Longitudinal Association Between Orthostatic Hypotension at 30 Seconds Post-Standing and Late-Life Depression

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See Editorial Commentary, pp 816–818

Abstract —There is an established cross-sectional association between orthostatic hypotension (OH) and late-life depression. The aim of this observational study was to clarify the longitudinal association between baseline symptomatic OH (sOH-30) and incident depression in a sample of >3000 older people without baseline depression (mean age: 62 years at baseline). This study was embedded within the Irish Longitudinal Study on Ageing using data from waves 1 to 3, collected between 2009 and 2014. At 2- and 4-year follow-up, a score ≥9 on the 8-item Center for Epidemiological Studies Depression Scale was used to define incident depression. sOH-30 was defined as a drop in systolic blood pressure ≥20 mm Hg or diastolic blood pressure ≥10 mm Hg at 30 seconds post-standing in conjunction with orthostatic symptoms, such as dizziness, using beat-to-beat measurements. Almost one fifth (proportion, 18%; 95% confidence interval [CI], 16–20) of the study sample had sOH-30. One tenth (proportion, 10%; 95% CI, 9–12) had incident depression. Participants with incident depression were twice as likely to have sOH-30 at baseline compared with those without incident depression (linear regression, 13% [95% CI, 8–19] versus 7% [95% CI, 6–8]). Weighted logistic regression models demonstrated that sOH-30 predicted incident depression with an odds ratio of 1.90 (95% CI, 1.15–3.15) after controlling for covariates, including subthreshold depression, hypotension, cognitive impairment, and antidepressant use. Asymptomatic OH at 30 seconds and initial OH did not predict depression. This study demonstrates that sOH-30 predicts incident depression in a population-representative sample of older people and may, therefore, represent a potentially modifiable risk factor for late-life depression. (***Hypertension*****. 2018;71:946-954. DOI: 10.1161/HYPERTENSIONAHA.117.10542.)** • **Online Data Supplement**

Key Words: blood pressure ■ depression ■ dizziness ■ hypotension, orthostatic ■ risk factors

Orthostatic hypotension (OH) is defined as a sustained drop in systolic blood pressure (BP) by at least 20 mm Hg or diastolic BP by at least 10 mm Hg within 3 minutes of standing.[1,2] OH is common, affecting 1 in 5 people aged ≥65 years, and this prevalence increases with further advancing age.[3]

Normally, when we stand from a seated or lying position, blood pools in the legs, causing a drop in venous return, cardiac filling pressure, cardiac output, and systemic BP. This drop in BP causes activation of baroreceptors, which act to normalize BP by increasing sympathetic outflow and reducing parasympathetic activity, resulting in peripheral vasoconstriction and tachycardia.[4] In later life, this baroreflex can become less sensitive, leading to prolonged times to stabilize BP and resulting in OH.[5] Prolonged hypotension can cause cerebral hypoperfusion, and OH increases the risk of conditions related to cerebral perfusion deficits, including dementia, falls, and stroke.[6–8]

Cerebral hypoperfusion has been implicated in late-life depression (LLD).[9,10] Decline in cerebral blood flow is associated with increased depressive symptoms in older people with chronic cardiovascular disease.[11,12] Reduced cerebral blood flow measured by transcranial Doppler ultrasound predicted incident depression in a sample of almost 1500 older people.[13] In a cohort with Parkinson disease, single-photon emission computed tomography demonstrated cerebral perfusion deficits in fronto-temporo-limbic regions in depressed participants compared with nondepressed controls.[14]

Studies in LLD have also demonstrated increased burden of cerebral white matter disease, specifically strategic white matter hyperintensities (WMH),[15] which can be caused by ischemic insults because of cerebral hypoperfusion.[16,17] WMH are more common and severe in older people with depression,[18] and higher burden of WMH is predictive of increased severity of depressive symptoms, as well as poorer response to treatment in older people.[19,20] Conditions predisposing to cerebral hypoperfusion and resultant WMH may, therefore, represent modifiable risk factors for LLD. Initial studies with

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some methodological limitations have demonstrated a cross-sectional association between OH and LLD, but a longitudinal relationship has yet to be investigated.[21–23]

A further orthostatic BP pattern, initial OH (IOH), has also been described and is defined as a transient BP drop within 15 seconds of standing, of >40 mm Hg systolic BP or >20 mm Hg diastolic BP, with symptoms of cerebral hypoperfusion.[24] Typically, BP has recovered within 30 seconds of standing. IOH is a common benign cause of dizziness and syncope in younger people but can also be seen in older adults, particularly those taking medications that may interfere with BP recovery after standing.[25] Prior evidence from TILDA (The Irish Longitudinal Study on Ageing) has shown that IOH does not predict unexplained or injurious falls within the TILDA cohort of older people, however.[8] The role of IOH in incident depression has not yet been investigated.

