RESEARCH ARTICLE

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Sub-clinical orthostatic hypotension is associated with greater subjective memory impairment in older adults

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Introduction: Orthostatic blood pressure (BP) is a measure of cardiovascular autonomic function. Orthostatic BP dysregulation may lie on the causal pathway to dementia. Subjective memory impairment (SMI) is commonly reported by older people some of whom may progress to dementia. We hypothesised that sub-clinical orthostatic hypotension would be associated with SMI and explored these associations according to sex.

Methods: Cross-sectional analysis of data from 4340 participants aged 50 and over collected during the first wave (2009–2011) of the cohort study, The Irish Longitudinal Study on Ageing. Subjective memory was rated according to a 5-point scale ranging from 'poor' to 'excellent'. BP was measured during orthostatic stress using continuous non-invasive beat-to-beat recording over 2 min.

Results: 2% reported 'poor' subjective memory, 12.3% 'fair' , 38% 'good', 33% 'very good' and 14.6% 'excellent'. After controlling for several potential confounding factors including cardiovascular risk, objective cognition, and depressive symptoms mean systolic orthostatic BP was lowest in those with poor subjective memory: 92.2 mmHg (CI95% = 87.1, 97.3) versus excellent 99.3 mmHg (CI95% = 97.4, 101.2); $p = 0.011$. Further adjustment for supine systolic BP suggested that men with poor subjective memory reached the lowest average systolic orthostatic BP and had the greatest impairment in systolic orthostatic BP stabilisation to baseline levels at 10 s post-stand (−6.64 mmHg; CI95% = −11.49, −1.79; $p = 0.007$).

Conclusions: Sub-clinical orthostatic hypotension is associated with SMI, and there are sex-specific relationships evident in this population-based cohort. Subtle cardiovascular autonomic dysfunction may represent a modifiable risk marker at an early stage of cognitive decline in older adults.

Key words: orthostatic hypotension; subjective memory; autonomic function
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Introduction

Despite controversy stemming from conflicting associations with objective cognitive deficits, and overlaps with psychiatric disorder, subjective memory impairment (SMI) remains one of the sole means by which the earliest stages of cognitive decline may be identified (Stewart, 2012). SMI in the absence of objective cognitive dysfunction in older adults has been conceptualised as a potential 'pre-clinical' phase of dementia (Jessen *et al.*, 2014). Multiple longitudinal studies have confirmed that SMI, even in the absence of baseline deficits on cognitive testing, is associated with an increased risk of future dementia (Knopman, 2012; Rönnlund *et al.*, 2015). The reasons for this are poorly understood.

Orthostasis invokes a re-balance of the sympathetic and parasympathetic output from the Central Nervous System. Measurement of orthostatic BP (OBP) assesses cardiovascular autonomic balance on a peripheral basis (Wieling *et al.*, 2007). Orthostatic hypotension (OH) is the clinical syndrome defined as a drop in systolic BP

of >=20 mmHg and/or diastolic BP of >=10 mmHg drop within 3 min of standing and in the clinical setting is most often measured using an oscillometric sphygmomanometer (Freeman *et al.*, 2011).

SMI and OH become increasingly common with ageing (Finucane *et al.*, 2014; Stewart, 2012), and both have been linked to sub-clinical vascular risk factors for dementia including reductions in cerebral blood flow and higher levels of white matter hyperintensities on neuroimaging (Ainslie, 2012; Colloby *et al.*, 2011; Hohman *et al.*, 2011; de Groot, 2001). Both OH and SMI have been associated with ischemic heart disease and stroke (Ricci *et al.*, 2015; Sajjad *et al.*, 2015).

Cross-sectional studies have reported a higher prevalence of OH in dementia syndromes (Freidenberg *et al.*, 2013; Passant *et al.*, 1996). It has been postulated that OH may be on the causal pathway to dementia either as a peripheral marker of central autonomic dysfunction or via repeated episodes of cerebral hypoperfusion during orthostatic stress (Yap *et al.*, 2008). Our group, among others, has described associations between deficits on formal cognitive testing and OH in an epidemiological setting (Frewen *et al.*, 2014; Frewen *et al.*, 2013; Rose *et al.*, 2010); however, neither SMI nor sub-clinical OH was explored until recently. Elmståhl and Widerström reported an association between baseline OH and SMI six years later (Elmståhl and Widerström, 2014). Although this relationship did not survive correction for age, they did describe prospective associations between orthostatic intolerance (defined as symptoms of cerebral hypoperfusion on standing) and both SMI and mild cognitive impairment. Orthostatic intolerance may have arisen from baseline sub-clinical OBP drops that the authors suggest were not detectable by traditional BP measurement using a sphygmomanometer.

