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Cognitive Status, Gray Matter Atrophy, and Lower Orthostatic Blood Pressure in Older Adults

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Abstract

Background—Associations between orthostatic blood pressure and cognitive status (CS) have been described with conflicting results.

Objective—We hypothesize that long-term exposure to lower orthostatic blood pressure is related to having worse CS later in life and that atrophy of regions involved in central regulation of autonomic function mediate these associations.

Methods—Three-to-four measures of orthostatic blood pressure were obtained from 1997–2003 in a longitudinal cohort of aging, and average systolic orthostatic blood pressure response (ASOBPR) was computed as % change in systolic blood pressure from sit-to-stand measured at one minute post stand. CS was determined in 2010–2012 by clinician-adjudication (n = 240; age = 87.1±2.6; 59% women; 37% black) with a subsample also undergoing concurrent structural neuroimaging (n = 129). Gray matter volume of regions related to autonomic function was measured. Multinomial regression was used to compare ASOBPR in those who were cognitively intact versus those with a diagnosis of mild cognitive impairment or dementia, controlling for demographics, trajectories of seated blood pressure, incident cardiovascular risk/events and medications measured from 1997 to 2012. Models were repeated in the subsample with neuroimaging, before and after adjustment for regional gray matter volume.

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Results—There was an inverse association between ASOBPR and probability of dementia diagnosis (9% lower probability for each % point higher ASOBPR: OR 0.91, CI95% = 0.85–0.98; $p = 0.01$). Associations were similar in the subgroup with neuroimaging before and after adjustment for regional gray matter volume.

Conclusion—ASOBPR may be an early marker of risk of dementia in older adults living in the community.

Keywords

Autonomic nervous system; blood pressure; cognition; dementia; hypotension; magnetic resonance imaging; orthostatic

Introduction

Lower orthostatic blood pressure (OBP), the impaired stabilization of blood pressure after standing, is common among older adults. Associations between lower OBP and poorer cognitive status (CS) have been described with conflicting results. Lower OBP has been associated prospectively with poorer CS in four large epidemiological samples [1–4]. Lower OBP has also been associated with conversion to dementia in two clinical studies of patients with Parkinson's disease [5] and mild cognitive impairment (MCI) [6]. Three other prospective population-based studies, however, found no longitudinal association [7–9]. Furthermore the associations described in the Atherosclerosis Risk in Communities study did not survive correction for demographic factors or conventional cardiovascular risk [1] and the most comprehensive cohort study to date did not investigate MCI [3]. The majority of prior studies have investigated screening tests of cognition rather than clinician-directed adjudicated diagnosis, and measured OBP at a single time point [10–12]. Moreover, measurement protocols and definitions of OBP investigated have varied across studies [1, 3, 6, 10].

We aimed to investigate the relationship between repeated measures of OBP and CS obtained 10 years later in a well-defined, prospectively-followed cohort of older adults. We also aimed to explore the mediating role of known magnetic resonance imaging (MRI) markers of brain health namely cerebral small vessel disease and gray matter atrophy. Examining the central nervous system pathways linking OBP to CS is important because accumulating evidence suggests that higher brain centers may be involved in cardiovascular autonomic regulation [13] and OBP levels [14]. Additionally, it has been postulated that lower OBP may relate to CS via cerebral hypoperfusion [14], to which watershed areas of the cortex may be particularly vulnerable [15]. Investigations incorporating neuroimaging are limited, with variable directions and strengths of associations described. For example lower OBP in patients has been associated with white matter hyperintensities (WMH) in patients with dementia [16]; however, Soennysn et al. [17] found no relationship between lower OBP and WMH in a clinical sample with ‘mild dementia’. Most studies including neuroimaging are in clinical cohorts or small samples and did not examine regional cortical gray matter atrophy [18–20].

We hypothesized that long-term exposure to lower OBP is related to having worse CS later in life and that this relationship may be mediated via smaller volume of regions involved in central regulation of autonomic function.

Materials and Methods

Study sample

Participants of this study were recruited from the Health Aging and Body Composition Study (ABC) at the Pittsburgh site. The Health ABC study began in 1997 in Memphis, TN and Pittsburgh, PA, USA with 3,075 community-dwelling white and black older adults aged 70–79, recruited from a random sample of Medicare eligible adults living within designated zip codes, with no difficulties performing activities of daily living, walking a quarter mile, or climbing 10 steps without rest, free of life-threatening cancers, and planned to remain within the study area for at least 3 years. Participants were invited to regular follow-up through 2012. Of the 1,527 participants enrolled in the study in 1997–1998 at the Pittsburgh site, 819 were alive and were contacted in 2006–2007 (year 10 of the parent Health ABC cohort) to participate in the Healthy Brain Project (HBP) a neuroimaging sub-study of cognition and mobility. Of the 314 enrolled in the HBP in 2006–2007, 246 returned in 2010–12 for a cognitive assessment and follow-up MRI (63 had died before cognitive adjudication was completed, and 5 did not have complete data to allow determination of CS). 240 of these participants had complete data on OBP from 1997–2003 of whom a subset of 129 participants also were eligible for brain MRI in 2010–2012 and had complete data on MRI outcomes of interest. The study population used in this analysis is depicted in Fig. 1.