An important limitation of many studies of OH is the method used to measure orthostatic BP.[21] Noninvasive beat-to-beat BP measurement by active stand using a finometer is a more sensitive diagnostic test for OH as it allows real-time continuous tracking of BP and gives waveform measurements similar to those seen in invasive intra-arterial monitoring.[26] It captures dynamic BP changes that are often missed with other techniques.[27]

Our hypothesis was that OH may represent a modifiable risk factor for depression in later life, and the aim of this study, therefore, is to clarify whether OH and IOH, divided into symptomatic and asymptomatic based on the presence or absence of orthostatic symptoms, measured by continuous BP values, predict incident depression in a cohort of community-dwelling older people.

Methods

Ethics

The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki. All assessments were performed by trained research nurses.

Anonymized data and materials have been made publicly available at the Irish Social Science Data Archive based in University College Dublin and the Interuniversity Consortium for Political and Social Research based in the University of Michigan and can be accessed at www.tilda.ie.

Study Design

This study is embedded within TILDA, a large population-based study of a nationally representative sample of community-dwelling older adults aged ≥50 years, with an initial study population of >8000 participants.

The TILDA design has been outlined previously.[28] We analyzed data from the first, second, and third wave of TILDA collected between 2009 and 2014. Participants were included in this study if they were ≥50 years of age and underwent a complete health assessment at wave 1, including measurement of orthostatic BP and screening for depression. Participants were excluded if they did not complete 4-year follow-up, including assessment of mood at both waves 2 and 3. Participants were also excluded at wave 1 if they had a preexisting diagnosis of dementia.

This is a longitudinal study establishing whether OH at baseline (wave 1), measured at 30 seconds post-standing, is a predictor of incident depression by 4-year follow-up. Therefore, participants with depression at wave 1 were excluded. The remaining participants were screened for depression at waves 2 and 3.

Orthostatic Hypotension

Orthostatic BP was measured by active stand using a Finometer MIDI as described previously.[29] The Finometer device has been validated against British Hypertension Society protocol and the criteria of the Association for the Advancement of Medical Instrumentation for measurement of finger BP noninvasively on a beat-to-beat basis.[30] Although clinical practice has generally shifted toward use of continuous BP measurement for OH rather than sphygmomanometer-based readings, it must be noted that these measurements also show low-to-moderate reliability and natural variation at short-term follow-up.[31] Furthermore, although continuous BP measurement is validated extensively as a reliable method to track changes in BP, because of differences between arterial waveforms at the finger compared with central arteries, finger systolic BP may be higher than invasive brachial BP, whereas finger diastolic BP may be lower.[24]

Briefly, participants lay in the supine position for 10 minutes in a quiet room, before standing in a timely manner (<5 seconds) and were aided by a research nurse to mobilize as necessary. After standing, systolic BP, diastolic BP, and heart rate were monitored for a further 120 seconds. Throughout the recording, subjects stood quietly. After the 2-minute period, subjects were asked to report occurrence of orthostatic symptoms (dizziness, light-headedness, or unsteadiness).

OH at 30 seconds (OH-30) was defined as a drop in systolic BP ≥20 mm Hg or drop in diastolic BP ≥10 mm Hg at 30 seconds compared with baseline BP. Time point values were 5-second moving averages, that is, the 30-second time point was the average of 27.5 to 32.5 seconds. Symptomatic OH at 30 seconds (sOH-30) was defined as OH at 30 seconds with associated orthostatic symptoms. Asymptomatic OH at 30 seconds (aOH-30) was defined as OH at 30 seconds without associated orthostatic symptoms. Thirty seconds was chosen as the cutoff point post-stand for several reasons. A recent large study has demonstrated that measurements of OH performed within 60 seconds of standing were the most strongly related to dizziness and adverse outcomes, such as syncope, injury, or death.[32] Furthermore, a prior study looking at normative changes in phasic BP in the TILDA cohort established that an initial BP drop immediately after standing is common but nonrecovery of BP should be considered abnormal by 30 seconds.[29]

IOH was defined as a drop in systolic BP >40 mm Hg or a drop in diastolic BP >20 mm Hg at 10 seconds post-standing compared with baseline BP with full recovery of BP to baseline BP value or higher by 30 seconds. Symptomatic IOH was defined as IOH with associated orthostatic symptoms.

Depression

Depressive symptoms were assessed at wave 1 using the 20-item Center for Epidemiological Studies Depression Scale (CES-D-20). A score of ≥16 was used to define cases of depression.[33] Participants with depression at wave 1 were excluded from the study.

