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# Orthostatic Hypotension Is Associated With Lower Cognitive Performance in Adults Aged 50 Plus With Supine Hypertension

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***Objectives.*** This study investigated the association between orthostatic hypotension (OH), supine hypertension (SH), and cognitive performance.

***Methods.*** Four thousand six hundred and ninety participants of The Irish Longitudinal Study on Ageing (TILDA) were studied. SH was defined as systolic blood pressure (SBP) greater than or equal to 140 mmHg and/or diastolic blood pressure (DBP) greater than or equal to 90 mmHg, measured following supine rest (10 minutes). OH was defined as a sustained drop of greater than or equal to 20 mmHg SBP or greater than or equal to 10 mmHg DBP at 20, 30, 60, and 90 seconds following orthostasis. Cognitive performance tests assessed global function, executive function, processing speed, memory, and attention from which z-scores were computed. Multivariate adjusted analysis was performed comparing cognitive scores by OH status overall and in SH and non-SH groups separately.

***Results.*** Thirty-nine percent had baseline SH ($n$ = 1,868) and demonstrated a greater orthostatic fall in SBP ($p <$ .0001) and DBP ($p <$ .0001). This group had a higher prevalence of OH at all time-points, and scored lower in tests across all cognitive domains. No overall association between OH and cognitive performance was seen. However, SH subjects with OH scored significantly worse (adjusted) than SH subjects without OH, in domains of global cognition (30 seconds poststand β = −0.15; 99% confidence interval −0.29, −0.14; $p$ = .004) and executive function (20 seconds poststand; β = −0.11; 99% confidence interval −0.22, −0.01; $p$ = .006). There was also an indication toward lower cognition in all nonsignificant analyses. OH was not associated with cognitive performance in non-SH subjects.

***Conclusion.*** In conclusion, individuals with SH (defined as BP > 140/90 mmHg) coupled with OH measured using phasic BP had lower global and executive cognitive performance than those with SH but without OH.

***Key Words:*** Blood pressure—Cognitive aging—Neurological disorders.

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ORTHOSTATIC hypotension (OH) is a highly prevalent age-related condition in both the community and health care settings; from 30% in older aged community-dwelling adults (1) to more than 50% in geriatric ward patients (2). OH is a strong predictor of all-cause mortality (3). The global aging demographic is likely to result in an increased health care burden of OH and other age-related conditions such as cognitive impairment in the foreseeable future.

Vascular risk factors for cognitive impairment and dementia are well recognized; however, preventative or curative strategies have yet to be established. Emphasis is placed on identifying potentially modifiable risk factors for cognitive decline. The association between hypertension and cognitive dysfunction is well recognized; however, a U-shaped relationship may exist such that both low and high blood pressure are associated with cognitive decline (4). Ample evidence indicates hypertension as a predictive factor for cognitive decline; however, evidence for the role of hypotension is less conclusive, with a recent review unable to determine whether hypotension is a cause or consequence of cognitive impairment in old age (5).

The current consensus-based definition of OH is a drop in systolic blood pressure (SBP) greater than or equal to 20 mmHg or a decrease in diastolic blood pressure (DBP) greater than or equal to 10 mmHg within 3 minutes of orthostasis (6). More recently, a refinement of this definition to greater than or equal to 30 mmHg SBP drop for subjects with baseline SBP greater than or equal to 160 mmHg has been proposed (6). BP and heart rate recovery are generally

complete by 30 seconds poststand such that the early stage of stabilization has been attained (7). Continuous methods for BP assessment detect beat-to-beat hemodynamic changes in response to orthostasis and have demonstrated a stronger association with clinical outcomes than traditional cuff-based BP measurement (8). Continuous methods also exhibit increased sensitivity to postural BP responses and improved identification of episodes of transient OH (8).

Studies that have examined the association between OH and cognition indicate conflicting results (9–11), and few have measured OH using continuous methods (12). The prevalence of OH is higher in hypertension (13) and supine hypertension (SH), which may indicate a dysautonomic pathogenesis when these conditions present together (14).

This study sought to investigate the association between OH (measured using continuous BP assessment) and cognitive performance, and the influence of SH on the association, in a representative sample of community-dwelling older adults.