Ethics

The study protocol was approved by the University of Pittsburgh Institutional Review Board. All participants provided written informed consent.

Magnetic resonance image

MRI scans were obtained at the MR Research Centre of the University of Pittsburgh with a 3Tesla Siemens TIM TRIO scanner equipped for echo-planer imaging. Acquisition and processing protocols have been published [21]. Brain tissue volumes (gray matter, white matter, cerebrospinal fluid) were quantified on skull-stripped T1-weighted images in native anatomical space. Scans with incidental findings were excluded following review by a clinical radiologist. A FLAIR was also acquired for WMH.

Gray matter volume (GMV)

Gray matter regions were identified using the automated anatomical labelling atlas [22]. Regions of interest were chosen *a priori* based on a recently published meta-analysis which produced a map of brain areas involved in central autonomic regulation, these included: dorsolateral prefrontal cortex, precuneus, lingual gyrus, cingulate cortex, insula, thalamus, amygdala, hippocampus, parahippocampus, angular gyrus, suprmarginal gyrus, and frontoinsular cortex [23]. An index of gray matter atrophy of total brain was calculated using the equation: 1– (total GMV/total intracranial volume).

Cerebral small vessel disease

Total brain WMH volume was estimated by summing all voxels classified as WMH, which were then further normalized by total brain volume [21].

Main predictor variable

Orthostatic blood pressure—The Health ABC study collected OBP in Years 1, 2, 4, and 6, i.e., from 1997–1998 until 2002–2003. BP was measured in the seated position at the brachial artery using a mercury sphygmomanometer. Average seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) were derived as the means of two consecutive BP measures. Following a quiet rest period of at least five minutes, the participant was asked to stand and BP was recorded at heart level after one minute. Standardized protocols were followed for all BP measurements. Quality assurance and control protocols were regularly implemented for the centrally trained clinic staff. Testers were required to gain re-certification of competence in assessments annually.

Longitudinal characterization of OBP

To be included in the analysis each participant had a minimum of three(from a maximum of four) annual observations of OBP. 174 (72.5%) of participants had four measures with 66 (27.5%) missing one OBP measure. In the neuroimaging subsample, 98 participants (75.97%) had four measures and 31 (24.03%) were missing one OBP measure from a maximum of four. Five participants who had only two measurements and one participant who had one measurement were excluded from this analysis (Fig. 1).

Three derived measures of OBP were of interest:

1. *Average Systolic OBP response (ASOBPR):* As per Hayakawa et al. [6], Lagro [24], Feeney et al. [25], and Romero-Ortuno et al. [26], systolic OBP response was computed as (standing SBP/seated SBP)*100, thus yielding a continuous variable expressed in percentage points. Standing BP may be higher or lower than seated BP, thus participants with a systolic OBP response >100% have a standing SBP that exceeds seated SBP. Systolic OBP response was computed as described above at each available time point for each individual and averaged across time points to obtain an index of prior exposure to systolic OBP response over time, i.e., ASOBPR. Average diastolic OBP response was calculated in the same manner. Trajectories describing the slope between annual observations of systolic OBP response were also computed.
2. *Consensus Orthostatic Hypotension (OH)* [27]: Upon standing, if a drop in SBP of ≥20 mmHg and/or drop in DBP of ≥10 mmHg occurred this was denoted using a dichotomous variable where consensus OH was defined as present or absent. A binary variable (no/yes) was then coded to denote those participants who met consensus OH criteria (i.e., baseline or incident consensus OH) at any point over the available annual measures.
3. *Absolute change in OBP:* OBP change was calculated for each year as ‘Delta SBP’ = seated SBP minus standing SBP; ‘Delta DBP’ = seated DBP minus

standing DBP. A positive Delta BP indicates that standing BP dropped lower than seated BP, whereas a negative Delta BP indicates that BP had risen above the seated measure when standing. Longitudinal average Delta SBP and Delta DBP were then calculated as the mean of available repeated annual observations.