At waves 2 and 3, the 8-item CES-D-8 was used to screen for depression. The CES-D-8 was introduced in the TILDA study at waves 2 and 3 to reduce the time taken to conduct participant assessments and to reduce respondent burden and fatigue, and previous work has confirmed its reliability in comparison to the CES-D-20 in terms of internal consistency and factor structure within the TILDA cohort.[34] A score of ≥9 on this scale was used to define cases of depression, and participants with a CES-D-8 score ≥9 at either wave 2 or 3 were defined as having incident depression.[35]

Other Measures

Detailed social and biological data were collected at wave 1. Functional impairment was defined as impairment in ≥1 instrumental activities of daily living, which includes cleaning and maintaining the house, managing money, moving within the community, and preparing meals. Alcohol abuse was defined as a score of ≥2 on the CAGE Alcohol Scale. Gait was assessed using the Timed Up and Go Test, where a score of ≥12 seconds was considered abnormal.[36] BP was measured twice in a seated position by a trained research nurse using the OMRON digital automatic BP monitor, and the mean value was used for the analysis. Cardiac disease was defined as self-report of prior myocardial infarct, cardiac failure, or cardiac arrhythmia.

Self-report was also elicited for prior stroke, diabetes mellitus, and Parkinson disease, as well as recent unintentional weight loss of ≥10 pounds. Participants were asked about physical activity within the last week, and those who were inactive for the full 7 days were defined as having low physical activity, compared with moderate (active 1–3 days) and high (active ≥4 days) physical activity levels. Medication records were examined for antihypertensive use (specifically for those with Anatomic Therapeutic Chemical Classification C02, C03, C07, C08, or C09) and antidepressant use (Anatomic Therapeutic Chemical Classification N06A). Cognitive impairment was defined as a Mini-Mental State Examination (MMSE) score ≤24.

Statistical Analysis

Data were analyzed using Stata (Stata Corp). Cross-sectional analysis was weighted. Weights were estimated by comparing the counts of individuals in the sample across age, sex, highest level of educational attainment, marital status, and urban or rural dwelling, with the counts in the population with the same characteristics using information from the Central Statistics Office of Ireland 2011 Census. Differences in baseline binary demographic and clinical variables between study groups were, therefore, presented as weighted prevalence estimates using proportional estimation. Continuous variables were analyzed by linear regression with study group as a predictor. To correct for non-normality of the distribution, reciprocal transformation was applied to the Timed Up and Go Test variables because they demonstrated a highly positive skew. Marginal mean values calculated post-estimation, and data were presented by recalculating as 1/(marginal mean).

Additionally, attrition weights were applied to the longitudinal analysis. These weights corrected for the difference in attrition rates over subgroups and reduced the bias caused by this difference in attrition rates. These weights are calculated based on the reciprocal of the probability of a wave 1 health assessment respondent completing a computer-assisted personal interview at waves 2 and 3.

Logistic regression models were used to estimate odds ratios (with 95% confidence intervals [CI]) for sOH-30 as a predictor of incident depression. Covariates were chosen a priori, based on their hypothesized role in modifying the relationship between baseline OH and incident depression.

On the basis of these regression models, average marginal effects were calculated for relevant predictor variables post-estimation. Per subject, each nominal predictor of interest was first assigned its base category level value while holding values of all other variables in the regression model for that subject constant; the probability of outcome was calculated. The process was then repeated, assigning the predictor of interest to its next value. The difference between the calculated probabilities for the levels of the predictor variable was the marginal effect; the average marginal effect for the sample was calculated as the mean of these values over the different levels of the predictor of interest.

To ensure findings were not related to antidepressant use, subgroups of participants taking antidepressant medication were excluded from the analysis, and logistic regression models were rerun to ensure that findings were not significantly different when these groups were omitted. Similarly, analysis was rerun excluding participants with an MMSE score <28 to ensure that findings were not affected by those with early or undetected cognitive impairment.

A P value ≤0.05 was considered statistically significant.

Results

Three thousand nine hundred and eighty-two participants met initial criteria for inclusion at wave 1. A further 8% of this group screened positive for depression at wave 1(CES-D-20 score ≥16) and were, therefore, excluded from the study, yielding an initial study sample of 3662 participants. Thirteen percent (488/3662) of this group did not complete 4-year follow-up, leaving a final study sample of 3174 participants. See Figure S1 in the online-only Data Supplement for flow diagram of study recruitment and attrition.

Over one sixth (proportion, 18%; 95% CI, 16–20) of the study sample had OH-30 and >40% (proportion, 42%; 95% CI, 38–47) of these were symptomatic. The baseline characteristics of the study sample by diagnosis of OH-30 are shown in Table 1. Participants with OH-30 were older and more likely to be female, functionally impaired, have a history of falls, and prescribed antidepressant and antihypertensive medication.

In terms of differences between those with sOH-30 and aOH-30, participants with sOH-30 had a lower systolic BP nadir (linear regression, 80.7 [95% CI, 68.7–92.7] versus 94.3 [95% CI, 91.1–97.4] mm Hg) and diastolic BP nadir (linear regression, 37.5 [95% CI, 26.4–48.7] versus 46.3 [95% CI, 44.5–48.1] mm Hg) during active stand testing compared with the aOH-30 group. Participants with sOH-30 were also more likely to have an initial drop (ie, at 10 seconds post-standing) in systolic BP >40 mm Hg compared with those with aOH-30 (61% [95% CI, 55–68] versus 58% [95% CI, 52–64]). There were similar rates of cardiovascular disease and antihypertensive use between groups (Figure 1; Table 1).