Continuous beat-to-beat non-invasive OBP measurement is a novel addition to epidemiological studies of ageing and has been used to explore sub-clinical patterns of OBP dysregulation (Romero-Ortuno *et al.*, 2011). Investigation of OH at arbitrary cut-offs may miss important information on sub-clinical OH and thus the earliest stages of autonomic dysfunction. It has been hypothesised that subtle cardiovascular autonomic dysfunction may occur early on the continuum towards dementia as brain areas involved in central cardiovascular autonomic control may be among those first affected by neurodegeneration (Royall *et al.*, 2006). If OBP dysregulation is on the causal pathway to dementia, then sub-clinical OH may accompany the earliest phases of cognitive decline such as SMI.

No study has previously investigated the impact of continuous measures of OBP on SMI. We hypothesised that sub-clinical OBP dysregulation measured using continuous beat-to-beat measurements and reflecting early cardiovascular autonomic dysfunction would be more common in those with SMI, potentially a preclinical phase of dementia. Given prior findings of differing patterns of OBP regulation and implications of SMI in men and women (Romero-Ortuno *et al.*, 2010; Tomita *et al.*, 2014), we secondly hypothesised that these relationships may differ between men and women.

Materials and methods

Sample

This study uses data collected during the first wave (2009–2011) of The Irish Longitudinal Study on Ageing (TILDA) that includes 8175 participants. The sampling procedure produced a representative sample of the community-dwelling Irish population aged 50 and over in Ireland. The household response rate was 62.0%. Data collection included a face-to-face in-home computer-assisted structured interview that was used to capture health related, social and demographic information. Each participant was also invited to attend a detailed physical health assessment. Further details of the sampling procedure, in-home interview and health assessment, are available elsewhere(Kearney *et al.*, 2011).

Ethics

Trinity College Dublin Health Research Ethics Committee granted Ethical Approval for the study. Each participant provided written informed consent prior to enrolment in the study. Those unable to give informed consent were excluded.

Measures

Subjective memory impairment. Subjective memory was assessed using the question: 'How would you rate your day-to-day memory at the present time?'. Participants were invited to respond according to the options 'poor, 'fair', 'good', 'very good' and 'excellent'. This measure was used in the Health and Retirement Study and The Aging, Demographics, and Memory Study sub-study (Langa *et al.*, 2005; Plassman *et al.*, 2008). We investigated 'impairment' in subjective

memory by comparing those who reported their memory as very good *or* good *or* fair *or* poor to those who reported excellent subjective memory.

Orthostatic challenge. Each participant performed a supervised lying-to-standing test ('Active Stand'), while BP was recorded peripherally using a beat-to-beat plethysomnography device (Finometer® MIDI device, Finapres Medical Systems BV, Amsterdam, The Netherlands, www.finapres.com). Participants lay quietly for 10 min to capture a stable resting supine measurement of BP. Participants then stood as quickly as possible (receiving assistance as necessary), while BP monitoring continued for 2 min. Further details of the processing and extraction of BP readings (at 10-s intervals) are available elsewhere (Finucane *et al.*, 2014). Participants were asked to report symptoms of dizziness, presyncope or light-headedness after standing coded as 'Orthostatic Intolerance' (Yes/No).

Orthostatic BP variables of interest. 'Nadir' was used to denote the lowest BP recorded at any point during the 120 s of recording. Subsequent analysis focused on *10–30 s* after standing as this is the period of maximum OBP change (Finucane *et al.*, 2014). We also assessed relative OBP 'stabilisation' during this period by accounting for differences in supine BP.

Other measures. Objective cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), which is an interviewer-administered paper and pencil test (Nasreddine *et al.*, 2005) with scores ranging from 0 to 30. Higher scores indicate better cognitive function; a cut-off of $>=26$ has been proposed for detection of mild cognitive impairment (Nasreddine *et al.*, 2005).

Depressive symptoms over the previous week were recorded using The Center for Epidemiological Studies Depression Scale (Sawyer Radloff and Teri, 1986), and a cut point of ≥ 16 was used to identify clinically significant depressive symptoms (Beekman *et al.*, 1997).

Self-reported doctor-diagnosed conditions (diabetes, lung disease, asthma, arthritis, osteoporosis, cancer, peptic ulcer and hip fracture) were summed to give an indication of chronic co-morbidities. Cardiovascular/cerebrovascular conditions were also summed to include a history of transient ischemic attack, stroke, high cholesterol, heart failure, heart 'murmur', cardiac arrhythmia and myocardial infarction. Smoking history was coded as 'current', 'past' or 'never'.