Main outcome of interest

Cognitive status—According to a protocol previously validated in the Cardiovascular Health Study [28], CS was clinically adjudicated on Health ABC participants who were seen at the year 14 site visit in 2010–2012, using all data from previous visits as well as cognitive assessments at the time of the MRI. An extensive battery of cognitive tests was administered, concurrent with brain MRI and assessment of neurological function. The neuropsychological testing took into account educational attainment and included: 1) pre-morbid intelligence: the American version of the National Reading test and Raven's Colored Progressive Matrices; 2) memory: California Verbal Learning Test, and Rey-Osterrieth figure; 3) language: Boston Naming Testandverbalfluencytest;4)visuo-perceptualand/or visuo-constructional: block design and copy of a geometric figure; and 5) executive function: Stroop test.

This neuropsychological battery was designed after extensive consultation with neurologists and dementia experts. It was based on two goals: 1) identifying deficits in specific cognitive domains that characterize MCI and its subgroups and 2) diagnosing dementia. This battery was sensitive to cognitive impairment, and detailed normative data have previously been obtained through the Cardiovascular health study.

Study dementia study [28]. Adjudicated outcomes took educational attainment into account and included: cognitively normal (n = 100), MCI (n = 80), dementia (n = 60), or no neurological data (n = 5) with the prevalence of cognitive impairment reflecting national estimates of the prevalence of dementia in those over 80 years [29].

Co-variates

Demographics, anthropometry, and health behaviors—Age, sex, and race were recorded at entry examination to the Health ABC study. Body mass index (kg/m^2) and smoking history (‘pack-years’) were also recorded at baseline. Average alcohol consumption throughout the study was based on participants' annual report of alcoholic drinks consumed per week over the last 12 months and was summarized as: 0 = ≤1 drink; 1 = >1–7 drinks per week; 2 = >1 daily alcoholic drink. Participants were given examples of what constituted a ‘standard drink’, e.g., 12 ounces of beer (1 can) and 5 ounces of wine (a full glass) as previously reported [30]. No information was collected on specific beverages

Adjudicated cardiometabolic conditions—Stroke, coronary heart disease, diabetes, and hypertension status were coded according to baseline prevalence and incidence during follow-up. This data was based on annually adjudicated health outcomes using a standardized protocol.

Longitudinal measures of seated BP—Seated BP was measured in years 1, 2, 4, 5, 6, and 8, and yearly from year 10–15. Trajectories of SBP change were calculated using annualized slopes of the repeated measures of seated SBP together with the variability in SBP between visits. Additionally, average seated SBP was calculated as the mean of SBP measurements from Year 1 (1997–1998) Health ABC until time of Cognitive Adjudication. No person was missing ≥7 years of data for any seated SBP measurement.

Medications—A medication inventory was completed at each annual clinic visit (except year 4, 7, and 9) including antihypertensive and antidepressant treatment. A variable was computed to report the percentage of annual visits a participant was on an antihypertensive or antidepressant, e.g., ranging from 0% for participants who were not taking an antihypertensive medication at any visit to 100% for a person who was recorded to have been taking the medication at every visit.

Statistical analysis

Continuous OBP variables were normally distributed; oneway ANOVA was used to assess the unadjusted relationship between adjudicated CS groups (i.e., normal versus MCI; normal versus dementia) and OBP. Multinomial regression models adjusted for age, sex, and race were used to characterize the relationship between adjudicated CS (i.e., normal versus MCI; normal versus dementia) and OBP. Other variables were added one at a time in separate blocks to this model and changes in the relationship between OBP and CS were examined: longitudinal average seated SBP; longitudinal trajectories of seated SBP; cardiometabolic conditions; health behaviors; antidepressants and antihypertensive medications. Parsimonious models included only variables that were significantly associated with CS in bivariate analysis.

The relationship between OBP and CS was also estimated in the subsample with concurrent neuroimaging adjusting for age, sex, and race; the neuroimaging measures were then added to this model to explore potential mediation effects of brain structural characteristics on the relationship between OBP and CS. Parsimonious models included only neuroimaging variables that were significantly associated with CS in correlations adjusted for age, sex, and race and total gray matter atrophy, corrected for multiple comparisons (given hypothesized lateralized relationships, Sidak correction for 14 comparisons was $p < 0.00366$).

Results

A total of 100 participants were determined to have normal cognition, 80 MCI, and 60 dementia. The mean age of the sample at the time of MRI was 87 years (SD 2.9); there was a female preponderance (59% women) and 37% of the sample was black. Compared to those who remained cognitively normal, those who received a final diagnosis of MCI or dementia were more likely to be black or to have had a stroke, and there were significant differences in alcohol consumption between groups although similar proportions of those with dementia and normal CS consumed alcohol daily (Table 1). There were no significant age or sex differences between CS groups at baseline.