## Methods

### *Study Population*

Data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) were analyzed (2009–2011). TILDA is a large prospective cohort study of ageing, comprising of community-dwelling people aged 50 and older resident in the Republic of Ireland. Detail of the study design is published elsewhere (15). Data collected within TILDA comprise of (i) computer-assisted personal interviewing (CAPI), carried out in the participant's home, (ii) self-completion questionnaire, and (iii) a physical health assessment carried out by trained study nurses in one of two dedicated health centers. Ethical approval was obtained, and all respondents provided signed informed consent prior to participation. All experimental procedures adhered to the Declaration of Helsinki.

### *Measurement and Classification of Blood Pressure Response to Orthostasis*

The BP response to orthostasis was recorded using the volume clamp method (Finometer MIDI, Finapres Medical Systems, Arnhem, The Netherlands). Recordings were obtained in a comfortably lit, quiet room at ambient temperature (21–23 °C). Following 10 minutes of supine rest, baseline SBP and DBP were measured as the mean of values recorded between 60 and 30 seconds prior to postural change. Physiocal was switched off immediately prior to standing. BP was subsequently recorded for 120 seconds in the standing position. The nadir was used to calculate the maximum orthostatic BP fall from baseline. BP was estimated at 10-second intervals using 5-second moving averages around each point (8). OH at each time-point after standing was defined as a "sustained" drop of greater than or equal to 20 mmHg SBP or greater than or equal to 10 mmHg DBP from baseline up to that point. Because a 10-second averaging window with 50% overlap (5 seconds) was used, the point at 120 seconds in most individuals would include edge effects. Time-points at 10-second intervals beginning at 20 seconds postorthostasis were tested in initial analysis. It was subsequently decided to report results for time-points at 30-second intervals once the observable effects stabilized. Hence, data at 20, 30, 60, and 90 seconds were used in analysis, which also delineates the initial response to the period of early BP stabilization in healthy individuals (7). Baseline SH was defined as SBP greater than or equal to 140 mmHg or DBP greater than or equal to 90 mmHg, as measured during 60–30 seconds before standing. This is the first stage of hypertension to confer a cardiovascular disease risk, modifiable by therapeutic management (16).

### *Assessment of Cognitive Function*

Cognitive function was assessed using a battery of cognitive tests. Composite scores for each cognitive domain were derived from a combination of test scores. Further detail on all cognitive tests administered is described elsewhere (17).

The composite score for global cognition was derived from the Mini-Mental State Examination (MMSE) (18) and the Montreal Cognitive Assessment (MOCA) test (19). MMSE and MOCA scores were added and then transformed using log([60 − sum score] +3) to eliminate skew and approximate a normal distribution. The negative form of each standardized score was computed resulting in lower values corresponding with lower performance.

Composite scores for all other domains were created based on an equally unit-weighted approach using standardized scores (z-scores), that is, composite z-score for tests A, B, and C was calculated by standardizing the sum of the z-scores for each test individually.

The composite score for executive function was derived from verbal fluency and visual reasoning tasks, and Color Trail 2 time.

The composite score for processing speed was derived from the Color Trail 1 time and the cognitive reaction time of the choice reaction time task (20).

The composite score for episodic memory was derived from a word recall test and a picture memory test.

The Sustained Attention to Response Task (SART) was used to measure sustained attention.

### *Covariates*

Other acquired measures included age, gender, educational attainment (primary, secondary, or tertiary), smoking status (never smoked, former, or current), alcohol intake (units weekly), physical activity (using the International Physical Activity Questionnaire short form, classified as low, medium, or high according to the standard scoring

protocol) (21), body mass index (BMI, kg/m$^2$), and total blood cholesterol (mmol/L).

The Center for Epidemiological Studies Depression scale was used with a cutoff score of 16 or more to define subjects as depressed (22). SBP and DBP were recorded during seated rest, using a digital automatic BP monitor (OMRON) as the mean of two readings. Self-reported cardiovascular diseases (CVD) were documented: history of angina, myocardial infarction, heart failure, diabetes mellitus, stroke, transient ischemic attack, and cardiac arrhythmias.

Medication use was recorded during the CAPI and confirmed by cross-checking the medication labels. Anatomical Therapeutic Classification (ATC) codes were subsequently recorded for categorization (23). BP-modifying medications were antiadrenergic agents (second-level ATC code C02), diuretics (C03), beta-blockers (C07), calcium channel blockers (C08), angiotensin-converting-enzyme inhibitors/angiotensin-receptor blockers (C09), and combinations of the above (C02). Antipsychotic medications (N05A) were also classified and controlled for in analysis.

