n=544, 33%). All other causes accounted for the remaining deaths (n=529, 32%). The most frequent ICD codes assigned to other deaths included respiratory, endocrine, injury and poisoning, parasitic and other infectious, and digestive pathologies.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>OH Positive (n=674)</th>
<th>OH Negative (n=12,478)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>57</td>
<td>54</td>
<td>0.00</td>
</tr>
<tr>
<td>Black, %</td>
<td>34</td>
<td>26</td>
<td>0.00</td>
</tr>
<tr>
<td>Male, %</td>
<td>45</td>
<td>45</td>
<td>0.82</td>
</tr>
<tr>
<td>Less than high school education, %</td>
<td>33</td>
<td>23</td>
<td>0.00</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>27.7</td>
<td>27.7</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean HDL cholesterol, mmol/L</td>
<td>1.30</td>
<td>1.34</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean LDL cholesterol, mmol/L</td>
<td>3.75</td>
<td>3.55</td>
<td>0.00</td>
</tr>
<tr>
<td>Mean glucose, mmol/L</td>
<td>6.2</td>
<td>5.4</td>
<td>0.00</td>
</tr>
<tr>
<td>Mean IMT, mm</td>
<td>0.82</td>
<td>0.75</td>
<td>0.00</td>
</tr>
<tr>
<td>Mean heart rate, bpm</td>
<td>66.5</td>
<td>69.1</td>
<td>0.00</td>
</tr>
<tr>
<td>Low ABI (&lt;0.90)</td>
<td>9</td>
<td>3</td>
<td>0.00</td>
</tr>
<tr>
<td>Diabetic, %</td>
<td>19</td>
<td>12</td>
<td>0.00</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>35</td>
<td>26</td>
<td>0.00</td>
</tr>
<tr>
<td>Mean sports index</td>
<td>2.4</td>
<td>2.5</td>
<td>0.40</td>
</tr>
<tr>
<td>Current alcohol use, %</td>
<td>48</td>
<td>57</td>
<td>0.00</td>
</tr>
<tr>
<td>Self-reported fair/poor health status, %</td>
<td>31</td>
<td>19</td>
<td>0.00</td>
</tr>
<tr>
<td>Dizziness upon standing, %</td>
<td>9</td>
<td>12</td>
<td>0.02</td>
</tr>
<tr>
<td>History of cancer, %</td>
<td>5.6</td>
<td>8.6</td>
<td>0.00</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>1.7</td>
<td>5.7</td>
<td>0.00</td>
</tr>
<tr>
<td>History of CHD, %</td>
<td>4.8</td>
<td>7.4</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*With the exception of age, race, and gender, all risk factors have been adjusted for age, race, and gender.
†Numbers for individual risk factors may vary slightly because of missing data.

The SBP response to a change in posture was approximately normally distributed. It averaged −0.44 mm Hg ([SD= 10.7 mm Hg] and ranged (first to 99th percentile) from −31.0 to +24.3 mm Hg. The average DBP change was 2.9 mm Hg ([SD= 5.7 mm Hg]) and ranged from −11.6 to +16.5 mm Hg. Only 5% of participants (n=674) met the consensus definition of OH (SBP decrease ≥20 mm Hg or DBP decrease ≥10 mm Hg). Of those, 457 (67.8%) met the criteria solely on the basis of SBP decreases, 91 (13.5%) met the criteria only on the basis of DBP decreases, and 126 (18.7%) met the criteria on the basis of both SBP and DBP decreases.

The Figure presents unadjusted Kaplan-Meier curves for all-cause mortality by OH status. A gradual increase in mortality was observed for those free of OH at baseline, with an overall mortality rate of 12% (n=1476) over the average of 13 years of follow-up. For the OH group, by contrast, the slope of the survival curve was steeper, and by the end of the follow-up period, 32% (n=217) of participants had died.