Antidepressant use was identified using the first four digits of the World Health Organization's Anatomical Therapeutic Chemical code ('N06A'). Antihypertensives were identified using the codes 'C02*' (anti-adrenergic agents) 'C03*' (diuretics), 'C07*' (beta-blockers), 'C08*'(calcium-channel blockers), 'C09*' (angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers) and combinations of the above (C02*). Binary variables (no/yes) were coded to indicate antihypertensive and antidepressant use.

Statistical analysis

Statistical analysis was conducted using Stata v12 (StataCorp LP, Texas, USA). The sample was described by subjective memory category according to demographic and health-related characteristics. ANOVA was used to test for linear trends according to categories of subjective memory in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the Nadir and at time points of interest. Linear regression analysis was used to estimate differences in SBP and DBP between subjective memory categories adjusting for covariates. Separate models were fit for each outcome variable (SBP or DBP) at the Nadir and at 10–30 s post-stand. Initial models (adjusting for age, age squared and sex—'Model 1') regressed mean SBP or DBP at the Nadir and at 10–30 s post-stand against subjective memory. Further multivariate analysis then adjusted for potential confounders: Model 2 = Model 1 + education, body mass index (BMI), depressive symptoms, objective cognitive deficits (MoCA), physical co-morbidities (chronic conditions and cardiovascular disease), medications (antidepressants and antihypertensives) and a history of smoking. In sensitivity analysis these models were re-estimated excluding those with low scores on the MoCA (i.e. <26; Nasreddine *et al.*, 2005).

To assess hemodynamic stabilisation after orthostasis, models were further adjusted for the appropriate supine BP measure (Model 3 = Model 2 + supine BP). If significant relationships with subjective memory remained after adjustment for supine BP, the associations according to sex were also estimated using a regression model now including the interaction terms between subjective memory and sex. Where significant interactions occurred subsequent analyses were stratified by sex.

Adjusted marginal means with 95% confidence intervals for the SBP and DBP variables for each level of subjective memory at the Nadir and each time point across 120 s were estimated (i.e. the values of these variables holding all other variables in the models constant) and plotted to improve interpretation of

patterns of OBP across all time points collected after standing.

Results

Five thousand thirty-five participants attended a health assessment and 4475 had usable continuous beat-to-beat OBP measurements. Participants missing data on any variable of interest were excluded (as were those with a history of Parkinson's disease ($n = 57$)) giving a final analytical sample of 4340. Descriptive statistics are shown in Table 1. Sensitivity analysis (results available upon request) using logistic regression suggested that those included in the final sample relative to the TILDA cohort as a whole were younger, more likely to be women, have better cognition and have less co-morbidity.

Mean unadjusted SBP and DBP during orthostasis varied according to the category of subjective memory (Table 2). Those with poor subjective memory reached the lowest Nadir post-stand compared with those in higher categories.

After minimal adjustment (Model 1) significant differences in SBP during orthostasis were evident among categories of subjective memory; predicted changes in SBP during orthostasis according to subjective memory are displayed in Figure 1.

Table 1 Descriptive statistics by subjective memory

	Total sample $n = 4340$	Excellent 635 (14.6)	Very Good 1431 (33.0)	Good 1651 (38.0)	Fair 535 (12.3)	Poor 88 (2.0)	*p*
Demographic characteristics							
Age (mean (SD))	61.5 (8.3)	59.6 (7.5)	61.0 (8.0)	62.2 (8.5)	63.1 (8.3)	62.5 (9.3)	<0.001
Body mass index (kg/m^2), mean SD	28.5 (4.8)	28.8 (4.9)	28.5 (4.9)	28.4 (4.7)	28.4 (5.0)	29.4 (5.8)	0.14
Education *n* (% primary only)	913 (21.0)	72 (11.3)	232 (16.2)	402 (24.4)	170 (31.8)	37 (42.1)	<0.001
Gender *n* (% female)	2334 (53.8)	325 (51.2)	770 (53.8)	922 (55.8)	281 (52.5)	36 (40.9)	0.029
Orthostatic intolerance *n* (%)	1661 (38.3)	191 (30.1)	535 (37.4)	649 (39.3)	239 (44.7)	47 (53.4)	<0.001
Mental health and cognition							
Depressive symptoms (median (IQR))	3 (7)	2 (5)	3 (6)	4 (7)	5 (10)	8 (13.5)	<0.001
Antidepressants treatment *n* (%)	254 (5.9)	22 (3.5)	55 (3.8)	94 (5.7)	63 (11.8)	20 (22.7)	<0.001
MoCA (median (IQR))	26 (4)	26 (4)	26 (4)	26 (5)	25 (4)	23 (6)	<0.001
Physical co-morbidity and cardiovascular risk							
Chronic conditions *n* (% ≥1)	2203 (50.8)	268 (42.2)	681 (47.6)	877 (53.1)	315 (58.9)	62 (70.5)	<0.001
Current smoker *n* (%)	641 (14.8)	82 (12.9)	197 (13.8)	248 (15.0)	96 (18.0)	18 (20.5)	<0.001
Antihypertensive treatment *n* (%)	1414 (32.6)	162 (25.5)	447 (31.2)	564 (34.2)	202 (37.8)	39 (44.3)	<0.001
CVD conditions *n* (% ≥1)	496 (11.4)	281 (44.3)	642 (44.9)	821 (49.7)	301 (56.3)	49 (55.7)	<0.001

