ORIGINAL RESEARCH

Is Baseline Orthostatic Hypotension Associated With a Decline in Global Cognitive Performance at 4-Year Follow-Up? Data From TILDA (The Irish Longitudinal Study on Ageing)

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***Background*—**It is postulated that orthostatic hypotension (OH), a reduction in blood pressure (≥20/10 mm Hg) within 3 minutes of standing, may increase cognitive decline because of cerebral hypoperfusion. This study assesses the impact of OH on global cognition at 4-year follow-up, and the impact of age and hypertension on this association.

***Methods and Results*—**Data from waves 1 and 3 of TILDA (The Irish Longitudinal Study on Ageing) were used. Baseline blood pressure response to active stand was assessed using beat-to-beat blood pressure monitoring. Two measures of OH were used—at 40 seconds (OH40) and 110 seconds (OH110). Global cognition was measured using the Montreal Cognitive Assessment. Mixed-effects Poisson regression assessed whether baseline OH was associated with a decline in global cognition at 4-year follow-up. The analysis was repeated, stratifying by age (age 50–64 years and age ≥65 years), and including an interaction between OH and hypertension. Baseline OH110 was associated with an increased error rate in Montreal Cognitive Assessment at follow-up (incident rate ratio 1.17, P=0.028). On stratification by age, the association persists in ages 50 to 64 years (incident rate ratio 1.25, P=0.048), but not ages ≥65 years. Including an interaction with hypertension found those with co-existent OH110 and hypertension (incident rate ratio 1.27, P=0.011), or OH40 and hypertension (incident rate ratio 1.18, P=0.017), showed an increased error rate; however, those with isolated OH110, OH40, or isolated hypertension did not.

***Conclusions*—**OH is associated with a decline in global cognition at 4-year follow-up, and this association is dependent on age and co-existent hypertension. **(*J Am Heart Assoc*. 2018;7:e008976. DOI: 10.1161/JAHA.118.008976.)**

Key Words: age • aging • cognition • cognitive impairment • hypertension • orthostatic hypotension

Orthostatic hypotension (OH) is traditionally defined as a sustained reduction in systolic blood pressure (BP) of at least 20 mm Hg or diastolic BP of 10 mm Hg within 3 minutes of standing.[1] It can occur within 30 seconds of stand (initial OH), between 30 seconds and 3 minutes of stand (classical OH), or after 3 minutes of stand (delayed OH).[2] The prevalence of OH increases with age, and previous analysis of the TILDA (The Irish Longitudinal Study on Ageing) data has found a prevalence of impaired BP stabilization on stand of 15.6% of participants, rising from 14.3% of men and 16.9% of women aged 50 to 59 years, to 43.4% of men and 39.9% of women over the age of 80 years.[3] Several mechanisms are responsible for impairment in BP control, including impaired baroreflex sensitivity, abnormal neurohumeral regulation, impaired thirst, dehydration, and impaired venomotor tone.[4,5]

Recently, more refined methods of measurement of BP behavior during orthostasis using technologies that measure beat-to-beat BP have demonstrated that failure to stabilize BP during early stages of stand are associated with falls and syncope,[2] depression,[6] and with cognitive impairment.[7]

Aging may be associated with a decline in cognitive abilities such as memory, attention, processing speed, language, and visuospatial and executive function.[8] The prevalence of age-associated cognitive decline is 15% in persons over 60 years.[9] Mild cognitive impairment is a decline in cognition that is worse than normative data for a

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Accompanying Tables S1 through S8 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.008976

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Clinical Perspective

What Is New?

- Baseline orthostatic hypotension (OH), assessed using beat-to-beat blood pressure response to stand, is associated with a decline in global cognitive performance at 4-year follow-up.
- This association is most evident in the middle-age group (50–64 years), who demonstrated a decline in cognition at follow-up.
- Participants with both OH and hypertension demonstrate the most dramatic decline in cognition.

What Are the Clinical Implications?

- OH in midlife (50–64 years) is associated with a decline in global cognitive performance at 4-year follow-up, and further studies are required to assess whether intervention in OH could prevent or slow cognitive decline.
- Recognition of co-existent OH in individuals with hypertension is important, given evidence of a decline in global cognition in these individuals.

set age and education level, but does not meet the criteria for the diagnosis of dementia.[10] Prevalence data for mild cognitive impairment vary greatly, with the prevalence of mild cognitive impairment having been reported as up to 42% of individuals.[9] The main differentiating criterion for dementia is the existence of functional impairment.[11] The brain is highly metabolically active, and precise regulation of cerebral blood flow (cerebral autoregulation) is required to maintain a constant nutrient and oxygen supply to the brain.[12] There is evidence that cerebral blood flow can be compromised in OH,[13,14] and it has been postulated that OH can increase the risk of cognitive impairment through alterations in cerebral blood flow. Several cross-sectional studies have shown an association between OH and cognitive decline,[7,15–18] including cross-sectional analysis of the first wave of the TILDA data set.[7,15] A number of longitudinal studies have investigated directionality of this association; however, in contrast to most cross-sectional studies, a majority did not find an association.[19–23] BP measurement in the majority of these studies was assessed using oscillometric lying and standing BP, a more crude method of BP measurement than beat-to-beat measurement.[19,20,22] The TILDA data set provides a unique opportunity to study the effect of more dynamic shifts in orthostatic BP, as measured by beat-to-beat BP, on cognitive function.

The aim of this study is to assess whether baseline OH at 40 and 110 seconds after stand is associated with a decline in cognitive scores at 4-year follow-up in a community-dwelling sample over the age of 50 years.

Methods

Study Sample

Data from TILDA (The Irish Longitudinal Study on Ageing) were used. The anonymized TILDA data set is available to researchers who meet the criteria for access from the Irish Science Data Archive at University College Dublin and the Interuniversity Consortium for Political and Social Research at the University of Michigan, and TILDA also considers applications for privileged access to the data set through an onsite "hot desk" facility (visit www.tilda.ie for further information).

TILDA is a large prospective cohort study comprising community-dwelling adults over the age of 50 years in the Republic of Ireland, repeatedly assessed at 2-year intervals. At wave 1, a nationally representative sample was drawn from a listing of all residential addresses in the Republic of Ireland using the RANSAM sampling procedure,[24] with a response rate of 62%. Details of the sampling method have been published elsewhere.[24] The TILDA study comprised (1) a computer-aided personal interview (CAPI), carried out by trained interviewers in participants' homes; (2) a self-completion questionnaire; and (3) a health assessment carried out by trained research nurses. All participants who completed the CAPI were invited to attend 1 of 2 health centers for health assessment. As part of a comprehensive health assessment, participants completed a cardiovascular assessment, which included beat-to-beat measurements of BP during active stand and the Montreal Cognitive Assessment (MOCA). This study included all participants who completed both the CAPI and health assessment at wave 1 (2009–2011) and had adequate active stand data for analysis of orthostatic BP behavior, as well as completing both the CAPI and MOCA at wave 3 (4-year follow-up period). Participants who had a self-reported doctor's diagnosis of dementia, a MOCA score <20, Parkinson's disease, or stroke at wave 1 or a subsequent diagnosis of Parkinson's or stroke between waves 1 and 3, were excluded from the analyses.

Ethical approval for TILDA was obtained from the Trinity College Research Ethics committee, and participants provided written informed consent.

BP Measurement

1. Participants who attended the health center underwent active stand, which noninvasively measures beat-to-beat BP response to orthostasis using digital photoplethysmography (Finometer MIDI device; Finapres Medical Systems). Participants underwent assessment of BP response to stand, following 10 minutes of supine rest. Baseline BP was measured as the mean value between 60 and 30 seconds before stand, during the supine rest period. BP response to stand was measured up to 110 seconds post stand. BP was

estimated at 10-second intervals, using 5-second moving averages around each point. Two measurements of OH were analyzed. OH at 40 seconds (OH40) was defined as a sustained drop of ≥20 mm Hg systolic BP (SBP) or ≥10 mm Hg diastolic BP (DBP) at each time point up to 40 seconds post stand. Previous analysis of the TILDA data has demonstrated that while there is a wide range of BP response patterns to active stand, the majority of participants stabilize their BP by 30 seconds,[3] and so we chose the 40 seconds cut-off to represent the participants who fail to stabilize their BP by this time point. A subset of these participants with OH at 110 seconds (OH110) was also analyzed and defined as a sustained drop of ≥20 mm Hg SBP or ≥10 mm Hg DBP at each time point up to 110 seconds post stand. As BP was estimated at intervals using 5-second moving averages, the point at 120 seconds (duration of the stand at wave 1) in most individuals would include edge effects and so we chose the 110-seconds point to assess a subset of the participants with OH that represent the "worst" group—that is, those who do not stabilize their BP throughout. Standardized protocols were used for the active stand procedure; however, it was not possible to control for factors such as last meal, smoking, and time of medication administration. Baseline OH as measured at wave 1 health center assessment using the finometer was used.

2. BP was also measured seated, using the traditional oscillometric methods. Two seated SBP and DBP measurements were obtained, separated by 1 minute, using an automatic digital BP monitor (Model M10-IT; OMRON, Kyoto, Japan). Seated hypertension was assessed using oscillometric BP. Hypertension was defined as a systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg.

Cognitive Assessment

Global cognitive function was assessed using the MOCA. The MOCA is a cognitive test including assessment of the cognitive domains of executive and visuospatial function, memory, language, and attention; the test yields a single score ranging from 0 to 30. MOCA was administered at the health center. The MOCA is used frequently in the clinical setting,[25] is sensitive to mild deficits, and is useful in identifying patients with mild cognitive impairment.[26] In addition to this, it demonstrates good test–retest and interrater reliability.[27] The MOCA was assessed as a total score to assess global cognition (maximum score 30). The results of MOCA were then divided into subdomains and assessed individually, including recall, visuospatial, executive function, attention, and working memory, language, and orientation. To assess recall, the delayed recall section of the MOCA was used (maximum score 5). To assess the visuospatial domain, cube drawing and clock drawing were used (maximum score 4). Executive function was assessed using the trail test within the MOCA, language fluency and a 2-item verbal abstraction task (maximum score 4). Attention and working memory was assessed using digits forward and backward, a sustained attention task, and serial subtraction task (maximum score 6). Language was assessed using animal naming, repetition, and the language fluency task (maximum score 6). Finally, orientation to time and place was assessed using questions regarding date, month, year, day, place, and city were used (maximum score 6).