Table 3 presents the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between OH and mortality. In unadjusted models, those with OH had a 3.2-fold increase in risk of dying over the 13 years of follow-up. A 2.4-fold increase in risk remained after we controlled for age, race, and gender. Controlling for risk factors and behaviors
associated with OH and mortality further reduced the magnitude of this association, but a 1.7-fold increase in risk of death persisted. Further adjustment for prevalence of cancer, CHD, stroke, and diabetes at baseline did not further reduce the HR.

Alternately, we calculated propensity scores\(^3\) and then performed analyses stratified by quintile of the propensity score, and we included the propensity score as a covariate in our models. Results did not differ substantially from those presented in Table 3 (data not shown).

An assessment of effect modification of the OH mortality association by covariates revealed statistically significant effect modification of the OH mortality association by age and race. Thus, race- and age-specific models were also conducted. In fully adjusted models, the association of OH with mortality was stronger among younger than older participants (HR = 3.69 [95% CI, 2.10 to 6.49] for ages 45 to 49 years; HR = 1.75 [95% CI, 1.12 to 2.75] for ages 50 to 54 years; HR = 1.69 [95% CI, 1.23 to 2.32] for ages 55 to 59 years; HR = 1.61 [95% CI, 1.27 to 2.03] for ages 60 to 64 years). In addition, the association of OH with mortality was modestly stronger among blacks than for whites (HR = 2.21 [95% CI, 1.71 to 2.85] for blacks; HR = 1.55 [95% CI, 1.24 to 1.90] for whites).

After we excluded 203 participants who died within during the first 2 years, our results did not change substantially (Table 3). Alternatively, when we excluded 5881 participants who had hypertension, diabetes, cancer, stroke, CHD, or perceived fair/poor health at baseline, HRs from unadjusted and sociodemographic-adjusted models were virtually identical to the models that included all participants. In the risk factor–adjusted model, the strength of the association was modestly higher in the model limited to those without selected health conditions (Table 3).

Table 4 presents the HRs and 95% CIs for the association between OH and cause-specific mortality. OH was associated with a >4-fold increase in risk of CVD mortality, a 2-fold increase in risk of dying from cancer, and a >3-fold increase in risk of dying from other non–cancer-related deaths. After adjustment for baseline risk factors and prevalent health conditions, these associations were strongly attenuated, although a 2-fold significant increase in risk persisted. In contrast, the association of OH with cancer mortality did not persist after adjustment for baseline risk factors and health conditions.

**Discussion**

OH was predictive of mortality over 13 years of follow-up in the middle-aged ARIC cohort. A >3-fold increased risk of deaths from all causes among those with OH was partly explained by age, sociodemographic characteristics, risk factors, and comorbid health conditions. Even after these factors

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<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>OH Positive (n=674)†</th>
<th>OH Negative (n=12 478)†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SBP, mm Hg</td>
<td>128 122</td>
<td>128 122</td>
<td>0.00</td>
</tr>
<tr>
<td>Mean DBP, mm Hg</td>
<td>75 73</td>
<td>75 73</td>
<td>0.00</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>53 33</td>
<td>53 33</td>
<td>0.00</td>
</tr>
<tr>
<td>Hypertensives (n=4521), %, using</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any antihypertensive medication</td>
<td>76 72</td>
<td>76 72</td>
<td>0.10</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>11 10</td>
<td>11 10</td>
<td>0.44</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>28 25</td>
<td>28 25</td>
<td>0.25</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>10 7</td>
<td>10 7</td>
<td>0.05</td>
</tr>
<tr>
<td>Diuretics</td>
<td>43 43</td>
<td>43 43</td>
<td>0.94</td>
</tr>
<tr>
<td>Medicated hypertensives (n=3271) by control status (JNC VII), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>25 27</td>
<td>25 27</td>
<td>0.01</td>
</tr>
<tr>
<td>Pre</td>
<td>36 42</td>
<td>36 42</td>
<td>0.05</td>
</tr>
<tr>
<td>Stage 1</td>
<td>22 22</td>
<td>22 22</td>
<td>0.93</td>
</tr>
<tr>
<td>Stage 2</td>
<td>17 9</td>
<td>17 9</td>
<td>0.00</td>
</tr>
</tbody>
</table>


*Adjusted for age, race, and gender.