P vales are from ANOVA for normally distributed continuous variables, Kruskal–Wallis for non-normal and chi squared for categorical variables; SD, standard deviation; IQR, intraquartile range; MoCA, Montreal Cognitive Assessment; CVD, cardiovascular disease.

Table 2 Orthostatic blood pressure by subjective memory (*unadjusted*)

	Excellent	Very good	Good	Fair	Poor	*p*
$n = 4340$	635 (14.6)	1431 (33.0)	1651 (38.0)	535 (12.3)	88 (2.0)	
Systolic BP mean mmHg (*SD*)						
Supine	137.1 (20.9)	136.5 (21.9)	135.7 (22.7)	136 (22.9)	136 (22.3)	0.73
Nadir	98.6 (23.4)	97.4 (23.2)	96.8 (24.7)	95.3 (25.5)	93 (26.1)	0.080
10 s	110.3 (24)	108.7 (24)	107.9 (25.3)	106.9 (25.8)	104.9 (28.2)	0.092
20 s	134.6 (24.9)	132.6 (24.8)	131 (26.7)	128.8 (28.1)	128.8 (30)	0.001
30 s	137.2 (24.4)	135.6 (23.7)	134.3 (25.6)	132.3 (26.3)	133.5 (26.7)	0.007
Diastolic BP mean mmHg (*SD*)						
Supine	74.5 (10.7)	73.5 (11)	72.8 (11.5)	72.9 (11.5)	73.4 (11.8)	0.015
Nadir	48.6 (13.3)	47.8 (13.4)	47.1 (13.8)	46.9 (14)	45.8 (14.3)	0.075
10 s	56 (13.6)	54.8 (13.8)	54.2 (14.1)	54 (14.1)	53.8 (15.1)	0.062
20 s	70.3 (14.1)	68.9 (13.9)	67.7 (14.6)	66.8 (15.2)	67.4 (15.3)	<0.001
30 s	74.1 (12.9)	72.7 (12.6)	71.6 (13.3)	70.8 (13.6)	71.7 (13.3)	<0.001

P vales are from ANOVA; 'BP', blood pressure; 'Nadir', lowest blood pressure recorded post-stand; 'mmHg', millimetres of mercury.

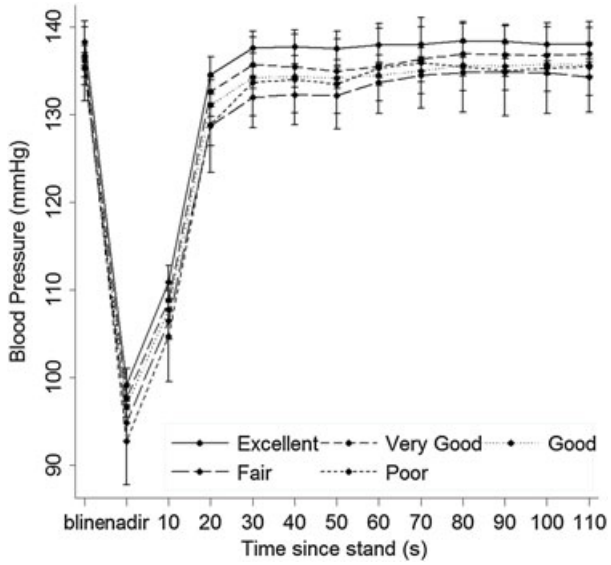

Figure 1 Systolic orthostatic blood pressure by subjective memory. Systolic blood pressure from supine to standing across subjective memory categories adjusted for age, age squared and sex; 'bline', baseline supine blood pressure; 'Nadir', lowest blood pressure recorded poststand; 's', seconds; 'mmHg', millimetre of mercury \r\n.