Does OH-30 at Wave 1 Predict Incident Depression?

One tenth (proportion, 10%; 95% CI, 9–12) of the study sample had incident depression by 4-year follow-up, that is, depression at either wave 2 or 3. This includes 138 participants with depression at wave 2 and a further 162 with incident depression at wave 3.

Participants with incident depression were almost twice as likely to have sOH-30 at wave 1 compared with those without incident depression (linear regression, 13 [95% CI, 8–19] versus 7% [95% CI, 6–8]). Proportions of participants with incident depression by OH-30 group are shown in Figure 2.

Weighted logistic regression models demonstrated that sOH-30 predicted incident depression with an odds ratio of 1.92 (95% CI, 1.18–3.11) after controlling for covariates. Other significant predictors of incident depression were female sex, high-normal CES-D scores, and current antidepressant use. aOH-30 did not predict incident depression (Table 2).

Average marginal effects, calculated post-estimation, demonstrated that the average marginal probability of incident depression in participants with sOH-30 was 0.16 (95% CI, 0.11–0.21; z=5.84; P<0.001), compared with 0.10 (95% CI, 0.08–0.11) and 0.10 (95% CI, 0.07–0.14) for those with both no OH-30 and aOH-30, respectively. The dy/dx for the sOH group (with no OH-30 group as a reference) was, therefore, 0.06 (95% CI, 0.01–0.12; z=2.25; P=0.025), suggesting that the probability of developing incident depression in those with sOH-30 at baseline is >6% in those without OH-30.

Subgroup Analysis

For OH-30 as a predictor of incident depression, separate analyses were also performed excluding participants taking antidepressants (n=132), as well as those with MMSE score <28 (n=468), and results were not attenuated significantly (Table 3).

Does IOH at Wave 1 Predict Incident Depression?

Almost half (proportion, 46%; 95% CI, 44–48) of the study sample had IOH, with 40% of these participants having

Table 1. Baseline Characteristics of Study Sample by Diagnosis of OH-30 at Wave 1

Baseline Characteristics	No OH-30, n=2643	Asymptomatic OH-30, n=305	Symptomatic OH-30, n=226
Age, y, mean (95% CI)	61.4 (60.9–61.8)	67.3 (66.0–68.6)	66.6 (65.2–68.0)
Females, prop (95% CI)	0.48 (0.46–0.50)	0.61 (0.54–0.67)	0.56 (0.49–0.63)
Third-level education, prop (95% CI)	0.26 (0.25–0.28)	0.21 (0.17–0.26)	0.25 (0.20–0.31)
Married, prop (95% CI)	0.74 (0.72–0.77)	0.67 (0.61–0.73)	0.66 (0.58–0.73)
Alcohol abuse, prop (95% CI)*	0.14 (0.12–0.15)	0.11 (0.07–0.14)	0.13 (0.08–0.18)
≥1 IADL impairment, prop (95% CI)†	0.03 (0.02–0.04)	0.04 (0.01–0.07)	0.06 (0.02–0.10)
TUG, s, mean (95% CI)	8.2 (8.2–8.3)	8.8(8.6–9.0)	8.9(8.6–9.1)
Falls in past 12 mo, prop (95% CI)	0.18 (0.17–0.20)	0.22 (0.17–0.27)	0.30 (0.23–0.37)
Weight loss >10 lbs, prop (95% CI)	0.05 (0.04–0.06)	0.07 (0.04–0.11)	0.07 (0.03–0.12)
Low physical activity, prop (95% CI)‡	0.69 (0.67–0.71)	0.74 (0.68–0.79)	0.74 (0.68–0.80)
Systolic BP, mm Hg (95% CI)§	134.4 (133.6–135.2)	140.3 (137.8–142.8)	136.5 (133.7–139.4)
Diastolic BP, mm Hg (95% CI)§	82.6 (82.1–83.0)	82.1 (80.7–83.6)	81.0 (79.4–82.7)
Myocardial infarction, prop (95% CI)	0.04 (0.03–0.05)	0.03 (0.01–0.06)	0.06 (0.02–0.10)
Cardiac failure, prop (95% CI)	0.01 (0.00–0.01)	0.01 (0.00–0.01)	0.03 (0.00–0.05)
Cardiac arrhythmia, prop (95% CI)	0.06 (0.05–0.07)	0.14 (0.09–0.19)	0.12 (0.08–0.17)
Prior stroke, prop (95% CI)	0.01 (0.00–0.01)	0.02 (0.00–0.04)	0.01 (0.00–0.02)
Diabetes mellitus, prop (95% CI)	0.07 (0.05–0.08)	0.09 (0.05–0.13)	0.09 (0.05–0.14)
Parkinson disease, prop (95% CI)	0.00 (0.00–0.01)	0.00 (0.00–0.01)	0.00 (0.00–0.02)
Antihypertensive use, prop (95% CI)‖	0.31 (0.29–0.33)	0.45 (0.38–0.51)	0.39 (0.32–0.46)
Antidepressant use, prop (95% CI)	0.03 (0.03–0.04)	0.07 (0.04–0.11)	0.12 (0.07–0.17)
Cognitive impairment, prop (95% CI)¶	0.03 (0.02–0.04)	0.04 (0.01–0.06)	0.06 (0.02–0.10)