†Numbers for individual risk factors may vary slightly because of missing data.

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were taken into account, a 1.7-fold increase in risk of death persisted. A previous study of the elderly reported a significant 1.6-fold increase in all-cause mortality among those with OH. To our knowledge, ours is the first study to report on this association in a middle-aged population.

Some suggest that among the elderly OH is an indicator of a general lessening of physical strength or frailty and thus a portent of death. Although general frailty is not common in middle-aged populations, chronic health conditions associated with increased mortality are, and we observed substantial differences in the occurrence of measured risk factors, health conditions, and perceived health status in our population. Controlling for these factors, in fact, partially accounted for the OH-mortality associations noted. We explored other methods of determining whether the risk attributable to OH was because it is a marker for underlying poor health. Excluding participants who died within the first 2 years of follow-up did not appreciably change the results. Furthermore, we restricted our analyses to the subset of approximately half of the participants who were identified, via measurements taken at the baseline examination and self-reporting, as being ostensibly healthy at baseline. Exclusions constituted those with selected conditions (CHD, stroke, cancer, diabetes, hypertension) as well those with self-reported fair/poor health status. Although the latter is a somewhat vague and subjective measure, it was chosen because it has been associated with the risk of mortality.

Among these ostensibly healthy adults, those with OH had a >2-fold increase in risk of dying even after we controlled for risk factors associated with adverse health outcomes. Interestingly, and also not supportive of a frailty hypothesis, were the findings of significant effect modification of the OH-mortality association by age: Among the youngest (45 to 49 years) participants, the increased risk of mortality associated with OH was markedly stronger than the increased risk among the oldest (aged 60 to 64 years) participants (adjusted HR of 3.7 and 1.6, respectively). Although baroreceptor dysfunction, structural changes in the vascular system, and aging are thought to underlie OH, its cause is not completely understood. Furthermore, most knowledge about this condition is based on the elderly and other high-risk groups such as those with hypertension, diabetes, and

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**TABLE 3. HR and 95% CI for Association Between OH and All-Cause Mortality Among the ARIC Cohort (1987–2001)**

<table>
<thead>
<tr>
<th>Model</th>
<th>All Deaths (n of Deaths/N=1693/13152)</th>
<th>Deaths Within First 2 Years of Follow-up Excluded (n of Deaths/N=1490/12949)</th>
<th>Comorbidities at Baseline Excluded* (n of Deaths/N=418/6554)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>3.19 (2.76–3.67)</td>
<td>3.06 (2.62–3.58)</td>
<td>3.09 (2.10–4.53)</td>
</tr>
<tr>
<td>Sociodemographic‡</td>
<td>2.41 (2.08–2.78)</td>
<td>2.32 (1.99–2.72)</td>
<td>2.35 (1.60–3.46)</td>
</tr>
<tr>
<td>Risk factor§</td>
<td>1.69 (1.42–2.01)</td>
<td>1.69 (1.40–2.04)</td>
<td>1.99 (1.22–3.22)</td>
</tr>
<tr>
<td>Health conditions∥</td>
<td>1.71 (1.44–2.04)</td>
<td>1.68 (1.39–2.02)</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are HR (95% CI).
*Participants with the following conditions at baseline were excluded: CHD, stroke, cancer, hypertension, diabetes, and fair or poor perceived health status.
‡Total numbers vary across models because of missing covariate data.
§Adjusted for race, gender, and age.
∥Adjusted for race, gender, age, education, SBP, smoking status, alcohol use, HDL and LDL cholesterol, physical activity, BMI, low ABI, IMT, glucose, resting heart rates, dizziness on standing, and selected medications (eg, antihypertensives, anti-Parkinsonian drugs, tricyclic antidepressants, benzodiazepines, phenothiazines).
\*Adjusted for variables included in model 3, plus presence of selected conditions (diabetes, CHD, stroke, cancer, and fair/poor perceived health).