Even after full adjustment for confounders (Model 2) those with poorer subjective memory had the lowest SBP Nadir: lowest adjusted mean SBP post-orthostasis in those with 'poor' subjective memory was 92.2 mmHg (CI95% = 87.1, 97.3), while in those with excellent subjective memory it was 99.3 mmHg (CI95% = 97.4, 101.2); $p = 0.011$. These differences tended to occur along a linear gradient and persisted throughout the first 30 s. Sensitivity analysis excluding those with poorer scores (<26) on the MoCA demonstrated a similar linear pattern of orthostatic SBP responses across groups although the smaller sample size resulted in less certainty around the estimates (Table 3).

Significant differences in DBP were evident during orthostasis both after minimal adjustment and after full adjustment for confounders (not shown). In line with the changes observed in SBP, Nadir DBP was lowest in those with poor subjective memory (−3.28 mmHg; CI95% = −6.38, −0.18).

Investigation of SBP stabilisation after standing by adjustment for supine SBP in the models largely attenuated the differences across groups; however, those with poor subjective memory had the lowest Nadir SBP (−4.33 mmHg; CI 95% = −8.22, −0.45) and had a greater SBP deficit at 10 s post-stand (−4.00 mmHg; CI 95% = −7.82, −0.17) relative to those with excellent subjective memory. This association was modified by sex (interaction significant at the $p < 0.1$ level) such that it remained only among men. The analysis was subsequently stratified by sex. After accounting for supine SBP, on average men with poor subjective memory had a Nadir SBP that was −6.14 mmHg lower (CI95% = −10.96, −1.31; $p = 0.013$) than men with excellent subjective memory, and a prolonged time to SBP stabilisation at 10 s post-stand (−6.64 mmHg; CI95% = −11.49, −1.79; $p = 0.007$) (Figures 2a and 2b).

There were no differences in stabilisation of DBP among the categories of subjective memory after adjustment for baseline DBP. DBP stabilisation among the categories of subjective memory did not vary by sex.

Sensitivity analysis

Model 2 (Table S1) and Model 3 (Table S2) were re-estimated excluding those with diabetes (*model a*), existing cardiovascular disease (*model b*), clinically significant depressive symptoms (*model c*), those on antidepressant medications (*model d*) and finally excluding all of the above (*model e*). Any substantive conclusions regarding the pattern of associations remained unchanged.

Discussion

In this paper we present comprehensive data from a large community-dwelling population-based sample demonstrating an association between lower OBP and poorer subjective memory. This relationship tended to occur in a linear 'dose–response' pattern and persisted after making adjustments for age, sex, education, BMI, cardiovascular/cerebrovascular conditions, smoking, medications and importantly both depression and the MoCA, a clinically established objective measure of cognition sensitive to the presence of mild cognitive impairment—suggesting that neither depressive symptoms nor objective cognitive deficits alone explain this association (Nasreddine *et al.*, 2005). In keeping with prior studies investigating the effects of OBP on outcomes in older adults, the associations were stronger with SBP but nevertheless accompanied by consistent patterns in DBP (Romero-Ortuno *et al.*, 2011).

We hypothesised that subtle cardiovascular autonomic dysfunction may be present in SMI and thus reflected in sub-clinical OH. OBP is regulated by the autonomic nervous system, and accumulating evidence suggests that higher brain centres may be involved in cardiovascular autonomic regulation (Cheshire, 2014). These regions may be among the first to be affected in dementia associated neurodegeneration and thus account for the relationships shown here (Royall *et al.*, 2006). SMI, in the absence of objective cognitive deficits, is proposed as an early stage of

Table 3 Systolic orthostatic blood pressure by subjective memory (adjusted)