Differences in categorical variables presented as weighted prevalence estimates using proportional estimation. Continuous variables were analyzed by linear regression with study group as a predictor. ATC indicates anatomic therapeutic chemical; BP, blood pressure; CI, confidence interval; IADL, instrumental activities of daily living; OH-30, orthostatic hypotension at 30 s post-stand during active stand test; Prop, proportion; and TUG, Timed Up and Go Test.

*Alcohol abuse defined as a score ≥2 on the CAGE alcohol scale.

†IADL impairments include impairments in cleaning and maintaining the house, managing money, moving within the community, and preparing meal.

‡Low physical activity defined as no physical activity on any day in the past week.

§BP was measured twice with sphygmomanometer in seated position, and the average of 2 readings was used.

‖Antihypertensive use defined as being prescribed any antihypertensive medication with ATC Classification Codes C02, C03, C07, C08, and C09.

¶Cognitive impairment defined as Mini-Mental State Examination score <24.

symptomatic IOH. The baseline characteristics of the study sample by diagnosis of IOH are shown in Table S1. There was no significant age or sex difference across groups defined by diagnosis of IOH.

Weighted logistic regression models demonstrated that neither symptomatic IOH nor asymptomatic IOH predicted incident depression (Table S2).

Discussion

This study shows that in a large sample of nondepressed community-dwelling older people, participants with sOH-30 after standing had a 2-fold higher risk of incident depression during 4-year follow-up after controlling for covariates including cognitive impairment and antidepressant use. Average marginal effects scores demonstrate that, in a group of otherwise average individuals, sOH-30 at baseline increases the probability of incident depression by 6%.

This is the first longitudinal study to investigate the relationship between OH and depression.[21] Our findings are supported by prior studies that identified a cross-sectional association between finometer-defined OH and LLD but were limited by small numbers and high prevalence of current antidepressant use among participants.[22,37] A larger cross-sectional study of the TILDA cohort also identified an association between current depression and symptomatic OH diagnosed with sphygmomanometer-based BP data.[23]

Although our findings are not sufficient to imply causation, OH-related cerebral hypoperfusion may represent the mechanism for this association. Orthostatic drops in BP are associated with higher burden of frontal WMH in older people with depression.[38] Several studies have demonstrated loss of frontal lobe integrity in LLD.[9,39,40] The frontal lobe is relatively sensitive to hypoperfusion,[41] and age-related changes in cerebral perfusion are most marked in this region,[42] increasing the likelihood that reductions in cerebral blood flow because of OH would lead to loss of white matter integrity there. Damage to the frontal–subcortical pathway, which links the frontal lobe to the subcortex, can result in executive dysfunction, as well as psychomotor retardation, loss of interest, and functional impairment, hallmarks of depression in later life.[43] Prior