Baseline results of MOCA from wave 1 and follow-up MOCA scores at wave 3 were used.

Covariates

Results were adjusted for variables that have a known association with OH and cognitive decline. Information on age, sex, education attainment, smoking status, and alcohol use (using the CAGE questionnaire[28]) was collected during the CAPI. The CAPI also collected information on self-reported comorbidities including self-reported hypertension, heart failure, angina, myocardial infarction, diabetes mellitus, stroke, transient ischemic attack, murmur, atrial fibrillation, or other arrhythmia. Mean of 2 seated BP measurements was used to assess as objective BP measurements. In wave 1, depressive symptoms were assessed using the Centre for Epidemiological Studies Depression scale.[29] A cut-off score of 16 was used to assess the presence of depression. In wave 3, a short form of the Centre for Epidemiological Studies Depression scale was used,[30] with a cut-off score of 10 used to assess the presence of depression. Height and baseline BP were measured at the health assessment. Frailty was assessed using the Fried Frailty scale,[31] and individuals were grouped in 3 groups—not frail, pre-frail, or frail.

All medications were recorded at the CAPI and classified according to the Anatomical therapeutic classification codes. Medication categories adjusted for were antihypertensive agents ("CO2"), diuretics ("C03"), β-blockers ("C07"), calcium channel blockers ("C08"), angiotensin converting enzyme inhibitors ("C09"), antipsychotic ("N05A"), antidepressants ("N06A"), anxiolytics ("N05B"), hypnotics and sedatives ("N05C"), anticholinergic agents ("N04A"), anticholinesterases ("N06DA"), and diabetic medication ("A10").

Statistical Analysis

All statistical analyses were carried out using STATA 14 (Stata Corporation). For description of data, normally distributed continuous variables were compared using *t* tests; nonnormally distributed continuous variables were compared using Mann–Whitney tests and categorical variables were compared using χ^2 tests. Q-Q plots were used to assess normality.

MOCA scores showed a left-skewed distribution at waves 1 and 3. Therefore, we calculated the number of errors on MOCA at each wave (ie, 30 minus MOCA score), and modeled the change in participants' MOCA error rates between waves using mixed effects Poisson models. Interactions with a variable representing wave (wave 1—baseline assessment; wave 3—assessment at 4-year follow-up interval) for each predictor variable were included to probe change in number of errors on the MOCA (presented as incident rate ratio [IRR]). Wave was also included as a fixed effect predictor in the model. For analysis of subdomains in MOCA, the number of errors was calculated by subtracting the score obtained for that domain from the maximum score possible for the domain. Separate models were fitted to assess the impact of OH40 and OH110 on MOCA. All models treated participant as a random effect, with random intercept (ie, MOCA errors at wave 1 and wave 3 were nested participant-wise). Three models were fitted for OH40 and for OH110; model A, with fixed effect of OH only; model B, a multivariable model controlling for fixed effects of age, sex, and education; and model C, a multivariable model controlling for fixed effects of age, sex, education, self-reported hypertension, self-reported heart failure, number of cardiovascular conditions, diabetes mellitus, alcohol use, smoking status, depression, height, frailty, baseline SBP, pulse pressure, heart rate before stand (wave 1), and medication use (grouped as antihypertensive use, antidepressant use, antipsychotic use, and anticholinesterase, anticholinergic or sedative use, and antidiabetic use). Covariates were chosen based on clinical relevance and current literature. Variables were assessed for multicollinearity using variance inflation factors with a cut-off score of 10, with the exception of interactions and the fixed effect for wave. Information on available covariates from both waves was included in the fully adjusted model, and an interaction with the variable representing wave was included.

Models were then repeated testing the interaction between OH and the presence or absence of hypertension; this was assessed by including a 3-way interaction term between the variable representing wave, OH, and hypertension. All models were then repeated including only age group 50 to 64 years and including only age group ≥65 years, both with and without inclusion of a 3-way interaction with wave, OH, and hypertension. This was to assess the impact of the presence of hypertension as well as to assess how the results differ in the younger and older age groups.

Results

In total, 8175 participants over the age of 50 years were recruited to wave 1 of the TILDA study, of whom 5035 attended the health center for assessment at wave 1. There were 4475 participants ≥50 years of age with adequate active stand data for analysis, of whom 4172 fulfilled inclusion criteria. Of these individuals, 3338 were present at the wave 3 health center for assessment and did not receive a diagnosis of Parkinson's disease or stroke between waves 1 and 3, and were included in the study. Figure 1 details a flow chart of participants included for analysis. Characteristics of participants who were included in the baseline sample but did not have a follow-up MOCA and therefore were not included in the final sample are provided in Table 1. Participants who did not have a follow-up MOCA assessment were older, with lower MOCA scores and higher prevalence of OH.

Population characteristics are described in Table 2. OH40 was present in 9.46% of participants, and OH110 was present in 4.22% of participants included for analyses. Individuals with OH40 and OH110 on active stand were older, showed lower levels of education, had higher systolic BP, lower baseline heart rate, and higher burden of cardiovascular disease. They were more likely to be taking both antihypertensive and antidepressant medications. Those with OH40 also had higher levels of frailty.

The change between waves in number of errors on MOCA in individuals with OH40 is described in Table 3, with change in rates of errors presented as IRR. Participants with OH40 at baseline had an increase in rates of errors over the 4 years in model A (IRR 1.12, 95% confidence interval [CI], 1.04–1.21, P=0.004); however, this was no longer significant when controlling for age, sex, and level of education (IRR 1.05, 95% CI, 0.97–1.15, P=0.205), or on controlling for all covariates (IRR 1.09, 95% CI, 0.99–1.20, P=0.067). Results of the full multivariable analysis are provided in Table S1. There was no significant increase in rates of errors in MOCA between the 2 waves including only participants in the age group 50 to 64 years, or including only participants in the age group ≥65 years (Table 3).

The change between waves in rates of errors in MOCA in individuals with OH110 compared with those without OH110 is also described in Table 3. Participants with OH110 had an increase in number of errors in MOCA compared with those without OH110 on univariate analysis (IRR 1.17, 95% CI, 1.04–1.31, P=0.007); this remained significant on controlling for all covariates (1.17, 95% CI, 1.02–1.33, P=0.028). Results of the full multivariable analysis for the full age cohort are provided in Table S2. The analysis was then repeated including only age group 50 to 64 years and including only age group ≥65 years, and results are also presented in Table 3. In the age group 50 to 64 years, individuals with OH110 had an increase in rates of errors on the MOCA between waves, compared with those without OH on univariate analysis (IRR 1.22, 95% CI, 1.01–1.47, P=0.038), which remained significant on controlling for all confounders (IRR 1.25, 95% CI, 1.01–1.57, P=0.048). In the age group ≥65 years there was no significant increase in rates of errors on MOCA in those with OH110 compared with those

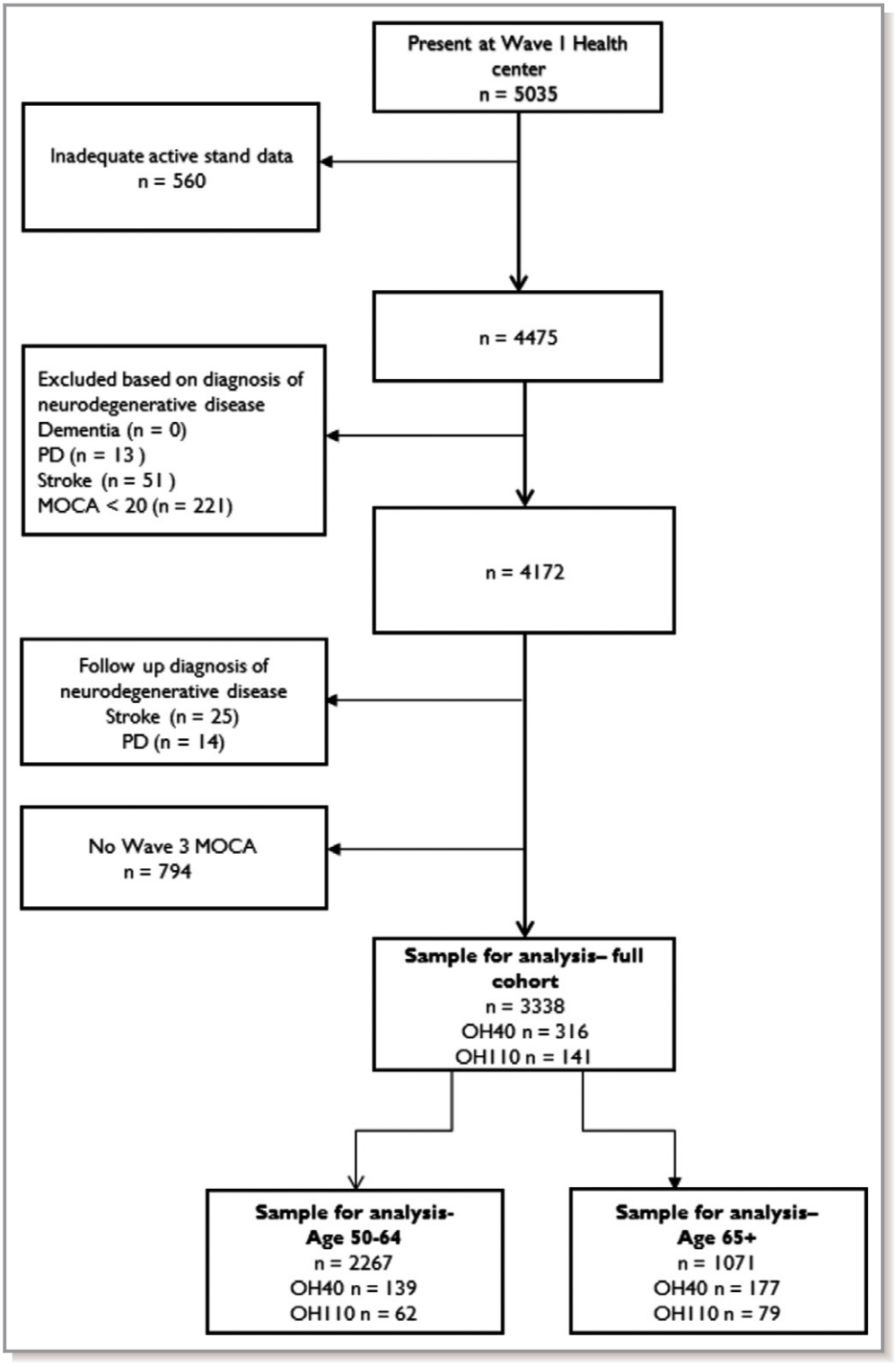

Figure 1. Sample for analysis. MOCA indicates Montreal Cognitive Assessment; OH110, orthostatic hypotension sustained up to 110 seconds post stand; OH40, orthostatic hypotension sustained up to 40 seconds post stand; PD, Parkinson's disease.