### *Statistical Analysis*

Statistical analysis was performed using Stata version 12 (StataCorp, College Station, TX). Intercorrelation of composite scores within each cognitive domain was assessed using Cronbach's alpha coefficient. Values greater than 0.5 were considered adequate reliability between variables. Time-based test scores were inversed prior to standardization, resulting in positive values correlating with higher performance for all cognitive measures. Distribution of continuous variables was assessed using Q–Q plots and histograms. For descriptive analyses, normally distributed continuous variables were described as means and standard deviation, and were compared by sex using independent *t*-tests. Non-normally distributed continuous variables were described as medians and percentiles and compared using Mann-Whitney tests, whereas categorical variables were compared using chi-square tests. Data on cognitive tests were largely complete (no more than 11% missing for any test), and subjects with missing data were subsequently excluded on a case-wise basis.

Multivariate linear regression analysis was performed to compare cognitive performance between OH and non-OH subjects. The z-scores for each cognitive domain were used as outcome variables to allow comparison of performance between groups on a common scale for all cognitive domains. Subjects without OH at 20 seconds (ie, those whose blood pressure had recovered before 20 seconds poststanding) were considered the reference group. A single model was fitted for each cognitive outcome, adjusting for age (linear and nonlinear effects), sex, education, smoking, alcohol intake, exercise, BMI, cholesterol level, history of CVD, depression, and medications. Errors of omission and commission were additionally adjusted for in analysis of sustained attention. OH and non-OH subjects were first compared in the whole cohort and subsequently according to baseline SH. In our analysis, we only considered tests as significant where $p$ value was less than .01, due to the large number of independent hypotheses being considered, and report 99% confidence intervals (CIs) for estimates of effects.

## Results

In total, 8,175 participants aged 50 years and older were recruited to the TILDA study (15). Of these, 5,036 agreed to undergo an in-center health assessment, 4,690 of whom had technically adequate data for orthostatic BP analysis. They were younger and had healthier physical, behavioral, and cognitive characteristics than others who underwent home-based assessment or no health assessment (17).

The mean age was 60.9, and 2,599 (55%) were females. Demographic and clinical characteristics of the study cohort are outlined in Table 1. Thirty-nine percent of subjects had baseline SH ($n$ = 1,868). These subjects were older and had a higher BMI, cholesterol level, seated BP, and antihypertensive medication use. They demonstrated a greater orthostatic fall in SBP (−44.4 vs −35.6; $p < .0001$) and DBP (−27.2 vs −24.8; $p < .0001$) on standing (nadir-baseline). Oscillometric-recorded SBP and DBP were also higher in this group. The non-SH group had higher education and history of smoking (current and former) and heart failure. Gender, alcohol consumption, physical activity, depression, and prevalence of other CVD were similar between groups.

Cognitive performance across all tests used to derive z-scores is reported in Table 2. Test scores for MMSE, word fluency, visual reasoning, Color Trails 1 and 2, immediate and delayed memory recall, and SART were poorer among subjects with SH. These differences only remained statistically significant for SART, however, following adjustment for age.

The proportion of subjects with OH at each time-point is listed in Table 3. Overall, 15% of subjects had sustained OH at 30 seconds, which fell to 4.6% at 90 seconds. Subjects with SH had a higher prevalence of OH at all times. At 20 seconds poststand 37.2% ($n$ = 695) of supine hypertensive and 23.9% ($n$ = 673) of nonhypertensive subjects had OH, which decreased to 6.7% ($n$ = 125) and 3.2% ($n$ = 91) by 90 seconds poststand, respectively.

Figure 1 presents the standardized z-scores for OH subjects across the five domains of cognition stratified by OH at each time-point relative to non-OH subjects. Analysis was adjusted for all covariates, covering demographics, behavioral and mental health, clinical profile, CVD, and medication use. Overall, there was a trend toward lower cognitive performance among OH subjects; however, this was not significant at $p$ value less than .01 in any domain at each time. Subjects with OH at 20 seconds scored worse overall in domains of executive function ($\beta$ = −0.052; 99%