n = 4340	Excellent	Very good	*p*	Good	*p*	Fair	*p*	Poor	*p*
Model 1									
Supine BP	*Ref.*	−1.53 (−3.57,0.51)	0.141	−2.93 (−4.93, −0.93)	0.004	−3.04 (−5.56, −0.52)	0.018	−2.16 (−7.02,2.70)	0.384
Nadir	*Ref.*	−1.57 (−3.82,0.67)	0.170	−2.53 (−4.74, −0.32)	0.025	−4.35 (−7.13, −1.57)	0.002	−6.43 (−11.79, −1.07)	0.019
10 s	*Ref.*	−2.03 (−4.34,0.28)	0.085	−3.13 (−5.41, −0.86)	0.007	−4.42 (−7.28, −1.55)	0.002	−6.18 (−11.70, −0.66)	0.028
20 s	*Ref.*	−1.92 (−4.36,0.51)	0.122	−3.47 (−5.87, −1.08)	0.005	−5.84 (−8.86, −2.83)	<0.001	−5.68 (−11.49,0.14)	0.056
30 s	*Ref.*	−1.90 (−4.23,0.43)	0.110	−3.39 (−5.68, −1.10)	0.004	−5.61 (−8.49, −2.73)	<0.001	−3.92 (−9.48,1.63)	0.166
Model 2									
Supine BP	*Ref.*	−1.59 (−3.63,0.45)	0.126	−3.29 (−5.32, −1.27)	0.001	−3.79 (−6.37, −1.21)	0.004	−3.55 (−8.54,1.44)	0.163
Nadir	*Ref.*	−1.65 (−3.90,0.60)	0.150	−2.76 (−4.99, −0.52)	0.016	−4.69 (−7.54, −1.85)	0.001	−7.12 (−12.63, −1.61	0.011
10 s	*Ref.*	−2.04 (−4.35,0.27)	0.084	−3.31 (−5.60, −1.01)	0.005	−4.75 (−7.67, −1.83)	0.001	−6.96 (−12.62, −1.30)	0.016
20 s	*Ref.*	−1.57 (−3.99,0.84)	0.201	−2.94 (−5.34, −0.54)	0.016	−4.98 (−8.04, −1.92)	0.001	−4.51 (−10.43,1.41)	0.136
30 s	*Ref.*	−1.61 (−3.93,0.70)	0.173	−2.96 (−5.27, −0.66)	0.012	−4.90 (−7.83, −1.97)	0.001	−2.89 (−8.57,2.79)	0.318
Sensitivity Analysis: *Model 2 MoCA > =26 : n = 2320/4340*									
Supine BP	*Ref.*	−1.39 (−3.97,1.18)	0.290	−2.34(−4.95,0.27)	0.078	−3.98 (−7.51, −0.44)	0.027	−2.72 (−11.62,6.18)	0.554
Nadir	*Ref.*	−2.52 (−5.34,0.35)	0.086	−2.79 (−5.71, −0.13)	0.061	−5.12 (−9.07, −1.17)	0.011	−7.67 (−17.63,2.29)	0.131
10 s	*Ref.*	−3.03 (−5.98, −0.07)	0.045	−3.29 (−6.29, −0.29)	0.032	−4.72 (−8.78, −0.66)	0.023	−9.01 (−19.25,1.23)	0.085
20 s	*Ref.*	−1.96 (−5.04,1.12)	0.213	−2.41 (−5.53,0.72)	0.131	−3.70 (−7.94,0.53)	0.086	−4.94 (−15.61,5.74)	0.365
30 s	*Ref.*	−1.12 (−4.10,1.86)	0.461	−1.57 (−4.59,1.45)	0.309	−2.69 (−6.73−1.46)	0.207	−0.92 (−11.22,9.40)	0.862

Data are regression coefficients (95% confidence Intervals) and associated *p*-values for differences between categories of subjective memory; 'Nadir', lowest blood pressure recorded post-stand; Model 1 = age, age squared and sex; Model 2 = Model 1 + education level, BMI, depressive symptoms, objective cognitive deficits (MoCA), physical co-morbidities (chronic conditions and cardiovascular disease), medications (antidepressants and antihypertensive) and a history of smoking.