without OH110 between waves (Table 3). The results of the full multivariable models for age group 50 to 64 years are presented in Tables S3 and S4. The results of the full multivariable models for age group ≥65 years are presented in Tables S5 and S6. The decrease in absolute MOCA scores in those with OH110 compared with those without OH110 is small (0.65 points on

Table 1. Description of Attrition

	No Follow-up MOCA (N=794)	Analytic Sample (N=3338)
Age, mean±SD	61.9±8.7*	61.1±8.0
MOCA, mean±SD	25.0±2.7‡	25.9±2.5
OH40, % (n)	12.5% (99)*	9.5% (316)
OH110, % (n)	4.9 (39)	4.2% (141)
Female, % (n)	54.3% (431)	54.2% (1808)
Education, % (n)		
Primary	24.1% (191)‡	17.4% (581)
Secondary	44.2% (352)‡	42.3% (1411)
Higher	31.5% (250)‡	40.3% (1347)
Smoking status, % (n)		
Current	20.15% (160)‡	13.6% (454)
CVD disease prevalence, % (n)		
≥2 cardiovascular diseases	12.3% (98)	11.9% (396)
Seated systolic BP, mean±SD	131.6±21.6*	129.8±20.3
Seated diastolic BP, mean±SD	68.6±10.8	68.0±10.7
Taking antihypertensive medications, % (n)	12.3% (98)	11.9% (396)
Taking antidepressant medications, % (n)	6.7% (53)	5.2% (174)
Frailty, % (n)		
Pre frail/frail	30.8% (237)‡	24.1% (789)

BP indicates blood pressure; CVD, cardiovascular disease; MOCA, Montreal Cognitive Assessment; OH110, orthostatic hypotension sustained to 110 seconds post stand; OH40, Orthostatic hypotension sustained to 40 seconds post stand.
*P<0.05.
†P<0.01.
‡P<0.001.

MOCA); however, there is a clear divergence between the 2 groups seen in the results (Figure 2).

All analyses were then repeated testing for the interaction with the presence of hypertension at baseline in the full age cohort, in the age group 50 to 64 years and in the age group ≥65 years. These results are presented in Table 4. In the full age cohort, individuals with both OH40 and hypertension were more likely to show an increased rate of MOCA errors over the 4-year follow-up period, which was significant on controlling for all confounders (IRR 1.18, 95% CI, 1.03–1.34, P=0.017). Individuals with OH40 alone or hypertension alone were no more likely to show a difference in error rate than those without OH40 or hypertension on controlling for confounders (Table 4). In the age group 50 to 64 years, participants with OH40 and hypertension at baseline had an increase in the rates of errors on MOCA, which was significant on controlling for all confounders (IRR 1.29, 95% CI, 1.03–1.62, P=0.025). Again, those with OH40 alone or hypertension alone were no more likely to show an increase in rates of errors compared with those with no OH40 and no hypertension (Table 4). Results of the full multivariable analysis for OH40 in the full cohort are presented in Table S7.

Participants with OH110 and hypertension also showed an increase in rates of errors in MOCA between the time points, compared with those with no OH110 and no hypertension, which was significant on controlling for all confounders (IRR 1.27, 95% CI, 1.06–1.53, P=0.011). Results of the full multivariable analysis are presented in Table S8. Repeating the analysis including only those in the 50 to 64 year age group at baseline showed similar results, with those with both OH110 and hypertension showing an increase in the rates of errors on the MOCA (IRR 1.52, 95% CI, 1.08–2.15, P=0.017) compared with reference (no OH, no hypertension). Again there was no significant increase in rates of errors in those with OH110 alone or those with hypertension alone, nor was there any significant increase in those aged ≥65 years (Table 4).

When analyzing the results of individual subdomains assessed by MOCA, there is an increase in the rate of errors in the domain of executive function in those with OH40 (IRR 1.32; 95% CI, 1.11, 1.57; P=0.002), which remains significant on controlling for all confounders (IRR 1.27; 95% CI, 1.03, 1.56; P=0.027). Those with OH110 also showed an increase in the rate of errors made in

Table 2. Population Characteristics by Presence of OH

Characteristics	OH40 (n=316)	OH110 (n=141)	No OH (n=3023)
Age, mean±SD	66.1±8.7*	65.3±8.3*	60.7±7.7
Female, % (n)	60.3% (193)†	66.9% (95)‡	53.2% (1623)
Education, % (n)			
Primary	23.8% (76)†	23.9% (34)†	16.9% (517)
Secondary	39.1% (125)†	45.1% (64)†	42.5% (1297)
Third/higher	37.2% (119)†	30.2% (44)†	40.6% (1239)
Smoking status, % (n)			
Never	45.6% (146)	47.9% (68)	47.3% (1443)
Past	40.0% (128)	34.5% (49)	39.1% (1194)
Current	14.4% (46)	17.6% (25)	13.6% (416)
Alcohol (CAGE)			
0	75.9% (230)	75.7% (100)	75.6% (2048)
1	10.9% (33)	10.6% (14)	12.6% (355)
2	8.3% (25)	4.6% (6)	9.5% (268)
3	1.0% (3)	1.0% (3)	0.7% (19)
Height, mean±SD	165.1±9.0†	164.1±9.2*	166.7±9.1
MOCA, mean±SD	25.6±2.6†	25.8±2.6	26.0±2.5
Self-reported hypertension, % (n)	38.8% (124)‡	40.9% (58)†	30.9% (944)
Self-reported heart failure, % (n)	0.6% (2)	n=0	0.8% (25)
Self-reported diabetes mellitus, % (n)	6.9% (22)	7.8% (11)	6.0% (183)
Disease prevalence, % (n)			
≥2 CVDs	16.9% (54)*	14.8 (20)†	11.6% (355)
Seated systolic BP, mean±SD	136.9±23.8*	140.3±23.2*	129.1±19.8
Seated diastolic BP, mean±SD	67.8±11.1*	70.6±11.5‡	70.1±11.1
Taking antihypertensive medications, % (n)	39.1% (125)*	39.4% (56)‡	29.8% (909)
Taking antidepressant medications, % (n)	8.8% (28)†	9.2% (13)†	4.9% (148)
Taking antipsychotic medications, % (n)	1.3% (4)	0.7% (1)	0.9% (28)
Taking antidiabetic medication, % (n)	5.3% (17)	6.3% (9)	4.3% (132)
Frailty, % (n)			
Pre-frail/frail	31.2% (97)‡	28.1% (39)	23.5% (706)
CES-D score, mean±SD	4.8±5.8	4.3±4.8	5.2±6.5
Baseline HR, mean±SD	62.5±10.1%*	61.8±934*	65.2±9.8

BP indicates blood pressure; CAGE, CAGE Questionnaire; CES-D, Centre for Epidemiological Studies Depression; HR, heart rate; MOCA, Montreal Cognitive Assessment; OH, orthostatic hypotension; OH110, OH up to 110 seconds; OH40, OH up to 40 seconds.
*P<0.001.
†P<0.05.
‡P<0.01.

the domain of executive function (IRR 1.53; 95% CI, 1.18, 1.99; P=0.002), and again this remained significant on controlling for all confounders (IRR 1.40; 95% CI, 1.03, 1.94; P=0.032). There was no significant increase in error rates seen in the other subdomains assessed by MOCA.

Discussion

Adults with OH are more likely to show an increase in rate of MOCA errors at 4-year follow-up, which remains significant following adjustment for confounders. The association is strongest in participants who fail to recover blood pressure

Table 3. Change in Global Cognition Between Waves for All Ages Based on Baseline OH40 and OH110

	OH40		OH110	
	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Full cohort, N=3338				
Model A	1.12 (1.04, 1.21)	0.004*	1.17 (1.04, 1.31)	0.007*
Model B	1.05 (0.97, 1.14)	0.205	1.11 (0.99, 1.25)	0.065*
Model C	1.09 (0.99, 1.20)	0.067	1.17 (1.02, 1.33)	0.028*
Age 50 to 64 y, N=2267				
Model A	1.09 (0.96, 1.24)	0.170	1.22 (1.01, 1.47)	0.038*
Model B	1.09 (0.96, 1.24)	0.197	1.22 (1.02, 1.48)	0.034*
Model C	1.13 (0.98, 1.31)	0.104	1.25 (1.01, 1.57)	0.048*
Age ≥65 y, N=1071				
Model A	1.05 (0.95, 1.17)	0.306	1.06 (0.92, 1.22)	0.441
Model B	1.02 (0.92, 1.13)	0.688	1.05 (0.90, 1.21)	0.549
Model C	1.05 (0.92, 1.19)	0.459	1.09 (0.91, 1.30)	0.370

Model A—Univariate; Model B—Controls for age, sex, and education; Model C—Controls for all covariates—age, sex, education level, self-reported cardiovascular conditions, diabetes mellitus, alcohol use, smoking status, medications, depression, frailty, mean blood pressure, pulse pressure height, and baseline heart rate. CI indicates confidence interval; IRR, incidence rate ratio; OH110, orthostatic hypotension sustained to 110 seconds; OH40, orthostatic hypotension sustained to 40 seconds.
*Statistically significant *P* values.

throughout the 110-seconds stand. There is evidence that cerebral perfusion is impaired in OH,[13,14] and we hypothesize that those individuals who fail to recover their BP throughout the 110 seconds stand at baseline are therefore exposed to the highest "load" of cerebral hypoperfusion. This association may reflect periods of cerebral hypoperfusion. The association appears to be dependent on the presence of coexistent hypertension, and on age. Individuals with both OH (OH40, OH110) and hypertension showed an increase in rates of errors on MOCA between waves, but this was true only in those aged <65 years. On analysis of the domains assessed by the MOCA individually, it is the domain of executive dysfunction within the MOCA that appears to drive this increase in errors on MOCA. Hypoperfusion of the prefrontal cortex has been reported in OH compared with controls,[32] which may explain these results because executive function is largely controlled by the prefrontal cortex.