Table 1. Characteristics of the Study Sample, and According to Supine Blood Pressure

| Characteristics | Total Cohort ($n$ = 4,690) | No Supine Hypertension ($n$ = 2,822) | Supine Hypertension ($n$ = 1,868) | $p$* |
|---|---|---|---|---|
| Age, mean ± *SD* | 60.9 ± 5.8 | 59.7 ± 8.5 | 62.8 ± 8.7 | <.0001 |
| Female, % ($n$) | 55.4 (2,599) | 54 (1,533) | 57 (1,066) | .06 |
| Education, % ($n$) | | | | |
| Primary | 20.4 (955) | 18.5 (521) | 23.3 (434) | |
| Secondary | 42.2 (1,980) | 42.4 (1,195) | 42.1 (785) | .003 |
| Tertiary | 37.4 (1,753) | 39.2 (1,105) | 34.7 (648) | <.0001 |
| Smoking status, % ($n$) | | | | |
| Never | 45.8 (2,150) | 43.5 (1,227) | 49.4 (923) | |
| Former | 39.1 (1,830) | 39.7 (1,120) | 38 (710) | .008 |
| Current | 15.1 (710) | 16.8 (475) | 12.6 (235) | <.0001 |
| Standard drinks consumed weekly† | 3 (1.2, 7.5) | 3 (0.24, 7.5) | 3 (0.12, 8.8) | .6 |
| Level of physical activity (IPAQ), % ($n$) | | | | |
| Low | 27.6 (1,283) | 27.6 (775) | 27.5 (508) | |
| Medium | 35.7 (1,661) | 34.9 (978) | 37 (683) | .4 |
| High | 36.7 (1,708) | 37.5 (1,051) | 35.6 (657) | .5 |
| Body mass index (kg/m$^2$), mean ± *SD* | 28.5 ± 4.9 | 28 ± 5.1 | 29 ± 4.7 | .03 |
| Total cholesterol (mmol/L), mean ± *SD* | 5.2 ± 1.1 | 5.1 ± 1.1 | 5.2 ± 1 | .0005 |
| Seated SBP‡ (mmHg), mean ± *SD* | 134 ± 19 | 126 ± 16 | 144 ± 19 | <.0001 |
| Seated DBP‡ (mmHg), mean ± *SD* | 82 ± 12 | 79 ± 9.7 | 87 ± 11.1 | <.0001 |
| Mental health, % ($n$) | | | | |
| Depression (CES-D ≥ 16) | 9.4 (442) | 9 (254) | 10.1 (188) | .2 |
| Disease prevalence, % ($n$) | | | | |
| Angina | 4.2 (198) | 4.2 (118) | 4.3 (80) | .8 |
| Myocardial infarction | 3.8 (176) | 4.2 (118) | 3.1 (58) | .06 |
| Heart failure | 0.8 (36) | 1.1 (31) | 0.3 (5) | .001 |
| Diabetes | 6.3 (294) | 5.7 (162) | 7.1 (132) | .07 |
| Stroke/TIA | 2.6 (123) | 2.5 (71) | 2.8 (52) | .5 |
| Cardiac arrhythmia | 6.9 (325) | 6.7 (189) | 7.3 (136) | .4 |
| On antihypertensive medication, % ($n$) | 31.6 (1482) | 29.8 (842) | 34.3 (640) | .001 |
| On antipsychotic medication, % ($n$) | 1 (49) | 1.24 (35) | 0.8 (14) | .1 |
| Supine SBP, mean ± *SD* | 135.9 ± 22.2 | 121.6 ± 12.6 | 157.4 ± 15.3 | <.0001 |
| Supine DBP, mean ± *SD* | 73.2 ± 11.2 | 68 ± 8.5 | 81 ± 10.2 | <.0001 |
| Maximum orthostatic SBP difference, mean ± *SD* | −39.1 ± 17.8 | −35.6 ± 9.9 | −44.4 ± 19 | <.0001 |
| Maximum orthostatic DBP difference, mean ± *SD* | −25.7 ± 10.3 | −24.8 ± 9.9 | −27.2 ± 10.8 | <.0001 |

*Notes*: CES-D = Center for Epidemiologic Studies Depression scale; DBP = diastolic blood pressure; IPAQ = International Physical Activity Questionnaire; SBP = systolic blood pressure; *SD* = standard deviation; TIA = transient ischemic attack.

*$p$ values based on test statistics comparing subjects with and without supine hypertension.

†Summarized as median (25th percentile, 75th percentile) because of skewed distribution.

‡Measured using oscillometric blood pressure equipment.

CI −0.12, 0.02; $p$ = .06) and sustained attention (β = −0.06; 99% CI −0.14, 0.01; $p$ = .03).