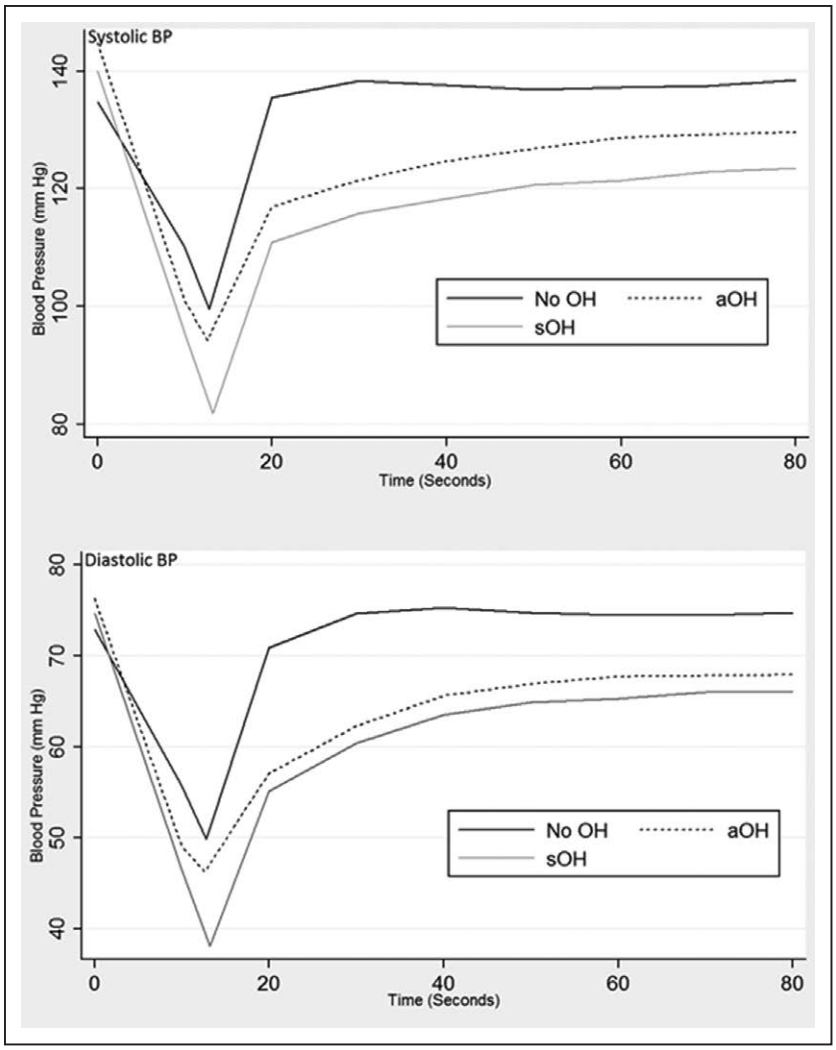

Figure 1. Mean blood pressure (BP) values from active stand comparing symptomatic orthostatic hypotension (sOH) and asymptomatic orthostatic hypotension (aOH) at 30 s post-standing (OH-30) groups to non–OH-30 group. Time represents seconds post-stand during active stand test.

studies have also identified an association between other conditions potentially caused by low BP and deficits in cerebral perfusion, including stoke, syncope, and unexplained falls.[44–46]

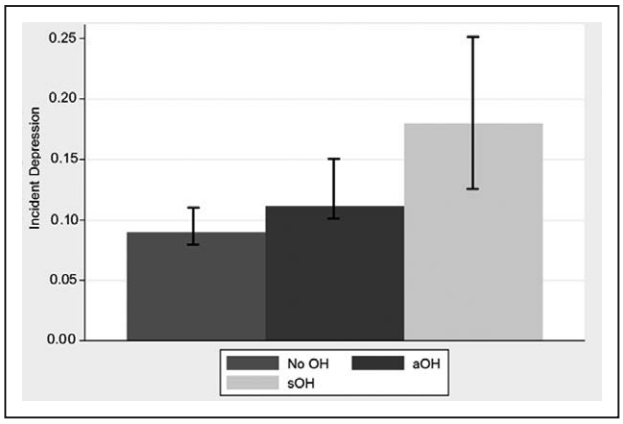

Figure 2. Proportion of participants (with 95% confidence intervals) with incident depression by orthostatic hypotension at 30 s post-standing at wave 1 (OH-30) group. n=3174 (no OH-30=2643; asymptomatic orthostatic hypotension at 30 s post-standing [aOH]-30=305; symptomatic orthostatic hypotension at 30 s post-standing [sOH]-30=226). Differences in incident depression presented as weighted prevalence estimates using proportional estimation. Incident depression defined as 8-item Center for Epidemiological Studies Depression Scale ≥9 at wave 2 or 3.

aOH-30 did not predict depression. There were no significant differences between those with sOH-30 and aOH-30 in terms of age, sex, cardiovascular disease, or use of culprit medications. However, the sOH-30 group had a lower nadir BP on active stand testing, as well as a more prolonged BP recovery, reflecting a greater degree of hypotensive burden, causing orthostatic symptoms, and potentially increasing the risk of cerebral hypoperfusion.[47] IOH also did not predict incident depression. This is not surprising given prior evidence demonstrating that IOH does not increase the risk of falls in the same TILDA population[8] and that although the IOH group had a profound initial drop in BP, in almost two thirds of participants with IOH, BP had recovered to baseline by 30 seconds after standing.

After exclusion for baseline depression by CES-D, almost 9% of participants with OH-30 were prescribed antidepressants, 3 times more than those without OH-30. Antidepressants, particularly tricyclic antidepressants, increase the risk of OH and are prescribed regularly for indications other than depression, such as chronic pain or anxiety.[48] We, therefore, reran our regression analyses to demonstrate that our findings were not significantly attenuated when antidepressant users were excluded. It is apparent, therefore, that this association is independent of antidepressant use.