In the group as a whole, ASBOPR was above 100% in 185 (77.1%) participants and below 100% in 55 (22.9%) participants. ASOBPR was significantly lower in those with dementia (101.99 (SD 4.37)) or MCI (102.99 (SD 4.95)) as compared to those with normal CS (103.95 (SD 4.96)), in 2010–2012, $p = 0.04$ for linear trend (Fig. 2). There were no significant differences between CS groups in consensus OH or in the slope of change of the trajectory of longitudinal OBP ($p > 0.1$), nor were there differences between CS groups in average diastolic OBP response or Delta DBP ($p > 0.1$).

In multinomial regression analysis adjusted for age, sex, and race, ASOBPR was lower for those with dementia as compared to those who had normal CS (Model 1). Each percentage point greater rise in ASOBPR was associated with a 9% reduced odds of a final dementia diagnosis (Table 2). Additionally, there was a trend towards a relationship between lower ASOBPR and MCI, although this did not reach statistical significance ($p = 0.12$). Further adjustment for relevant co-variates did not meaningfully alter these relationships (Models 2, 3, 4, 5). Results were similar when adjusting for alcohol intake and stroke.

Of the 129 participants in the neuroimaging sub-sample, the mean age at time of MRI was 86 years (SD 2.7), 61.2% were female, and 42.6% were black. After adjustment for age, sex, race, and total atrophy index, lower ASOBPR was associated with lower GMV in subcortical regions spatially co-localized within the medial temporal lobe and lateralized to the right hemisphere (right hippocampus, right parahip-pocampus, and the right middle cingulate gyrus) in addition to the right dorsolateral prefrontal cortex and right lingual gyrus (Table 3). Using the most conservative adjustment for multiple comparisons ($p < 0.00366$), associations remained significant with the right dorsolateral prefrontal cortex and right lingual gyrus. Associations with WMH were not significant.

In this subsample, the relationship between lower ASOBPR and dementia status remained significant after initial adjustment for age, sex, and race and was similar in magnitude and in the same direction to the relationship in the larger sample (Table 4). The relationship between lower ASOBPR and dementia status was similar after adjustment for GMV. Table 4 shows results of the parsimonious models, adjusted for the regions of right dorsolateral prefrontal cortex or right lingual gyrus, associated with OBP after correction for multiple comparisons.

Sensitivity analysis

Educational attainment was accounted for during cognitive adjudication; however, given the importance of educational attainment to CS, we re-estimated models additionally adjusting for years of high school educational attainment (Supplementary Table 1). Given that the magnitude of OBP drop upon standing tends to correlate with a higher baseline BP, we also re-estimated the relationship between ASOBPR and CS adjusting for seated SBP contemporaneous to the measures of standing SBP (Supplementary Table 2). The direction and size of the reported relationships remained unchanged. We also tested for a U-shaped relationship between OBP and CS, as reported by prior studies [4], however, non-linear effects of ASOBPR (tested by addition of a quadratic ASOBPR term to regression models) were not significant.

Mean standing SBP was higher than mean seated SBP in all CS groups—accordingly ASOBPR in each group was above 100%. Given that our hypothesis related to exposure to lower OBP and its relationship with CS, we additionally created a binary variable which categorized participants into groups: those among whom ASOBPR was ≥100% (n = 185 (77.1%)) and <100% (n = 55 (22.9%)). Of participants with ASOBPR <100%, 40/55 (72.7%) were classified as having either MCI or dementia versus 100/185 (54.1 %) of those with a response >=100% (p = 0.01) with similar patterns of association with CS evident as with the continuous variable including after adjusting for age, sex, and race (Supplementary Table 3).

Finally we explored the relationship between the absolute change in SBP (Delta SBP) and CS noting that after adjustment for age, sex, and race similar associations were evident with CS as described for ASOBPR. These associations remained after adjustment for seated BP and other relevant co-variates (Supplementary Table 4).

Given the potential importance of co-medication on OBP, we additionally computed variables to reflect the burden of prescription medication during the period of OBP collection, i.e., 1997–2003. This included exposure to polypharmacy (defined as ≥4 prescribed medications), medications used to treat prostate disorders (e.g., alpha blockers such as tamulosin), and use of anti-depressants and anti-hypertensives. There were no significant differences in ASOBPR between participants exposed versus not exposed to these medications 1997–2003 (Supplementary Table 5).