Stratified analysis in subjects with and without baseline SH is also illustrated in Figure 1. SH subjects with OH scored significantly worse than SH subjects without OH, in domains of global cognition (at 20 and 30 seconds poststand; 30-second β = −0.15; 99% CI −0.29, −0.01; $p$ = .004) and executive function (at 20 seconds poststand; β = −0.11; 99% CI −0.22, −0.01; $p$ = .006).

We compared the magnitude of cognitive performance between OH and non-OH groups with modeled age coefficients to determine the equivalent age-related difference in cognition. This was performed comparing the OH regression coefficients presented in Figure 1 with the age coefficient in the same model. The age coefficient corresponding to the association model between sustained OH at 20 seconds in the SH group, and global performance is −0.02. Hence, the effect of OH (β = −0.13) is equivalent to approximately 6 years of cognitive ageing in non-OH subjects with SH.

Across all other domains and at each time, there was some evidence of lower cognition in this group (significant at $p < .05$ in five tests), with results generally consistent with the effect among those with OH at 20 seconds but with insufficient power available to detect a statistically significant difference from the non-OH group. There was no evidence of lower or higher cognition in OH subjects in the non-SH group. Regression models including terms for interactions showed that the difference between SH and non-SH groups in terms of the association between global cognitive function and OH at 20 seconds ($p$ = .004) was statistically significant, and there remained a trend at 30 seconds ($p$ = .02). As a sensitivity analysis, participants were also stratified based on cuff-measured hypertension, and

Table 2. Cognitive Performance of the Study Sample and According to Supine Blood Pressure

| Cognitive performance | Total Cohort ($n$ = 4,690) | No Supine Hypertension ($n$ = 2,822) | Supine Hypertension ($n$ = 1,868) | $p$* |
|---|---|---|---|---|
| Global cognition | | | | |
| MMSE† | 29 (28, 30) | 29 (28, 30) | 29 (28, 30) | .2 |
| MOCA† | 26 (24, 28) | 26 (24, 28) | 26 (23, 28) | .4 |
| Executive function | | | | |
| Word fluency, mean ± *SD* | 21.7±6.9 | 22±7 | 21.4±7 | .3 |
| Letter fluency, mean ± *SD* | 12.3±5 | 12.3±5 | 12.4±5 | .2 |
| Visual reasoning, mean ± *SD* | 3.2±1.3 | 3.2±1.3 | 3.1±1.3 | .6 |
| Color Trail 2 (s)† | 98 (80, 124) | 96 (78, 121) | 102 (83, 128) | .9 |
| Processing speed | | | | |
| Color Trail 1 (s)† | 48 (38, 63) | 47 (37, 61) | 50 (40, 66) | .9 |
| Cognitive RT (ms)† | 484 (433, 547) | 482 (431, 544) | 489 (434, 550) | .4 |
| Memory | | | | |
| Immediate recall, mean ± *SD* | 6±1.6 | 6.1±1.6 | 5.9±1.6 | .5 |
| Delayed recall, mean ± *SD* | 6.3±2.2 | 6.4±2.2 | 6.2±2.2 | .3 |
| Picture recall, mean ± *SD* | 3.2 1.1 | 3.2±1.1 | 3.2±1.1 | .4 |
| Picture recognition† | 6 (5, 6) | 6 (5, 6) | 6 (5, 6) | .23 |
| Sustained attention | | | | |
| Mean SART (ms)† | 364 (301, 437) | 358 (298, 427) | 375 (309, 451) | .003 |
| *SD* SART (ms)† | 92 (66, 134) | 91 (65, 133) | 94 (68, 137) | .09 |

*Notes*: MMSE = Mini-Mental State Examination; MOCA = Montreal Cognitive Assessment test; RT = reaction time, SART = Sustained Attention to Response Task; SD = standard deviation.

*$p$ values based on test statistics comparing subjects with and without supine hypertension, adjusted for age.

†Summarized as median (25th percentile, 75th percentile) because of skewed distribution.∞ P-values based on test statistics comparing subjects with and without supine hypertension, adjusted for age.SD = standard deviation, MMSE = Mini-Mental State Examination, MOCA = Montreal Cognitive Assessment test, RT =reaction time, SART =Sustained Attention to Response Task.