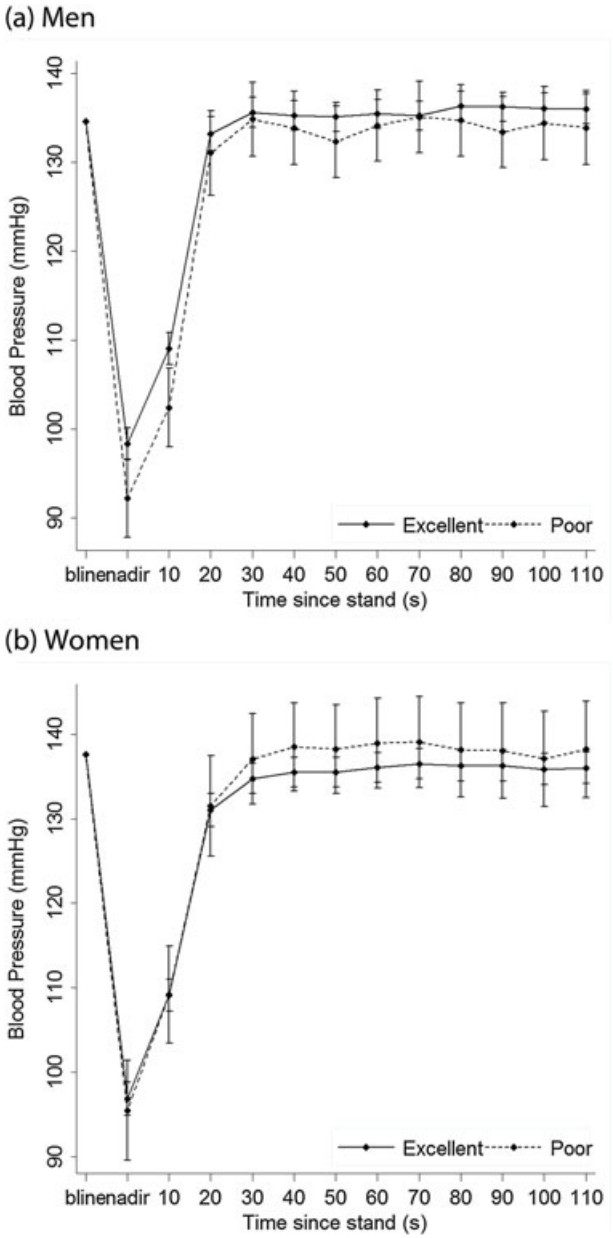

Figure 2 Systolic orthostatic blood pressure stabilisation by subjective memory stratified by sex. Systolic orthostatic blood pressure stabilisation after standing: 'excellent' subjective memory versus 'poor' subjective memory in (a) men and (b) women adjusted for age, age squared, education level, BMI, depressive symptoms, objective cognitive deficits, co-morbidities, medications, smoking and supine systolic blood pressure (Model 3); 'bline', baseline supine blood pressure; 'Nadir', lowest blood pressure recorded post-stand; 's', seconds; 'mmHg, millimetre of mercury.

cognitive decline (Jessen *et al.*, 2014). Our findings were robust to adjustment for objective cognitive function and in sensitivity analysis including only those with the highest scores on the MoCA.

This is the first study to assess the relationship between SMI and OBP measures using continuous BP recordings at a population level. Elmståhl and Widerström previously reported associations with symptoms of orthostatic intolerance and SMI (Elmståhl and Widerström, 2014). Orthostatic intolerance is classically attributed to cerebral hypoperfusion, and continuous monitoring of OBP may detect subtle BP changes in those experiencing orthostatic intolerance not detectable using traditional methods (Finucane *et al.*, 2014). Sub-clinical OBP dysregulation may be related to cognitive decline via cerebral hypoperfusion (Collins and Kenny, 2007). Our results suggest that the absolute lowest BP (or 'Nadir') reached post-stand

may be important in determining the consequences for the cerebral circulation. We note that the predicted mean SBP reached post-stand in those with poor subjective memory was 92.2 mmHg (CI95% = 87.1, 97.3) relative to 99.3 mmHg (CI95% = 97.4, 101.2) among those with excellent subjective memory. A SBP of <90 mmHg is classically taken to represent critical hypotension; however, this threshold may be higher in elders (Oyetunji *et al.*, 2011). The differences in OBP we have demonstrated among the different categories of subjective memory are comparable to the BP lowering effect of antihypertensive monotherapy (Musini *et al.*, 2014) and may reflect subtle autonomic dysfunction similar to that detected by continuous BP monitoring in early Parkinson's disease (Hellman *et al.*, 2015).

In line with our results, Scuteri *et al.* previously reported that hypotensive episodes (defined as at least one reading <100 mmHg) during 24-h ambulatory monitoring—which could plausibly have resulted from daytime orthostatic fluctuations—were more common in those with SMI (Scuteri *et al.*, 2013). The HUNT study, which sampled a population of 12 225 participants, aged 65 and over, found that relative to moderate sitting SBP levels, higher seated SBP was associated with better subjective memory—in line with our results suggesting that lower supine BP drives lower SBP following orthostatic stress (Langballe *et al.*, 2012). Lower OBP, even at sub-clinical levels, may not be effectively compensated by auto-regulatory processes, and this may result in inadequate hemodynamic responses to cognitive demands (Tzeng and Ainslie, 2013). High metabolic requirements necessitate careful regulation of cerebral blood flow; there is precise coupling of regional brain activity to regional blood flow, and this may contribute to the auto-regulation of cerebral perfusion (Willie *et al.*, 2014). In older adults, PET imaging in subjects with SMI demonstrated less efficient coupling of blood flow to regional brain activity (Hohman *et al.*, 2011).