Table 2. Logistic Regression Reporting OR for Association Between Symptomatic Orthostatic Hypotension at Wave 1 and Incident Depression

Incident Depression	OR (Weighted)	*P* Value	*t*	95% CI	OR (Unweighted) With 95% CI
Model 1					
sOH-30 at wave 1*	2.13	0.002	3.15	1.33–3.42	2.02 (1.39–2.95)
aOH-30 at wave 1†	1.19	0.443	0.77	0.76–1.85	1.13 (0.76–1.68)
Model 2					
sOH-30 at wave 1*	2.07	0.004	2.88	1.26–3.41	1.95 (1.31–2.92)
aOH-30 at wave 1†	1.13	0.600	0.52	0.72–1.78	1.05 (0.69–1.60)
Age, y					
65–74	0.71	0.064	–1.85	0.50–1.02	0.81 (0.60–1.11)
≥75	1.07	0.804	0.25	0.63–1.82	1.06 (0.66–1.69)
Female sex	1.49	0.009	2.63	1.11–2.00	1.57 (1.20–2.05)
Educational attainment					
Secondary	0.65	0.017	–2.39	0.45–0.92	0.68 (0.49–0.95)
Tertiary	0.65	0.028	–2.20	0.45–0.96	0.72 (0.52–1.01)
Marital status					
Single	0.78	0.347	–0.94	0.49–1.29	0.90 (0.55–1.47)
Separated/divorced	1.46	0.139	1.48	0.88–2.42	1.29 (0.81–2.05)
Widowed	0.99	0.976	–0.03	0.57–1.72	1.02 (0.66–1.59)
CES-D					
6–10	2.24	<0.001	4.63	1.59–3.15	2.32 (1.73–3.10)
11–15	5.78	<0.001	8.60	3.87–8.62	5.87 (4.24–8.11)
CAGE score					
1	0.92	0.750	–0.32	0.57–1.50	0.85 (0.56–1.29)
2	1.31	0.259	1.13	0.82–1.12	1.25 (0.83–1.89)
3	1.65	0.111	1.60	0.89–3.05	1.66 (0.96–2.88)
4	0.46	0.337	–0.96	0.09–2.25	1.04 (0.23–4.74)
Model 3					
sOH-30 at wave 1*	1.91	0.009	2.62	1.18–3.09	1.79 (1.19–2.70)
aOH-30 at wave 1†	1.10	0.673	0.42	0.70–1.75	1.00 (0.66–1.54)
Age, y					
65–74	0.66	0.024	–2.26	0.45–0.95	0.75 (0.55–1.03)
≥75	0.85	0.568	–0.57	0.48–1.50	0.87 (0.53–1.43)
Female sex	1.40	0.037	2.09	1.02–1.91	1.51 (1.15–1.99)
Educational attainment					
Secondary	0.67	0.033	–2.14	0.46–0.97	0.73 (0.52–1.02)
Tertiary	0.73	0.105	–1.62	0.49–1.07	0.81 (0.53–1.43)
Marital status					
Single	0.77	0.274	–1.10	0.47–1.24	0.86 (0.53–1.42)
Separated/divorced	1.40	0.202	1.28	0.83–2.36	1.29 (0.81–2.07)
Widowed	1.01	0.985	0.02	0.57–1.77	1.04 (0.66–1.62)
CES-D					
6–10	2.02	<0.001	4.03	1.44–2.91	2.16 (1.61–2.91)

(*Continued*)

Table 2. Continued

Incident Depression	OR (Weighted)	*P* Value	*t*	95% CI	OR (Unweighted) With 95% CI
11–15	5.44	<0.001	7.96	3.58–8.25	5.49 (3.95–7.64)
CAGE score					
1	0.87	0.588	–0.54	0.51–1.46	0.81 (0.53–1.24)
2	1.29	0.309	1.02	0.79–2.12	1.22 (0.80–1.86)
3	1.67	0.112	1.59	0.89–3.13	1.71 (0.98–2.98)
4	0.36	0.249	–1.15	0.07–2.03	0.92 (0.20–4.29)
Weight loss >10 lbs	2.02	0.007	2.70	1.21–3.36	1.82 (1.15–2.89)
IADL impairment‡	0.70	0.442	–0.77	0.28–1.74	0.72 (0.36–1.46)
Gait abnormality§	1.44	0.349	0.94	0.67–3.08	1.55 (0.85–2.82)
Cardiac disease‖	1.24	0.141	1.47	0.93–1.66	1.17 (0.90–1.52)
Hypotension¶	1.38	0.510	0.66	0.53–3.61	1.11 (0.54–2.26)
Stroke	0.62	0.556	–0.59	0.13–3.01	0.58 (0.13–2.57)
Diabetes mellitus	1.06	0.823	0.22	0.63–1.79	1.39 (0.87–2.22)
Parkinson disease	4.10	0.173	1.36	0.54–31.26	4.08 (0.72–23.04)
Antidepressant use	1.87	0.037	2.10	1.04–3.35	1.97 (1.23–3.15)
Cognitive impairment#	1.22	0.646	0.46	0.52–2.91	1.30 (0.60–2.81)

n=3174. aOH-30 indicates asymptomatic orthostatic hypotension at 30 s; BP, blood pressure; CES-D, Center for Epidemiological Studies Depression Scale; CI, confidence interval; IADL, instrumental activities of daily living; OR, odds ratio; and sOH-30, symptomatic orthostatic hypotension at 30 s.

*Drop in systolic BP ≥20 mm Hg or diastolic BP ≥10 mm Hg from baseline at 30 s post-standing during active stand test with associated orthostatic symptoms.