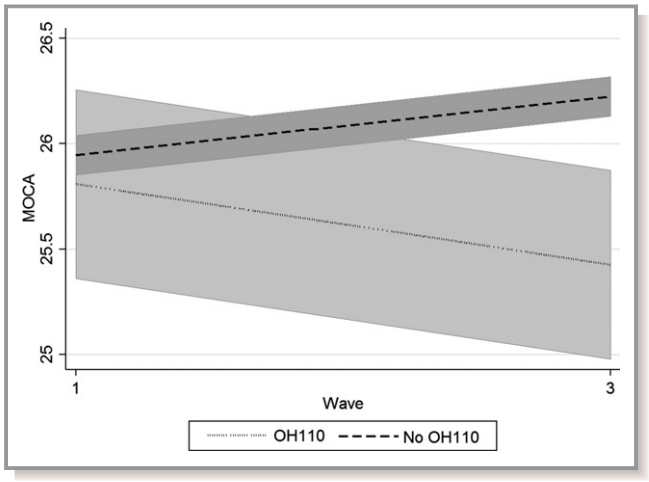

Figure 2. MOCA at wave 1 and wave 3 with 95% CI by presence of OH110 at wave 1. CI indicates confidence interval; MOCA, Montreal Cognitive Assessment; OH110, orthostatic hypotension sustained to 110 seconds.

The relationship between BP and cognitive function is complex, with both high and low BP being linked with cognitive decline and dementia.[33] A nonlinear, U-shaped relationship between BP and cognitive function has been proposed, with individuals with both high and low BP performing worse on cognitive tests than individuals with BP in the midrange.[34] Hypertension has been consistently linked with cognitive impairment and dementia, particularly midlife hypertension.[33] It is postulated that microvascular dysfunction and damage induced by hypertension leads to white matter disease, microinfarcts, and microhemorrhages, which are correlated with cognitive dysfunction.[35] Several mechanisms are proposed to explain the association between cognitive decline and OH. Cerebral autoregulation may be attenuated with aging, with subsequent failure to adapt to repeated oscillations in BP.[36] This may result in impaired cerebral perfusion and cell damage.[14,37] Enhanced white matter hyperdensities are evident in such circumstances,[18] and increasing white matter lesion burden is associated with an increased risk of dementia and also predicts an increased risk of cognitive decline in mild cognitive impairment.[5]

In the current study, individuals with both OH and hypertension exhibited a higher rate of decline in cognitive test scores, whereas individuals with isolated OH or isolated hypertension did not show a decline. Both hypertension[38] and OH[39] are associated with impaired baroreflex, and coexistent OH and hypertension represents a more severe baroreflex dysfunction and exaggerated BP variability. Hypertension causes alterations in the structure and function of cerebral arteries, with loss of elasticity and compliance, resulting in increased myogenic tone, affecting cerebral autoregulation.[5] Thus, hypertension coupled with OH leads to greater BP variability as well as a diminished ability to protect against periods of hypotension when SBP falls below a critical threshold.

These findings are in line with a number of recent longitudinal studies that have found an increase in the rate of incident dementia based on baseline OH, including the Rotterdam Study,[40] the Malmo Preventative Project,[41] and the Three-City Study.[42] The follow-up period for these studies is longer (12–28 years) than in the current study. All assessed incident dementia rather than change in global cognitive test scores such as MOCA. The baseline age ranges were

Table 4. Change in Global Cognition Between Waves Based on Baseline OH and Stratified by Baseline HTN

	OH40		OH110	
	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Full cohort, N=3338				
Model A (base No OH, no HTN)				
No OH, HTN	1.09 (1.01, 1.12)	0.013*	1.07 (1.02, 1.13)	0.006*
OH, No HTN	1.08 (0.94, 1.23)	0.262	1.12 (0.92, 1.37)	0.264
OH and HTN	1.19 (1.09, 1.32)	<0.001*	1.25 (1.09, 1.44)	0.001*
Model B (base No OH, no HTN)				
No OH, HTN	1.03 (0.97, 1.08)	0.326	1.03 (0.98, 1.08)	0.241
OH, No HTN	1.01 (0.88, 1.15)	0.907	1.08 (0.89, 1.32)	0.438
OH and HTN	1.10 (0.99, 1.22)	0.06	1.16 (1.01, 1.33)	0.042*
Model C (base No OH, no HTN)				
No OH, HTN	1.03 (0.95, 1.11)	0.478	1.04 (0.96, 1.13)	0.365
OH, No HTN	1.00 (0.86, 1.17)	0.976	1.07 (0.84, 1.35)	0.594
OH and HTN	1.18 (1.03, 1.34)	0.017*	1.27 (1.06, 1.53)	0.011*
Age 50–64 y, N=2267				
Model A (base No OH, no HTN)				
No OH, HTN	1.03 (0.97, 1.10)	0.330	1.04 (0.97, 1.10)	0.265
OH, No HTN	1.00 (0.83, 1.21)	0.982	1.08 (0.83, 1.41)	0.562
OH and HTN	1.20 (1.01, 1.42)	0.036*	1.42 (1.09, 1.85)	0.010*
Model B (base No OH, no HTN)				
No OH, HTN	1.03 (0.96, 1.10)	0.394	1.03 (0.97, 1.10)	0.314
OH, No HTN	0.98 (0.82, 1.20)	0.909	1.08 (0.82, 1.41)	0.577
OH and HTN	1.20 (1.01, 1.43)	0.035*	1.43 (1.10, 1.87)	0.008*
Model C (base No OH, no HTN)				
No OH, HTN	1.00 (0.91, 1.11)	0.940	1.01 (0.91, 1.13)	0.762
OH, No HTN	1.01 (0.82, 1.24)	0.932	1.07 (0.79, 1.45)	0.670
OH and HTN	1.29 (1.03, 1.62)	0.025*	1.52 (1.08, 2.15)	0.017*
Age ≥65 y, N=1071				
Model A (base No OH, no HTN)				
No OH, HTN	1.05 (0.96, 1.14)	0.302	1.05 (0.96, 1.14)	0.269
OH, No HTN	1.07 (0.89, 1.29)	0.484	1.11 (0.82, 1.50)	0.518
OH and HTN	1.09 (0.96, 1.24)	0.187	1.08 (0.92, 1.28)	0.346
Model B (base No OH, no HTN)				
No OH, HTN	1.03 (0.94, 1.12)	0.573	1.03 (0.95, 1.12)	0.517
OH, No HTN	1.02 (0.84, 1.24)	0.837	1.09 (0.81, 1.48)	0.577
OH and HTN	1.04 (0.92, 1.19)	0.511	1.06 (0.89, 1.25)	0.529
Model C (base No OH, no HTN)				
No OH, HTN	1.09 (0.96, 1.25)	0.160	1.09 (0.97, 1.24)	0.148
OH, No HTN	1.05 (0.82, 1.34)	0.690	1.07 (0.73, 1.57)	0.716
OH and HTN	1.15 (0.96, 1.34)	0.126	1.19 (0.95, 1.50)	0.123

Results of comparison to base of No OH and no HTN. Model A—Univariate; Model B—Controls for age, sex, and education; Model C—Controls for all covariates. CI indicates confidence interval; HTN, hypertension; IRR, incidence rate ratio; OH110, orthostatic hypotension sustained to 110 seconds; OH40, orthostatic hypotension sustained to 40 seconds.
*Statistically significant *P* values.

68.5±8.6 years in the Rotterdam Study, 45±7 and 50±5 years in the Dementia-negative and Dementia-positive groups, respectively, in the Malmo Preventative Project, and 74±5 in the Three-City Cohort. It is not reported that younger individuals within these groups showed a stronger association with dementia. In all 3 studies OH was assessed using traditional oscillometric methods. Phenotypes of OH as defined in the current study (OH40 and OH110) were not assessed, and therefore it is not possible to elicit whether individuals with a higher "load" of cerebral hypoperfusion (ie, OH110 in the current study) were more likely to develop dementia. However, in the Three-City Study, they assessed the traditional thresholds for OH, as well as assessing increasing levels of severity, based on the size of the BP drop, and found that there was a stronger association with the severe OH group. Similarly, in the Rotterdam study, OH was characterized into 3 groups of increasing "severity" of OH; however, in this study they did not observe that increasing severity of OH influenced the association with dementia, possibly because individuals with more severe OH have higher morbidity and mortality.[43] In the Malmo Preventative Study, postural changes in SBP and DBP were assessed as well as the presence of OH as defined traditionally, and found the association between postural DBP changes and dementia was strongest. These studies did not report that the association between OH and dementia was dependent on coexistent hypertension.