Table 3. Number of Subjects With Orthostatic Hypotension at Time-Points Following Orthostasis, According to Baseline Blood Pressure

| | Total Cohort ($n$ = 4,690) | No Supine Hypertension ($n$ = 2,822) | Supine Hypertension ($n$ = 1,868) | |
|---|---|---|---|---|
| | Orthostatic Hypotension, % ($n$) | | | $p$* |
| Sustained at 20 s | 29.2 (1,368) | 23.9 (673) | 37.2 (695) | <.0001 |
| Sustained at 30 s | 15 (702) | 11.4 (321) | 20.4 (381) | <.0001 |
| Sustained at 60 s | 6.6 (308) | 4.6 (130) | 9.5 (178) | <.0001 |
| Sustained at 90 s | 4.6 (216) | 3.2 (91) | 6.7 (125) | <.0001 |

*Note*: *$p$ values based on test statistics comparing subjects with and without supine hypertension.

again hypertensive subjects with OH consistently scored poorer across all tests, with comparable significance (data not shown).

The data were also analyzed based on redefined OH classification (≥30 mmHg SBP drop for subjects with baseline SBP ≥ 160 mmHg) (6). Results were similar to the analysis shown, with significance confined to the association of lower global cognitive performance. As the number of subjects with OH according to this definition was fewer, the CI of each point estimate was wider.

## Discussion

The association between OH and cognitive performance appears to be dependent on supine BP in healthy middle-aged and older adults. Here, we report an independent association between OH and cognition in supine hypertensive subjects only, notably in the domains of global and executive function. Early OH (sustained at 20–30 seconds poststand) is most clearly associated with lower performance. These findings are independent of potential confounders; namely demographics, clinical profile, behavioral and mental health, CVD, and medications including antihypertensives. Where results were not statistically significant, there remained a trend toward lower cognition in SH cases with OH; whereas no trend towards lower or higher cognition was observed for OH subjects without SH.

Although the literature states that BP and HR are recovered around 30 seconds (7), in this population-based study of older than 50s, 15% had not recovered their supine blood pressure by 30 seconds after standing. Hence, there is a significant potential burden of OH in the middle-aged and older population, given its known association with clinical conditions.

Results from similar studies are inconsistent, some reporting an inverse (9) and others no relationship (10) between