By adjusting for supine BP we additionally assessed BP stabilisation to seated levels after standing given that this may better determine the consequences of orthostatic stress over and above absolute BP reached post stand (Romero-Ortuno *et al.*, 2011). This highlighted sex differences showing that men with poor subjective memory had a larger orthostatic SBP deficit and slower SBP stabilisation than men with excellent subjective memory—a pattern consistent with impaired cardiovascular autonomic homeostasis. Although sex differences in cognitive deficits remain poorly understood (Mielke *et al.*, 2014), a recent study has suggested that SMI may reflect objective cognition in men but affective state in women (Tomita *et al.*, 2014); women reported poorer subjective memory despite having better objective cognition; men, however, were more accurate in self-appraisal of cognitive abilities. The HUNT study also described sex differences in their findings—in men, but not in women, lower seated systolic BP was related to greater SMI relative to moderate seated systolic BP (Langballe *et al.*, 2012). Interestingly, older men have previously been shown to have higher rates of OH-related hospitalisations and demonstrate poorer cerebral auto-regulation during standing than women (Deegan *et al.*, 2011).

Limitations to this work include that it is a cross-sectional analysis so causation cannot be established. In keeping with many studies investigating SMI this study includes a single-item measure of SMI and there remains a lack of consensus in the literature as to the best way to measure SMI (Abdulrab and Heun, 2008). Asking about decline in subjective memory may be a more reliable harbinger of dementia (Jessen *et al.*, 2010) and should be considered in future studies. Furthermore, respondents who attended the health centre assessment tended to be younger, better educated and in better health. In mitigation, it could be argued that this will have the effect of biasing the estimates downwards. Finally, we do not have access to corroborating measures of cerebral auto-regulation or neuroimaging in this cohort to further elucidate our hypotheses with regard to the underlying pathophysiology of these relationships.

SMI has known overlaps with psychiatric diagnoses (Stewart, 2012). Adjustment for measures of anxiety did not substantively alter the relationships shown here (results not shown). In those with established cardiovascular disease poorer autonomic function has been linked to greater depressive symptoms (Carney *et al.*, 2001). While in sensitivity analysis findings remained robust to exclusion of those with indicators of clinical depression and cardiovascular disease concomitant analysis of other markers of cardiovascular autonomic function; for example, heart rate variability and baroreflex sensitivity may have enriched our understanding of autonomic function in those with SMI. Both heart rate variability and baroreflex sensitivity, however, require the additional analysis of electrocardiographic tracings, which was beyond the scope of the current investigation.

We did not make corrections for multiple comparisons; thus, we acknowledge the possibility of type 1 error. We attempted to minimise repeated comparisons by investigating the relationship with the 'Nadir' and by focusing analysis on the first 30 s.

There is limited population data available on continuous OBP changes and as yet no definitive manner in which to approach this data (Cooke *et al.*, 2013). We thus treated the analysis as exploratory and have been careful to highlight results only where there were consistent patterns across groups.

While the oldest-old are those most at risk of developing dementia, the accompanying neuropathological changes may begin decades earlier (Bateman *et al.*, 2012). The wide age range of this sample (50–91 years) encompasses those at risk for future dementia; however, given that the mean age of the sample is 62 years, appropriate caution should be used in the extrapolation of these findings to older age groups—in particular to those aged 80+.

Despite such caveats we note that our results point towards potentially modifiable contributors to SMI. SMI has been consistently associated with poorer quality of life; thus, efforts focused on intervention should represent both a clinical and public health priority (Stewart, 2012). OBP dysregulation is treatable–often by employing simple conservative strategies including modification of culprit medications and ensuring adequate fluid intake(Logan and Witham, 2012).

Conclusion

We have demonstrated that sub-clinical OH is associated with SMI; these results add to evidence linking OBP dysregulation to cognitive dysfunction and to research examining the organic underpinnings of SMI. Continuous BP monitoring may provide detailed insights into OBP patterns accompanying early autonomic dysfunction, which is not detectable by standard methods. If these findings were to be replicated, subtle cardiovascular autonomic dysfunction as reflected in poorer BP response to orthostasis may represent a modifiable risk marker for SMI in older adults.

Conflict of interest

The authors report no conflict of interest.

Key points

- Lower orthostatic blood pressure is associated with greater subjective memory impairment.
- The association is independent of objective cognition, co-morbidity and antihypertensive medication.
- The association between systolic orthostatic BP and subjective memory impairment is stronger for men.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site.

Table 1. Systolic orthostatic blood pressure by subjective memory *(adjusted)*

Table 2. Systolic orthostatic blood pressure stabilisation by subjective memory stratified by sex (*adjusted for supine systolic BP*)