The increased rates of errors on MOCA are most robustly observed in the younger age group in our sample (age 50–64 years). This is consistent with studies on hypertension, where midlife hypertension is consistently linked with cognitive impairment. The picture is more complex in older adults, where the association between late-life measures of BP and cognition are less consistent.[44] Whether OH could represent an early, modifiable risk factor for cognitive impairment and dementia requires further exportation given these observational data. However, the management of supine hypertension coupled with OH is complicated because pharmacological interventions for OH exacerbate supine hypertension.[45] Management using conservative measures such as fluid hydration, physical counter maneuvers, and compression hosiery may provide a nonpharmacological alternative.[46,47] Supine hypertension and OH often coexist,[46] and hypertension can lead to alteration of cerebral autoregulation capacity, the process of maintaining stable cerebral perfusion despite variation in peripheral blood pressure,[12] further exposing individuals with hypertension to ischemia and hypoxia when systemic BP drops.[48]

There are some limitations to the current study. The follow-up period is relatively short for assessing decline in global cognition. Cardiovascular confounders that were controlled for relied on self-reported conditions, and exclusion based on a doctor's diagnosis of dementia also relied on self-reporting. The population included in the study was a predominantly white population. The MOCA was used to assess cognition as it is commonly used in clinical practice; however, it is not specifically designed to assess longitudinal changes in cognition. The principal strength of the current study is its use of beat-to-beat measurement of BP response to stand using a finometer, which allows a precise assessment of BP behavior in response to orthostasis and can detect more subtle fluctuations in BP. TILDA allows inclusion of a large number of confounders, including both self-reported and objective measures. It is noteworthy that individuals without OH110 showed a slight improvement in their MOCA scores, which may reflect in a practice effect.[49] In contrast, cognition declined in those with OH, indicating the potential detrimental effect of BP variability.

In conclusion, we found that OH is associated with a decline in global cognition over a 4-year follow-up period in a community-dwelling population over the age of 50 years. This association appears to be dependent on the presence of coexistent hypertension and is strongest in the middle-aged group. Follow-up at future waves of the TILDA data set will allow assessment of the impact of BP behavior on the rate of cognitive decline and rate of incident dementia in these individuals.

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Disclosures

None.

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Supplemental Material

Table S1. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH40 for full cohort.

Total Errors	IRR	95% CI	P- value
Wave	0.4887	[0.3316]--[0.7203]	0.0003
OH40, (base 0)	0.9883	[0.9091]--[1.0743]	0.7817
Age	1.0098	[1.0064]--[1.0133]	<0.0001
Sex	0.9182	[0.8565]--[0.9843]	0.0162
Education, (base “Primary/none”)			
Secondary	0.8584	[0.8036]--[0.9168]	<0.0001
Third level/higher	0.6678	[0.6234]--[0.7153]	<0.0001
No. Cardiovascular conditions, (base “0”)			
1	1.0507	[0.9781]--[1.1288]	0.1756
2	0.9697	[0.8695]--[1.0816]	0.581
Hypertension, (Base “No”)	0.9897	[0.9217]--[1.0627]	0.7747
Heart failure, (base “No”)	1.1446	[0.8911]--[1.4703]	0.2903
Diabetes, (base “No”)	1.116	[0.9411]--[1.3233]	0.2071
Alcohol CAGE score, (base 0)			
1	0.9347	[0.8698]--[1.0045]	0.066
2	0.8887	[0.8164]--[0.9674]	0.0064
3	0.928	[0.8301]--[1.0375]	0.1891
4	1.1398	[0.8788]--[1.4785]	0.324
Smoking status, (base “Never smoked”)			
Past smoker	0.9823	[0.9314]--[1.0360]	0.5106
Current smoker	1.1047	[1.0250]--[1.1905]	0.0091
Anticholinesterase or Anticholinergic	1.1857	[1.0362]--[1.3567]	0.0132
Antihypertensive medications	1.0168	[0.9444]--[1.0947]	0.6591
Antipsychotic medications	0.98	[0.7806]--[1.2304]	0.8618
Antidepressant medications	1.0261	[0.9225]--[1.1412]	0.6357
Diabetic medications	1.0122	[0.8344]--[1.2279]	0.902
Depression	1.0353	[0.9503]--[1.1280]	0.4271
Pulse pressure, mmHg	1.0003	[0.9972]--[1.0034]	0.8444
Systolic BP, mmHg	1	[0.9976]--[1.0024]	0.9805
Wave#OH40	1.0927	[0.9919]--[1.2037]	0.0726
Wave# age	1.0105	[1.0063]--[1.0147]	<0.0001
Wave# Sex	0.9768	[0.9192]--[1.0381]	0.4496
Wave# Education, base primary/none			
Secondary	0.9631	[0.8922]--[1.0397]	0.3359
Third/higher	0.9809	[0.9059]--[1.0620]	0.634
Wave# No. CVD conditions, (base 0)			
1	0.985	[0.8914]--[1.0884]	0.7666
≥2	1.0264	[0.8927]--[1.1801]	0.7146
Wave# Hypertension	1.0415	[0.9608]--[1.1289]	0.3228
Wave# heart failure	0.6684	[0.4514]--[0.9896]	0.0442
Wave# Diabetes	0.9542	[0.7516]--[1.2114]	0.7003
Wave# CAGE score, base 0			

1	0.9475	[0.8600]--[1.0440]	0.2761
2	0.993	[0.8873]--[1.1114]	0.9027
3	0.9571	[0.8212]--[1.1155]	0.575
4	0.7217	[0.4323]--[1.2050]	0.2124
Wave# Smoking status, base never			
Past	1.0226	[0.9619]--[1.0872]	0.474
Current	0.9905	[0.8957]--[1.0955]	0.8531
Wave# Anticholinesterase/Anticholinergic medication	0.9641	[0.8168]--[1.1380]	0.6659
Wave# Antihypertensive medication	0.979	[0.8821]--[1.0866]	0.6903
Wave# Anti-psychotic medication	1.2177	[0.9191]--[1.6134]	0.17
Wave# Anti-depressant	1.1454	[1.0072]--[1.3025]	0.0385
Wave# Diabetic medication	1.0481	[0.8050]--[1.3647]	0.7271
Wave# Depression	1.009	[0.8909]--[1.1428]	0.8879
Wave# Pulse Pressure	0.9975	[0.9930]--[1.0021]	0.2921
Wave# Mean SBP	1.0002	[0.9969]--[1.0035]	0.8949
Frailty, base not frail			
Pre-frail	1.0765	[1.0240]--[1.1317]	0.0038
Frail	1.111	[0.8524]--[1.4481]	0.4361
Height, sm	0.9956	[0.9921]--[0.9991]	0.0133
Baseline HR, bpm	1.0003	[0.9981]--[1.0025]	0.8148

IRR – Incidence rate ratio; OH40 – Orthostatic hypotension sustained to 40 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S2. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH110 for full cohort.

Total Errors	IRR	95% CI	P- value
Wave	0.4841	[0.3290]--[0.7124]	0.0002
OH110, (base 0)	0.9453	[0.8380]--[1.0665]	0.3609
Age	1.0099	[1.0064]--[1.0133]	<0.0001
Sex	0.9201	[0.8582]--[0.9864]	0.019
Education, (base “Primary/none”)			
Secondary	0.8583	[0.8036]--[0.9168]	<0.0001
Third level/higher	0.6671	[0.6227]--[0.7147]	<0.0001
No. Cardiovascular conditions, (base “0”)			
1	1.0508	[0.9782]--[1.1289]	0.1747
2	0.9704	[0.8701]--[1.0824]	0.59
Hypertension, (Base “No”)	0.9887	[0.9208]--[1.0617]	0.7547
Heart failure, (base “No”)	1.1406	[0.8879]--[1.4652]	0.3031
Diabetes, (base “No”)	1.1163	[0.9414]--[1.3238]	0.2057
Alcohol CAGE score, (base 0)			
1	0.9353	[0.8703]--[1.0051]	0.0686
2	0.8885	[0.8162]--[0.9672]	0.0063
3	0.9294	[0.8313]--[1.0391]	0.1982
4	1.1462	[0.8837]--[1.4868]	0.3038
Smoking status, (base “Never smoked”)			
Past smoker	0.9818	[0.9309]--[1.0355]	0.4994
Current smoker	1.105	[1.0254]--[1.1908]	0.0089
Anticholinesterase or Anticholinergic	1.1882	[1.0384]--[1.3595]	0.0121
Antihypertensive medications	1.018	[0.9456]--[1.0960]	0.6354
Antipsychotic medications	0.9746	[0.7762]--[1.2238]	0.8248
Antidepressant medications	1.0264	[0.9229]--[1.1415]	0.6313
Diabetic medications	1.0136	[0.8355]--[1.2296]	0.8912
Depression	1.0324	[0.9475]--[1.1249]	0.4663
Pulse pressure, mmHg	1.0003	[0.9972]--[1.0034]	0.8313
Systolic BP, mmHg	1	[0.9976]--[1.0024]	0.9979
Wave#OH110	1.1683	[1.0164]--[1.3430]	0.0286
Wave# age	1.0107	[1.0065]--[1.0149]	<0.0001
Wave# Sex	0.9752	[0.9176]--[1.0364]	0.4183
Wave# Education, base primary/none			
Secondary	0.9635	[0.8925]--[1.0400]	0.3402
Third/higher	0.9831	[0.9080]--[1.0645]	0.6753
Wave# No. CVD conditions, (base 0)			
1	0.9869	[0.8932]--[1.0906]	0.7964
≥2	1.0286	[0.8947]--[1.1825]	0.6919
Wave# Hypertension	1.0434	[0.9626]--[1.1310]	0.3013
Wave# heart failure	0.6742	[0.4554]--[0.9983]	0.049
Wave# Diabetes	0.9528	[0.7505]--[1.2096]	0.6914
Wave# CAGE score, base 0			

1	0.9466	[0.8591]--[1.0430]	0.2676
2	0.9929	[0.8871]--[1.1112]	0.9007
3	0.96	[0.8236]--[1.1188]	0.601
4	0.7168	[0.4294]--[1.1967]	0.203
Wave# Smoking status, base never			
Past	1.0242	[0.9634]--[1.0888]	0.4434
Current	0.989	[0.8943]--[1.0938]	0.8297
Wave# Anticholinesterase/Anticholinergic medication	0.9642	[0.8169]--[1.1380]	0.6662
Wave# Antihypertensive medication	0.9755	[0.8789]--[1.0826]	0.6402
Wave# Anti-psychotic medication	1.2216	[0.9219]--[1.6188]	0.1635
Wave# Anti-depressant	1.1494	[1.0110]--[1.3068]	0.0335
Wave# Diabetic medication	1.0484	[0.8051]--[1.3651]	0.7258
Wave# Depression	1.0112	[0.8927]--[1.1454]	0.8611
Wave# Pulse Pressure	0.9977	[0.9931]--[1.0022]	0.3161
Wave# Mean SBP	1.0001	[0.9968]--[1.0034]	0.9334
Frailty, base not frail			
Pre-frail	1.0769	[1.0244]--[1.1321]	0.0037
Frail	1.1056	[0.8482]--[1.4410]	0.4579
Height, sm	0.9957	[0.9922]--[0.9991]	0.0144
Baseline HR, bpm	1.0002	[0.9980]--[1.0024]	0.8502

IRR – Incidence rate ratio; OH110 – Orthostatic hypotension sustained to 110 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S3. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH40 for Age group ≥50 and <65.