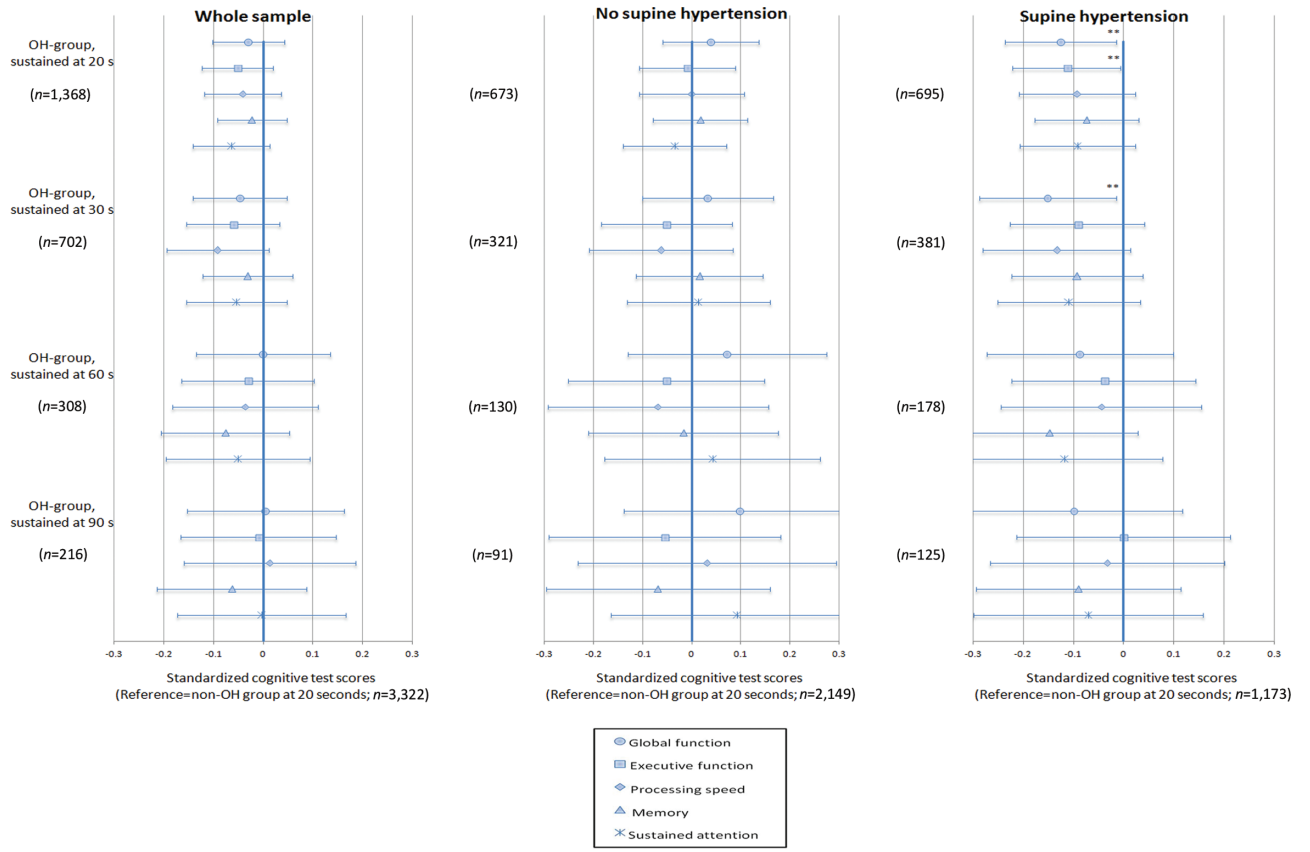


Figure 1. Forest plots illustrating the standardized cognitive scores for subjects with orthostatic hypotension (OH) relative to those without OH, in the whole sample and for subjects with and without supine hypertension. $^{**}p < .01$. Analysis was adjusted for age (linear and nonlinear effects), sex, education, smoking, alcohol intake, exercise, body mass index, cholesterol level, history of cardiovascular diseases, depression, and medications.

OH and cognition. In contrast to our findings, one study reported lower cognition in OH subjects with underlying hypotension, and higher performance in OH and hypertension (11). Cognition was defined using MMSE alone, which has recognized limited discriminatory power, and hypertension status included both self-reported and controlled BP cases. The authors suggest that the positive association may be due to the therapeutic effect of antihypertensive treatment. Elsewhere, SH but not orthostatic BP was associated linearly with fronto-executive impairment (24). Both studies had smaller sample sizes than the present study. A recent study reported hypertension to be a risk factor for global and executive function decline, without impact on attention and processing speed, similar to the domains affected here (25). Our group recently investigated the association between cognitive performance and OH as defined using automatic digital BP measurements. The results also indicated an association between presence of OH and lower cognition—specifically in the subdomains of global performance and memory (26).

A higher prevalence of OH in the presence of SH has been established (SH–OH) (27). Subjects with both SH and OH exhibit both markedly decreased baroreflex-cardiovagal gain and attenuated plasma noradrenaline responses, which implicates baroreflex failure in its pathogenesis. Cerebral autoregulation is impaired in cases of OH (28), resulting in pressure-dependent perfusion. Both high and low BP alter autoregulation, raising the lower BP limit, narrowing the BP range, and steepening the cerebral blood flow–BP curve (29). Impaired vasodilatation in low BP states and higher vasoconstriction at higher BP may result from this dysautoregulatory state. In our study, the SH group also demonstrated a greater orthostatic fall in both DBP and SBP, which can potentially result in greater impairment to blood flow and cerebral perfusion capacity. Subanalysis adjusting for maximum BP drop did not attenuate results, indicating that the association was not explained by the degree of drop.

Long-standing hypertension is known to predispose to cognitive decline (5). As hypertension is also a risk factor for OH, it leads that its prevalence is higher in cases of long-standing hypertension. Hence, duration of hypertension may explain a relationship between OH and lower cognitive function. Duration of preceding hypertension was not recorded in wave 1 of the TILDA study, so we were unable to control of this in analysis. However, future waves

of the study will allow for investigation of the role of long-standing hypertension on the subject.

The pathogenesis of cerebral damage comprises of a cascade of pathophysiological events, principally cerebral small vessel disease (mainly arteriosclerosis and cerebral amyloid angiopathy) and white matter damage, which are associated with cerebral hypoperfusion (30). White matter lesions predict cognitive decline and dementia (31). Small vessel disease is associated with more than two times increased risk of dementia at 75 years (32). Hypoperfusion of the prefrontal cortex has been reported in OH patients compared with controls (33), which may explain our association between OH and executive function, a domain controlled by the prefrontal cortex.