†Drop in systolic BP ≥20 mm Hg or diastolic BP ≥10 mm Hg from baseline at 30 s post-standing during active stand test without associated orthostatic symptoms.

‡Impairment in cleaning and maintaining the house, managing money, moving within the community, or preparing meal by self-report.

§Timed Up and Go Test score ≥12 s.

‖Self-report of prior myocardial infarction, cardiac arrhythmia, congestive heart failure, or hypertension.

¶BP measured in seated position of systolic <100 mm Hg or diastolic <60 mm Hg.

#Mini-Mental State Examination score ≤24.

Our findings also mirror those seen in studies of OH and dementia, where OH has also been shown to predict incident dementia in older people.[6] There is a complex relationship between depression and dementia in later life with recent research suggesting that LLD represents a prodromal phase before the onset of clinically significant cognitive deficits.[49] This is supported by the overlapping clinical features between LLD and early dementia, particularly vascular dementia, including executive dysfunction and apathy, and our study suggests a potentially shared mechanistic pathway.[43]

Table 3. Logistic Regression Reporting ORs (With 95% CIs) of Symptomatic Orthostatic Hypotension Predicting Incident Depression

OR for sOH-30 Predicting Incident Depression When Subgroups Excluded			
	Model 1	Model 2	Model 3
Excluding antidepressant users (n=3042)	OR=1.74 (1.14–2.65) *P*=0.010 *z*=2.56	OR=1.72 (1.09–2.69) *P*=0.019 *z*=2.35	OR=1.65 (1.05–2.61) *P*=0.031 *z*=2.15
Excluding participants with MMSE score <28 (n=2706)	OR=2.13 (1.40–3.23) *P*<0.001 *z*=3.54	OR=2.01 (1.29–3.15) *P*=0.002 *z*=3.07	OR=1.86 (1.18–2.94) *P*=0.008 *z*=2.66

Model 1 is unadjusted. Model 2 controls for age, sex, marital status, CAGE score, and baseline depression scores. Model 3 controls for model 2 covariates and functional impairment, gait abnormalities, heart disease, low blood pressure, weight loss, physical activity, stroke, diabetes mellitus, Parkinson disease, antidepressant use, and cognitive impairment. CI indicates confidence interval; OR, odds ratio; MMSE, Mini-Mental State Examination; sOH-30, symptomatic orthostatic hypotension at 30 s post-standing.

This study has some limitations that must be noted. Incident depression was defined by 8-item CES-D and not by gold-standard psychiatric interview. The shortform 8-item CES-D has been validated against the 20-item CES-D within the TILDA population, however.[50] Several variables, including cardiovascular disease, are based on self-report and may, therefore, be limited by recall bias.[51]

Additionally, although participants with preexisting clinically diagnosed dementia were excluded at wave 1 from the TILDA study, it is well recognized that cognitive impairment is often undetected and underdiagnosed.[52] Furthermore, an MMSE cutoff score of 24, which we used in this study, may not be sensitive enough to detect cognitive impairment in a well older population.[53] We, therefore, performed our regression analysis excluding all participants with MMSE score <28, and sOH-30 remained a significant predictor of depression.

The strengths of this study include the large study sample, with detailed social and biological data, allowing us to robustly control for important covariates, as well as the continuous measurement of orthostatic BP, which is unique for a study of this scale.

Depression confers significant disability on the older people, as well as an increased mortality risk.[54] These findings are important because OH may, therefore, represent a potentially modifiable risk factor for LLD. Forty percent of participants with OH-30 in this study were prescribed antihypertensive therapy, whereas almost one tenth were prescribed antidepressant medication, despite the absence of clinically significant depressive symptoms at baseline. Treatment of OH in the first instance often involves discontinuation of culprit medications.[1] Increased awareness of the risks of overtreatment of BP in older people and resultant hypotension is imperative especially in the context of recent large international research advocating more aggressive BP lowering in this group.[55]

Perspectives

This study demonstrates that symptomatic OH at 30 seconds post-standing is associated with a 2-fold increased risk of incident depression in a large population-representative sample of older people. This finding is important because, given the higher burden of cerebral white matter disease in LLD, cerebral hypoperfusion caused by OH may be the mechanism for this association, and OH may, therefore, represent a modifiable risk factor for depression in older people.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This is the first study to investigate the longitudinal relationship between orthostatic hypotension and depression in older people.
- It includes a large, well-described population-representative sample of older people with a diagnosis of orthostatic hypotension based on continuous beat-to-beat readings.

What Is Relevant?

- Orthostatic hypotension may be a modifiable risk factor for depression in later life.
- These findings are also relevant in the context of recent international research demonstrating better outcomes after more aggressive blood pressure control in older people.

Summary

Participants with symptomatic orthostatic hypotension had a 2-fold increased risk of depression during 4-year follow-up, independent of other risk factors including subthreshold depressive symptoms.