Total Errors	IRR	95% CI	P- value
Wave	0.7484	[0.3947]--[1.4194]	0.3749
OH40, (base 0)	0.9539	[0.8340]--[1.0910]	0.4909
Age	1.0082	[1.0004]--[1.0160]	0.0397
Sex	0.9379	[0.8557]--[1.0281]	0.1713
Education, (base "Primary/none")			
Secondary	0.8326	[0.7581]--[0.9145]	0.0001
Third level/higher	0.6226	[0.5644]--[0.6867]	<0.0001
No. Cardiovascular conditions, (base "0")			
1	1.062	[0.9660]--[1.1675]	0.2132
2	0.8917	[0.7625]--[1.0429]	0.1515
Hypertension, (Base "No")	0.9941	[0.9030]--[1.0945]	0.9044
Heart failure, (base "No")	1.264	[0.8949]--[1.7852]	0.1837
Diabetes, (base "No")	1.1788	[0.9216]--[1.5078]	0.1902
Alcohol CAGE score, (base 0)			
1	0.96	[0.8803]--[1.0469]	0.3558
2	0.8995	[0.8142]--[0.9938]	0.0373
3	0.9138	[0.7999]--[1.0439]	0.1842
4	1.3093	[0.8760]--[1.9569]	0.1888
Smoking status, (base "Never smoked")			
Past smoker	0.9807	[0.9143]--[1.0521]	0.5873
Current smoker	1.0848	[0.9907]--[1.1879]	0.0787
Anticholinesterase or Anticholinergic	1.1647	[0.9201]--[1.4744]	0.2049
Antihypertensive medications	1.0322	[0.9324]--[1.1427]	0.5414
Antipsychotic medications	1.0612	[0.8226]--[1.3690]	0.6477
Antidepressant medications	0.9891	[0.8633]--[1.1333]	0.8746
Diabetic medications	1.0445	[0.7910]--[1.3791]	0.759
Depression	1.0343	[0.9298]--[1.1506]	0.5346
Pulse pressure, mmHg	1.0005	[0.9963]--[1.0047]	0.8184
Systolic BP, mmHg	0.9998	[0.9967]--[1.0029]	0.9143
Wave#OH40	1.1318	[0.9750]--[1.3137]	0.1036
Wave# age	1.0028	[0.9939]--[1.0116]	0.5412
Wave# Sex	0.9407	[0.8710]--[1.0160]	0.1197
Wave# Education, base primary/none			
Secondary	0.94	[0.8449]--[1.0457]	0.2551
Third/higher	0.9927	[0.8883]--[1.1093]	0.8966
Wave# No. CVD conditions, (base 0)			
1	1.0065	[0.8879]--[1.1409]	0.9193
≥2	1.1145	[0.9193]--[1.3510]	0.2698
Wave# Hypertension	1.0201	[0.9165]--[1.1353]	0.716
Wave# heart failure	0.5107	[0.3071]--[0.8493]	0.0096
Wave# Diabetes	0.9037	[0.6435]--[1.2689]	0.5586
Wave# CAGE score, base 0			

1	0.9645	[0.8582]--[1.0840]	0.5444
2	1.0134	[0.8904]--[1.1534]	0.8401
3	0.9727	[0.8118]--[1.1654]	0.7639
4	0.5464	[0.2912]--[1.0256]	0.0599
Wave# Smoking status, base never			
Past	1.026	[0.9485]--[1.1098]	0.5219
Current	1.0141	[0.9019]--[1.1403]	0.8148
Wave# Anticholinesterase/Anticholinergic medication	0.9725	[0.7400]--[1.2781]	0.8417
Wave# Antihypertensive medication	0.9434	[0.8232]--[1.0812]	0.4024
Wave# Anti-psychotic medication	1.1553	[0.8386]--[1.5915]	0.3772
Wave# Anti-depressant	1.2183	[1.0407]--[1.4261]	0.014
Wave# Diabetic medication	1.1246	[0.7701]--[1.6421]	0.5434
Wave# Depression	0.9944	[0.8549]--[1.1567]	0.9424
Wave# Pulse Pressure	0.9955	[0.9895]--[1.0016]	0.1492
Wave# Mean SBP	1.0015	[0.9972]--[1.0057]	0.4966
Frailty, base not frail			
Pre-frail	1.0509	[0.9821]--[1.1246]	0.1506
Frail	1.4248	[0.9445]--[2.1492]	0.0914
Height, sm	0.9949	[0.9904]--[0.9995]	0.0309
Baseline HR, bpm	0.9999	[0.9969]--[1.0028]	0.922

IRR – Incidence rate ratio; OH40 – Orthostatic hypotension sustained to 40 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate. (N=2148)

Table S4. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH110 for Age group ≥50 and <65.

Total Errors	IRR	95% CI	P- value
Wave	0.7537	[0.3974]--[1.4296]	0.3867
OH110, (base 0)	0.9157	[0.7473]--[1.1220]	0.3953
Age	1.0081	[1.0003]--[1.0159]	0.0419
Sex	0.9393	[0.8569]--[1.0296]	0.181
Education, (base "Primary/none")			
Secondary	0.8342	[0.7595]--[0.9161]	0.0002
Third level/higher	0.6233	[0.5651]--[0.6875]	<0.0001
No. Cardiovascular conditions, (base "0")			
1	1.0604	[0.9645]--[1.1658]	0.225
2	0.8916	[0.7624]--[1.0427]	0.1509
Hypertension, (Base "No")	0.9929	[0.9019]--[1.0932]	0.8848
Heart failure, (base "No")	1.2675	[0.8974]--[1.7904]	0.1785
Diabetes, (base "No")	1.1849	[0.9263]--[1.5157]	0.1769
Alcohol CAGE score, (base 0)			
1	0.9602	[0.8805]--[1.0471]	0.358
2	0.8996	[0.8143]--[0.9939]	0.0375
3	0.9139	[0.8001]--[1.0440]	0.1851
4	1.3139	[0.8791]--[1.9636]	0.183
Smoking status, (base "Never smoked")			
Past smoker	0.9799	[0.9135]--[1.0512]	0.5714
Current smoker	1.0857	[0.9914]--[1.1889]	0.076
Anticholinesterase or Anticholinergic	1.1697	[0.9239]--[1.4809]	0.1929
Antihypertensive medications	1.033	[0.9332]--[1.1436]	0.5309
Antipsychotic medications	1.0533	[0.8164]--[1.3590]	0.6896
Antidepressant medications	0.9876	[0.8621]--[1.1314]	0.8572
Diabetic medications	1.0375	[0.7855]--[1.3704]	0.7952
Depression	1.0319	[0.9276]--[1.1480]	0.5633
Pulse pressure, mmHg	1.0005	[0.9964]--[1.0047]	0.8025
Systolic BP, mmHg	0.9998	[0.9967]--[1.0029]	0.9134
Wave#OH110	1.2541	[1.0012]--[1.5709]	0.0488
Wave# age	1.0029	[0.9941]--[1.0117]	0.5263
Wave# Sex	0.9379	[0.8683]--[1.0131]	0.1034
Wave# Education, base primary/none			
Secondary	0.9365	[0.8417]--[1.0419]	0.2279
Third/higher	0.991	[0.8868]--[1.1075]	0.8738
Wave# No. CVD conditions, (base 0)			
1	1.0097	[0.8908]--[1.1445]	0.8798
≥2	1.1135	[0.9186]--[1.3499]	0.2735
Wave# Hypertension	1.0228	[0.9189]--[1.1384]	0.6801
Wave# heart failure	0.5102	[0.3068]--[0.8485]	0.0095
Wave# Diabetes	0.9014	[0.6419]--[1.2658]	0.5489
Wave# CAGE score, base 0			

1	0.9623	[0.8562]--[1.0816]	0.5195
2	1.0134	[0.8904]--[1.1533]	0.8405
3	0.9773	[0.8157]--[1.1710]	0.8033
4	0.5434	[0.2896]--[1.0199]	0.0576
Wave# Smoking status, base never			
Past	1.0273	[0.9497]--[1.1112]	0.502
Current	1.0138	[0.9016]--[1.1399]	0.8194
Wave# Anticholinesterase/Anticholinergic medication	0.9655	[0.7345]--[1.2691]	0.8011
Wave# Antihypertensive medication	0.9406	[0.8208]--[1.0780]	0.3786
Wave# Anti-psychotic medication	1.1656	[0.8458]--[1.6062]	0.3491
Wave# Anti-depressant	1.2207	[1.0429]--[1.4287]	0.013
Wave# Diabetic medication	1.1339	[0.7764]--[1.6561]	0.5155
Wave# Depression	0.9958	[0.8561]--[1.1584]	0.9566
Wave# Pulse Pressure	0.9957	[0.9897]--[1.0018]	0.1678
Wave# Mean SBP	1.0013	[0.9971]--[1.0056]	0.5384
Frailty, base not frail			
Pre-frail	1.0513	[0.9825]--[1.1250]	0.1473
Frail	1.4186	[0.9404]--[2.1400]	0.0956
Height, sm	0.995	[0.9904]--[0.9996]	0.032
Baseline HR, bpm	0.9999	[0.9970]--[1.0028]	0.9303

IRR – Incidence rate ratio; OH110 – Orthostatic hypotension sustained to 110 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S5. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH40 for Age group ≥65.