As our study sample is selected from the healthy community-dwelling population, the effect size of our results is relatively small. This limits the clinical interpretation of our results; however, the role of our findings lies in the context of future research investigating biomarkers of cognitive ageing. The lack of a significant association between sustained OH at later times poststanding and cognition is unexpected, as prolonged hypotension should equate to greater hypoperfusion and cerebral damage. However, the CI for each test and at each time is consistent with a −0.1 *SD* cognitive difference, indicating that cognition may actually be lower among subjects with OH sustained at 60–90 seconds. The lack of precision of effect estimates, possibly due to smaller numbers in these groups, does not allow us to be certain of this nonetheless. Alternatively, an adaptive response to prolonged OH may adjust cerebral blood flow to compensate for sustained low BP, as cerebral autoregulation remains intact in a proportion of cases (28). As the standard method for BP measurement uses the seated position, SH may be underdetected in the clinical setting. Improved vigilance and diagnosis are needed, given its potential role in clinical outcomes. Management of individuals with both OH and SH is challenging, as the beneficial effects of pharmacological treatment of one condition may worsen the other (34). This remains, however, the subject of ongoing debate (35). Symptom relief remains a priority. Additionally, assessment using major-event predictive tools to determine which clinical sequelae pose a greater risk to the individual should be prioritized and guide management, for example, major vascular events or major injuries such as fractures (caused by a fall secondary to OH) (36).

Nonpharmacological management of OH includes increased salt and fluid intake, reducing/discontinuing culprit medications, performing physical counter-maneuvers and wearing custom-fitted elastic stockings, whereas management of SH includes the use of reclining chairs to avoid the supine position. Pharmacological treatment for SH with antihypertensive therapy worsens OH; hence, short-acting medications, administered at night-time, are recommended (37). OH is often treated with midodrine and pseudoephedrine; however, their use should be restricted to greater than 4 hours before recumbency (37).

The association between cognition and OH as measured with beat-to-beat BP monitoring at a population scale has not been assessed before. Beat-to-beat methods allow for more precise quantification of BP changes and capability of detecting more subtle fluctuations in response to orthostasis. We use comprehensive neuropsychological measures spanning numerous domains of cognition. Objective health measures were further assessed and controlled for in analysis. The protocol consisted of 10 minutes supine rest in a quiet room—the optimal period to obtain stable BP readings (38). The large nationally representative community-based design using rigorous measures of SH and OH strengthens the observations seen. Our study was designed as an epidemiological, point prevalence study and was therefore unable to draw any firm causation for the observed association. Causality will be explored in subsequent waves of the TILDA study. Subjects unwilling to undergo center-based health assessment were offered in-home assessment; however, continuous orthostatic BP response was not recorded here due to impracticality and financial limitations. Despite subject characteristics differing between these groups, we consider that the association between SH, OH, and cognitive performance would not be attenuated in the excluded group. As the sample group analyzed was healthier, the association reported in this study may have been stronger in the excluded group, given the higher levels of both physical and cognitive impairment. Measures within the same domain were weighted equally; hence, the different test accuracies for detecting reduced cognition were not adjusted for. Participants were not requested to refrain from eating, smoking, alcohol, caffeine, exercise, or medications prior to assessment, and time of day for assessment was not restricted, based on practicality of delivering health assessments to participants from all over the country. These factors may affect reproducibility of results; however, time of day and food ingestion did not influence orthostatic BP behavior in a substudy (39).

## Conclusion

In conclusion, individuals with supine hypertension (SH; defined as BP > 140/90 mmHg) coupled with OH measured using phasic BP had lower cognitive performance than those with hypertension but without OH. Sustained OH at 20–30 seconds post orthostasis yielded the strongest association in the cognitive domains of global and executive function. Future studies should recognize SH when investigating the association between OH and clinical outcomes, as nocturnal hypertension is increased in SH and increases the risk for cardiovascular and cognitive disorders. Clinicians should give consideration to the measurement of SH in addition to orthostatic BP, as SH–OH management guidelines differ from those for OH in isolation. Further investigation of the mechanisms and associations between autonomic and hemodynamic dysregulation will improve understanding of the process of transition from the cognitively functional to the cognitively impaired state.

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## Conflict of interest

None declared.

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