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**TABLE 4. HR and 95% CI for Association Between OH and Cause-Specific Mortality Among the ARIC Cohort (1987–2001)**

<table>
<thead>
<tr>
<th>Cause of Death/ (No. of Deaths)</th>
<th>Unadjusted</th>
<th>Age, Race, and Gender Adjusted</th>
<th>Risk Factor Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD (593)</td>
<td>4.33 (3.49 to 5.36)</td>
<td>3.27 (2.63 to 4.07)</td>
<td>2.04 (1.57 to 2.66)*</td>
</tr>
<tr>
<td>Cancer (544)</td>
<td>1.92 (1.41 to 2.60)</td>
<td>1.47 (1.08 to 2.04)</td>
<td>1.14 (0.80 to 1.62)†</td>
</tr>
<tr>
<td>Other (529)</td>
<td>3.44 (2.68 to 4.43)</td>
<td>2.56 (1.98 to 3.30)</td>
<td>2.12 (1.61 to 2.80)‡</td>
</tr>
</tbody>
</table>

Values are HR (95% CI).
*Adjusted for age, gender, race, educational attainment, SBP, smoking, alcohol intake, HDL and LDL cholesterol, glucose, BMI, low ABI, IMT, antihypertensive medication use, physical activity, and perceived health status.
†Adjusted for age, gender, race, educational attainment, smoking (past and current), alcohol intake, physical activity, BMI, glucose, and perceived health status.
‡Adjusted for age, gender, race, educational attainment, smoking (past and current), alcohol intake, physical activity, BMI, diabetes, glucose, perceived health status, resting heart rates, dizziness on standing, and selected medications (eg, antihypertensives, anti-Parkinsonian drugs, tricyclic antidepressants, benzodiazepines, phenothiazines).
neurological conditions. Among these groups, symptoms associated with OH, such as dizziness and syncope, bring the condition to the attention of clinicians. It is intriguing that OH is associated with an elevated mortality risk among the apparently healthy subgroup of ARIC participants free of diabetes, hypertension, cancer, stroke, CHD, and perceived fair/poor health status and that this risk is markedly higher among the youngest cohort members. It is possible that autonomic dysfunction that has not yet led to clearly identifiable clinical manifestations may be involved. The inclusion of measures of autonomic function in future studies may shed light on this issue.

The number of deaths was sufficient to conduct analyses with causes of death stratified into broad categories: cardiovascular, cancer, and other. In unadjusted and sociodemographic-adjusted analyses, those with OH were at increased risk of death compared with those without OH for all 3 groups. After adjustment for risk factors, a 2-fold increase in risk of death among those with OH persisted for cardiovascular deaths and other non–cancer-related deaths, whereas for cancer-related deaths the association was strongly attenuated and the CI included the null value. Previous studies limited to the elderly have been inconsistent. One study reported a significant increase in vascular but not nonvascular deaths among those with OH, whereas another reported no increase in risk of vascular mortality.

Our study has several limitations. Participants who underwent their baseline examination before the implementation of the ultrasound examination, which included the postural blood pressure measurements, were excluded. However, our concerns about this resulting in systematic bias are lessened because the examination dates were randomly assigned. In addition, earlier work in this cohort did not find major differences for key risk factors by inclusion status.

Our measure of cardiovascular response to a change in posture was limited to blood pressure. The inclusion of physiological measures not available in our study (eg, change in heart rate) in future work may provide additional clues to processes underlying this association. Although the measurement of blood pressure and related risk factors was standardized in ARIC, observational studies such as this one cannot rule out that confounding by risk factors not considered, or not optimally measured, may account for some of the association between OH and mortality. This may be particularly applicable to deaths unrelated to CVD.