Total Errors	IRR	95% CI	P- value
Wave	0.72	[0.3088]--[1.6788]	0.4469
OH40, (base 0)	1.012	[0.9146]--[1.1198]	0.8178
Age	1.0092	[1.0014]--[1.0171]	0.021
Sex	0.8872	[0.7983]--[0.9860]	0.0263
Education, (base "Primary/none")			
Secondary	0.8808	[0.8039]--[0.9651]	0.0065
Third level/higher	0.7326	[0.6665]--[0.8052]	<0.0001
No. Cardiovascular conditions, (base "0")			
1	1.0263	[0.9205]--[1.1442]	0.6405
2	1.0307	[0.8857]--[1.1994]	0.6961
Hypertension, (Base "No")	0.9829	[0.8854]--[1.0912]	0.7465
Heart failure, (base "No")	0.9763	[0.6710]--[1.4206]	0.9002
Diabetes, (base "No")	1.0359	[0.8238]--[1.3027]	0.7626
Alcohol CAGE score, (base 0)			
1	0.8781	[0.7689]--[1.0028]	0.0549
2	0.9131	[0.7701]--[1.0828]	0.2961
3	0.9969	[0.8069]--[1.2315]	0.9767
4	1.0424	[0.7436]--[1.4613]	0.8097
Smoking status, (base "Never smoked")			
Past smoker	0.9727	[0.8970]--[1.0548]	0.5031
Current smoker	1.1163	[0.9717]--[1.2824]	0.1202
Anticholinesterase or Anticholinergic	1.1725	[0.9997]--[1.3752]	0.0505
Antihypertensive medications	1.0025	[0.9018]--[1.1145]	0.9625
Antipsychotic medications	0.6929	[0.3782]--[1.2692]	0.2348
Antidepressant medications	1.0681	[0.8982]--[1.2701]	0.4563
Diabetic medications	0.9671	[0.7434]--[1.2583]	0.8035
Depression	1.0526	[0.9089]--[1.2190]	0.4937
Pulse pressure, mmHg	1.0002	[0.9955]--[1.0049]	0.9389
Systolic BP, mmHg	1.0001	[0.9962]--[1.0039]	0.9663
Wave#OH40	1.0497	[0.9232]--[1.1935]	0.4593
Wave# age	1.0075	[0.9976]--[1.0174]	0.1373
Wave# Sex	1.0359	[0.9359]--[1.1466]	0.496
Wave# Education, base primary/none			
Secondary	0.9927	[0.8847]--[1.1139]	0.9008
Third/higher	0.952	[0.8457]--[1.0715]	0.4147
Wave# No. CVD conditions, (base 0)			
1	0.928	[0.7821]--[1.1011]	0.392
≥2	0.9181	[0.7397]--[1.1394]	0.4379
Wave# Hypertension	1.0967	[0.9683]--[1.2422]	0.1464
Wave# heart failure	1.0682	[0.5719]--[1.9952]	0.836
Wave# Diabetes	1.0403	[0.7469]--[1.4489]	0.8152
Wave# CAGE score, base 0			

1	0.9363	[0.7836]--[1.1187]	0.4688
2	0.8692	[0.6866]--[1.1004]	0.2441
3	0.9162	[0.6799]--[1.2346]	0.5652
4	1.3827	[0.4941]--[3.8695]	0.5372
Wave# Smoking status, base never			
Past	1.0226	[0.9249]--[1.1305]	0.6628
Current	0.9643	[0.7845]--[1.1852]	0.7296
Wave# Anticholinesterase/Anticholinergic medication	0.9752	[0.7905]--[1.2030]	0.8144
Wave# Antihypertensive medication	1.0276	[0.8700]--[1.2139]	0.7483
Wave# Anti-psychotic medication	1.5783	[0.7966]--[3.1272]	0.1908
Wave# Anti-depressant	1.0672	[0.8501]--[1.3399]	0.5751
Wave# Diabetic medication	0.9847	[0.6828]--[1.4202]	0.9343
Wave# Depression	0.9976	[0.7957]--[1.2507]	0.9831
Wave# Pulse Pressure	1.0015	[0.9945]--[1.0086]	0.6758
Wave# Mean SBP	0.9973	[0.9921]--[1.0026]	0.325
Frailty, base not frail			
Pre-frail	1.1242	[1.0467]--[1.2075]	0.0013
Frail	0.9269	[0.6678]--[1.2866]	0.6501
Height, sm	0.9969	[0.9917]--[1.0020]	0.2321
Baseline HR, bpm	1.0004	[0.9972]--[1.0037]	0.8069

IRR – Incidence rate ratio; OH40 – Orthostatic hypotension sustained to 40 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S6. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH110 for Age group ≥65.

Total Errors	IRR	95% CI	P- value
Wave	0.6911	[0.3001]--[1.5919]	0.3855
OH110, (base 0)	0.9747	[0.8468]--[1.1220]	0.7214
Age	1.0094	[1.0017]--[1.0172]	0.0167
Sex	0.8897	[0.8005]--[0.9888]	0.0301
Education, (base "Primary/none")			
Secondary	0.8806	[0.8037]--[0.9650]	0.0064
Third level/higher	0.7314	[0.6653]--[0.8041]	<0.0001
No. Cardiovascular conditions, (base "0")			
1	1.0276	[0.9216]--[1.1457]	0.6241
2	1.0328	[0.8875]--[1.2018]	0.6768
Hypertension, (Base "No")	0.983	[0.8855]--[1.0914]	0.7485
Heart failure, (base "No")	0.9714	[0.6674]--[1.4140]	0.8796
Diabetes, (base "No")	1.0311	[0.8202]--[1.2961]	0.7931
Alcohol CAGE score, (base 0)			
1	0.8784	[0.7691]--[1.0031]	0.0556
2	0.9112	[0.7685]--[1.0804]	0.2846
3	0.9989	[0.8084]--[1.2342]	0.9916
4	1.0474	[0.7471]--[1.4684]	0.7884
Smoking status, (base "Never smoked")			
Past smoker	0.9729	[0.8972]--[1.0550]	0.5064
Current smoker	1.1208	[0.9767]--[1.2860]	0.1042
Anticholinesterase or Anticholinergic	1.1749	[1.0020]--[1.3777]	0.0472
Antihypertensive medications	1.0036	[0.9027]--[1.1157]	0.9477
Antipsychotic medications	0.6917	[0.3775]--[1.2673]	0.2328
Antidepressant medications	1.0699	[0.8997]--[1.2723]	0.4447
Diabetic medications	0.9743	[0.7487]--[1.2678]	0.8464
Depression	1.0495	[0.9059]--[1.2159]	0.52
Pulse pressure, mmHg	1.0001	[0.9954]--[1.0049]	0.9613
Systolic BP, mmHg	1.0002	[0.9964]--[1.0040]	0.9267
Wave#OH110	1.085	[0.9075]--[1.2971]	0.3707
Wave# age	1.008	[0.9983]--[1.0178]	0.1047
Wave# Sex	1.0353	[0.9352]--[1.1460]	0.5039
Wave# Education, base primary/none			
Secondary	0.9932	[0.8852]--[1.1144]	0.9077
Third/higher	0.9543	[0.8477]--[1.0743]	0.4388
Wave# No. CVD conditions, (base 0)			
1	0.9291	[0.7830]--[1.1023]	0.3989
≥2	0.9207	[0.7421]--[1.1424]	0.4529
Wave# Hypertension	1.0989	[0.9703]--[1.2445]	0.1376
Wave# heart failure	1.087	[0.5820]--[2.0305]	0.7935
Wave# Diabetes	1.0419	[0.7482]--[1.4508]	0.8081
Wave# CAGE score, base 0			

1	0.937	[0.7842]--[1.1196]	0.4737
2	0.8677	[0.6856]--[1.0983]	0.238
3	0.9179	[0.6811]--[1.2370]	0.5735
4	1.3721	[0.4903]--[3.8399]	0.5468
Wave# Smoking status, base never			
Past	1.0244	[0.9267]--[1.1325]	0.6373
Current	0.9608	[0.7818]--[1.1808]	0.704
Wave# Anticholinesterase/Anticholinergic medication	0.9766	[0.7917]--[1.2045]	0.8246
Wave# Antihypertensive medication	1.0236	[0.8666]--[1.2089]	0.7839
Wave# Anti-psychotic medication	1.5747	[0.7946]--[3.1207]	0.1932
Wave# Anti-depressant	1.0733	[0.8551]--[1.3471]	0.5418
Wave# Diabetic medication	0.9796	[0.6792]--[1.4129]	0.9121
Wave# Depression	0.9988	[0.7964]--[1.2526]	0.9917
Wave# Pulse Pressure	1.0016	[0.9946]--[1.0087]	0.6518
Wave# Mean SBP	0.9973	[0.9920]--[1.0026]	0.3104
Frailty, base not frail			
Pre-frail	1.1248	[1.0472]--[1.2081]	0.0013
Frail	0.9213	[0.6635]--[1.2793]	0.6247
Height, sm	0.997	[0.9918]--[1.0021]	0.2465
Baseline HR, bpm	1.0003	[0.9971]--[1.0036]	0.8449

IRR – Incidence rate ratio; OH110 – Orthostatic hypotension sustained to 110 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S7. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH40, stratified by the presence of baseline supine HTN for full cohort.

Total Errors	IRR	95% CI	P- value
Wave	0.4888	[0.3317]--[0.7205]	0.0003
OH40#HTN, (base No HTN, No OH40)			
No OH40, HTN	0.9896	[0.9204]--[1.0640]	0.7772
OH40, No HTN	0.9941	[0.8690]--[1.1372]	0.9315
OH40 and HTN	0.9751	[0.8647]--[1.0995]	0.6802
Age	1.0098	[1.0063]--[1.0133]	<0.0001
Sex	0.9179	[0.8562]--[0.9840]	0.0158
Education, (base “Primary/none”)			
Secondary	0.8583	[0.8036]--[0.9168]	<0.0001
Third level/higher	0.6675	[0.6231]--[0.7151]	<0.0001
No. Cardiovascular conditions, (base “0”)			
1	1.0517	[0.9790]--[1.1298]	0.1681
2	0.9705	[0.8701]--[1.0824]	0.5903
Heart failure, (base “No”)	1.1415	[0.8886]--[1.4663]	0.3004
Diabetes, (base “No”)	1.1167	[0.9418]--[1.3242]	0.2041
Alcohol CAGE score, (base 0)			
1	0.9351	[0.8701]--[1.0049]	0.0676
2	0.8887	[0.8164]--[0.9674]	0.0064
3	0.9273	[0.8294]--[1.0367]	0.1846
4	1.1428	[0.8810]--[1.4824]	0.3146
Smoking status, (base “Never smoked”)			
Past smoker	0.9819	[0.9310]--[1.0356]	0.5016
Current smoker	1.1049	[1.0252]--[1.1907]	0.009
Anticholinesterase or Anticholinergic	1.1845	[1.0351]--[1.3554]	0.0138
Antihypertensive medications	1.0163	[0.9440]--[1.0942]	0.6679
Antipsychotic medications	0.9785	[0.7793]--[1.2285]	0.8512
Antidepressant medications	1.0277	[0.9239]--[1.1432]	0.6146
Diabetic medications	1.0118	[0.8341]--[1.2274]	0.905
Depression	1.0351	[0.9500]--[1.1277]	0.4307
Pulse pressure, mmHg	1.0004	[0.9973]--[1.0035]	0.8138
Systolic BP, mmHg	1	[0.9976]--[1.0024]	0.9747
Wave#OH40#HTN, (base no OH40, no HTN)			
No OH40, HTN	1.0302	[0.9489]--[1.1184]	0.478
OH40, No HTN	1.0025	[0.8545]--[1.1761]	0.976
OH40 and HTN	1.1821	[1.0310]--[1.3553]	0.0165
Wave# age	1.0105	[1.0063]--[1.0148]	<0.0001
Wave# Sex	0.9771	[0.9194]--[1.0384]	0.4556
Wave# Education, base primary/none			
Secondary	0.9644	[0.8934]--[1.0411]	0.3532
Third/higher	0.9829	[0.9077]--[1.0643]	0.6702
Wave# No. CVD conditions, (base 0)			
1	0.984	[0.8905]--[1.0874]	0.7521

≥2	1.0238	[0.8904]--[1.1772]	0.7412
Wave# heart failure	0.6684	[0.4514]--[0.9897]	0.0443
Wave# Diabetes	0.961	[0.7569]--[1.2203]	0.7443
Wave# CAGE score, base 0			
1	0.9484	[0.8608]--[1.0450]	0.2847
2	0.9946	[0.8887]--[1.1132]	0.9256
3	0.9605	[0.8241]--[1.1196]	0.6066
4	0.7204	[0.4315]--[1.2027]	0.2098
Wave# Smoking status, base never			
Past	1.0231	[0.9624]--[1.0877]	0.4643
Current	0.9906	[0.8957]--[1.0955]	0.8541
Wave# Anticholinesterase/Anticholinergic medication	0.963	[0.8158]--[1.1366]	0.6555
Wave# Antihypertensive medication	0.9794	[0.8824]--[1.0870]	0.6951
Wave# Anti-psychotic medication	1.2161	[0.9179]--[1.6112]	0.1729
Wave# Anti-depressant	1.1416	[1.0038]--[1.2984]	0.0436
Wave# Diabetic medication	1.0398	[0.7984]--[1.3541]	0.7724
Wave# Depression	1.0114	[0.8929]--[1.1456]	0.8584
Wave# Pulse Pressure	0.9974	[0.9929]--[1.0020]	0.2719
Wave# Mean SBP	1.0003	[0.9970]--[1.0036]	0.8724
Frailty, base not frail			
Pre-frail	1.0763	[1.0239]--[1.1315]	0.0039
Frail	1.1115	[0.8528]--[1.4487]	0.4341
Height, sm	0.9956	[0.9921]--[0.9991]	0.013
Baseline HR, bpm	1.0002	[0.9980]--[1.0025]	0.8276

IRR – Incidence rate ratio; OH40 – Orthostatic hypotension sustained to 40 seconds post stand; HTN – Supine hypertension; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S8. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH110, stratified by the presence of baseline supine HTN for full cohort.

Total Errors	IRR	95% CI	P- value
Wave	0.4831	[0.3283]--[0.7110]	0.0002
OH110#HTN, (base No HTN, No OH110)			
No OH110, HTN	0.9861	[0.9179]--[1.0593]	0.701
OH110, No HTN	0.9115	[0.7453]--[1.1147]	0.3668
OH110 and HTN	0.9525	[0.8096]--[1.1206]	0.5569
Age	1.0098	[1.0064]--[1.0132]	<0.0001
Sex	0.9197	[0.8579]--[0.9860]	0.0184
Education, (base “Primary/none”)			
Secondary	0.8588	[0.8040]--[0.9173]	<0.0001
Third level/higher	0.6676	[0.6231]--[0.7152]	<0.0001
No. Cardiovascular conditions, (base “0”)			
1	1.0511	[0.9784]--[1.1291]	0.1728
2	0.9705	[0.8701]--[1.0824]	0.5907
Heart failure, (base “No”)	1.1407	[0.8880]--[1.4653]	0.3027
Diabetes, (base “No”)	1.1176	[0.9425]--[1.3252]	0.2011
Alcohol CAGE score, (base 0)			
1	0.9357	[0.8706]--[1.0055]	0.0703
2	0.8887	[0.8164]--[0.9674]	0.0064
3	0.9291	[0.8311]--[1.0388]	0.1967
4	1.1483	[0.8853]--[1.4895]	0.2973
Smoking status, (base “Never smoked”)			
Past smoker	0.9818	[0.9309]--[1.0355]	0.4985
Current smoker	1.1049	[1.0252]--[1.1907]	0.009
Anticholinesterase or Anticholinergic	1.1873	[1.0376]--[1.3586]	0.0126
Antihypertensive medications	1.0181	[0.9456]--[1.0961]	0.6338
Antipsychotic medications	0.9744	[0.7760]--[1.2236]	0.8236
Antidepressant medications	1.027	[0.9235]--[1.1422]	0.6229
Diabetic medications	1.0124	[0.8345]--[1.2281]	0.9008
Depression	1.0326	[0.9477]--[1.1251]	0.464
Pulse pressure, mmHg	1.0003	[0.9972]--[1.0035]	0.8253
Systolic BP, mmHg	1	[0.9976]--[1.0024]	0.9991
Wave#OH40#HTN, (base no OH110, no HTN)			
No OH110, HTN	1.0382	[0.9572]--[1.1259]	0.3658
OH110, No HTN	1.067	[0.8407]--[1.3542]	0.5939
OH110 and HTN	1.2731	[1.0583]--[1.5317]	0.0105
Wave# age	1.0107	[1.0065]--[1.0149]	<0.0001
Wave# Sex	0.9762	[0.9185]--[1.0376]	0.4394
Wave# Education, base primary/none			
Secondary	0.9654	[0.8942]--[1.0422]	0.3674
Third/higher	0.9853	[0.9099]--[1.0670]	0.7151
Wave# No. CVD conditions, (base 0)			

1	0.9864	[0.8926]--[1.0899]	0.7876
≥2	1.0269	[0.8931]--[1.1807]	0.7093
Wave# heart failure	0.6762	[0.4567]--[1.0011]	0.0506
Wave# Diabetes	0.9596	[0.7558]--[1.2185]	0.7353
Wave# CAGE score, base 0			
1	0.9481	[0.8605]--[1.0447]	0.282
2	0.9936	[0.8878]--[1.1121]	0.9116
3	0.9601	[0.8237]--[1.1190]	0.6023
4	0.7155	[0.4286]--[1.1945]	0.2004
Wave# Smoking status, base never			
Past	1.0245	[0.9637]--[1.0892]	0.4378
Current	0.9889	[0.8941]--[1.0936]	0.8274
Wave# Anticholinesterase/Anticholinergic medication	0.9648	[0.8174]--[1.1388]	0.6717
Wave# Antihypertensive medication	0.9757	[0.8791]--[1.0829]	0.6435
Wave# Anti-psychotic medication	1.218	[0.9191]--[1.6140]	0.1699
Wave# Anti-depressant	1.1496	[1.0111]--[1.3070]	0.0333
Wave# Diabetic medication	1.0404	[0.7989]--[1.3549]	0.7689
Wave# Depression	1.0127	[0.8941]--[1.1472]	0.8421
Wave# Pulse Pressure	0.9976	[0.9931]--[1.0022]	0.3121
Wave# Mean SBP	1.0002	[0.9969]--[1.0035]	0.9256
Frailty, base not frail			
Pre-frail	1.0769	[1.0244]--[1.1321]	0.0037
Frail	1.1068	[0.8491]--[1.4425]	0.453
Height, sm	0.9956	[0.9921]--[0.9991]	0.013
Baseline HR, bpm	1.0002	[0.9980]--[1.0024]	0.8345

IRR – Incidence rate ratio; OH110 – Orthostatic hypotension sustained to 110 seconds post stand; HTN – Supine hypertension; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.