Among the strengths of this study is data quality. Supine and standing blood pressure measurements were taken under standardized conditions by trained technicians using an automated device found to have high reliability. To account for blood pressure fluctuations that occur immediately on standing, we eliminated the first standing blood pressure. Most studies to date have been limited to elderly, frail populations. In contrast, our results are based on a middle-aged, community-based sample of men and women, which makes these results more generalizable and of wider interest. Finally, given the size of the cohort and the average of 13 years of follow-up, there was sufficient power to conduct subgroup analyses among the ostensibly healthiest subgroups of the cohort and to consider cause-specific mortality.

In summary, OH predicted mortality among middle-aged men and women in the ARIC cohort: one third of those with OH died over the 13 years of follow-up compared with 12% of those without OH. This association was only partly explained by measured risk factors, persisted in analyses that were limited to apparently healthy subgroups of the population, and was strongest among the youngest participants. OH was not common in this middle-aged cohort (5%), and therefore its contribution to overall mortality was modest. However, OH conferred a mortality risk comparable to that reported for other established risk factors (eg, smoking, hypertension), and therefore attention to increasing understanding of the mechanisms that potentially underlie its association with mortality is warranted.

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Disclosures

None.

References

Orthostatic hypotension (OH), a condition associated with considerable morbidity and mortality in the elderly and other high-risk populations, typically comes to the attention of clinicians when accompanied by symptoms such as dizziness and syncpe. Relatively little is known about this condition in ostensibly healthy, younger populations. This study investigated the association between OH and mortality among middle-aged persons from the Atherosclerosis Risk in Communities (ARIC) Study. Of 13,152 participants, 5% had OH at baseline, and 13% died over the average of 13 years of follow-up. In analyses that controlled for cardiovascular risk factors, symptoms of dizziness, and use of medications associated with OH, those with OH were more likely to die (hazard ratio = 1.71; 95% confidence interval, 1.44 to 2.04) than those without. This association was unlikely the result of concurrent disease. It persisted when early deaths were excluded, was stronger in younger than in older participants, persisted after cancer deaths were excluded, and was stronger in the subset of participants without diabetes, hypertension, coronary heart disease, stroke, cancer, or fair/poor perceived health status at baseline (hazard ratio = 1.99; 95% confidence interval, 1.22 to 3.22). Although OH is not common among middle-aged persons, the prospective results from the ARIC Study suggest that it confers a mortality risk comparable to that of other established risk factors.

**CLINICAL PERSPECTIVE**

Orthostatic hypotension (OH), a condition associated with considerable morbidity and mortality in the elderly and other high-risk populations, typically comes to the attention of clinicians when accompanied by symptoms such as dizziness and syncpe. Relatively little is known about this condition in ostensibly healthy, younger populations. This study investigated the association between OH and mortality among middle-aged persons from the Atherosclerosis Risk in Communities (ARIC) Study. Of 13,152 participants, 5% had OH at baseline, and 13% died over the average of 13 years of follow-up. In analyses that controlled for cardiovascular risk factors, symptoms of dizziness, and use of medications associated with OH, those with OH were more likely to die (hazard ratio = 1.71; 95% confidence interval, 1.44 to 2.04) than those without. This association was unlikely the result of concurrent disease. It persisted when early deaths were excluded, was stronger in younger than in older participants, persisted after cancer deaths were excluded, and was stronger in the subset of participants without diabetes, hypertension, coronary heart disease, stroke, cancer, or fair/poor perceived health status at baseline (hazard ratio = 1.99; 95% confidence interval, 1.22 to 3.22). Although OH is not common among middle-aged persons, the prospective results from the ARIC Study suggest that it confers a mortality risk comparable to that of other established risk factors.
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