Discussion

We report associations between the average of repeated observations of systolic OBP and later CS in a community-dwelling, bi-racial cohort of the oldest-old, followed prospectively over 15 years. Specifically, a lower standing SBP relative to seated SBP averaged over six years from study entry (ASOBPR) increased odds of a dementia diagnosis at the end of the study period. Furthermore, lower ASOBPR was also related to lower GMV in brain regions potentially related to autonomic regulation and vulnerable to hypoperfusion injury. This study extends previous investigations of the relationship between OBP and CS with analysis of repeated measures of OBP, neuroimaging, clinical adjudication of CS and 15 years of prospective follow-up data in a well-defined cohort aged 69+ at time of first OBP assessment.

Our findings are in line with a recent meta-analysis suggesting that lower OBP has independent prognostic value for end-organ disease [31]. The associations we report are independent of other cardio-metabolic risk factors, including longitudinal average seated SBP, seated SBP trajectories, and antihypertensive treatment. In this study, on average, standing BP was higher than mean seated BP (and therefore mean ASOBPR was >100%), which is in keeping with other study populations using a sit-to-stand OBP measurement protocol [32, 33]. Furthermore, although the magnitude of OBP drop upon standing tends to correlate with a higher baseline BP, additional sensitivity analysis adjusting for average seated SBP contemporaneous to OBP measures did not sub-stantively affect the associations reported here.

While other studies have suggested that higher OBP may also be associated with poorer CS [4, 20], there was no evidence of a U-shaped relationship between ASOBPR and CS in this cohort. Matsubayashi et al. previously reported a cross-sectional U-shaped relationship between OBP, white matter changes, and cognitive test scores [34]. More recently, Curreri et al reported prospective associations between elevated OBP and lower cognitive scores 4 years later [4]. Discrepancies may reflect the longer duration of longitudinal follow-up in the current study, our use of longitudinal OBP measurements and investigation of a clinically adjudicated cognitive outcome rather than cognitive scores. However both lower and elevated OBP may reflect increased OBP variability, which has also been linked to poorer CS but which requires additional standing OBP measures to calculate [3]. Therefore, the impact of elevated OBP may have been underestimated in the current study. Alternatively, as elevated OBP has also been hypothesized to reflect a pre-hypertension state [35], it may be less important in a cohort in whom dementia diagnosis was adjudicated aged 83+.

Prior studies of OBP and cognitive outcomes have focused on consensus OH [9–11]. We additionally investigated the more recently proposed characteristic of ASOBPR based on emerging literature using continuous beat-to-beat OBP measurements [25, 32, 33], which has recently been shown to predict conversion from MCI to dementia in a clinical sample [6]. Population norms derived from continuous OBP measurement indicate that an initial systolic OBP drop immediately after standing is a universal finding among adults aged 50+ [36]. With increasing age, time to stabilization of OBP to pre-stand levels and therefore the duration of exposure to lower blood pressure is prolonged [36]. Our findings, using more widely available and pragmatic standard clinical measures, mirror those using more sophisticated techniques. We therefore speculate that lower ASOBPR in those participants with dementia and MCI in this cohort may reflect larger initial OBP drops on standing and subsequent slower stabilization. This is further supported by sensitivity analyses categorizing ASOBPR indicating that the relationship with poorer CS was stronger in those with a systolic OBP response <100%. Thus, ASOBPR may be a more sensitive indicator of hemodynamic homeostasis than the simple presence or absence of consensus OH, or absolute change in OBP, as it takes into account relative baseline SBP. Conceptualized as a measure of hemodynamic homeostasis these findings investigating ASOBPR are perhaps akin to the stronger relationship reported in the Rotterdam cohort between a baseline measure of systolic OBP variability and later dementia than with consensus OH [3].

We hypothesized that the relationship between lower OBP and later CS may be mediated by lower GMV, possibly caused by central dementia-related [38] neurodegeneration and/or cerebral hypoperfusion arising from lower peripheral OBP [6]. Lower ASOBPR was related to smaller GMV of the right hippocampus, right parahippocampus, and right middle cingulate gyrus. Associations were strongest with regions of potential relevance to autonomic function and areas of the cortical borderzone territory including the right dorsolateral prefrontal cortex and the right lingual gyrus, and remained even after applying stringent conservative tests for significance due to multiple comparisons. Lateralized associations are in keeping with previously reported differential hemispheric vulnerability in the borderzone region of the right frontal cortex in Alzheimer's disease [15] and dorsolateral prefrontal cortex involvement in sympathetic regulation [23]. In this cohort, GMV did not, however, mediate the association between ASOBPR and CS, thus other pathways may exist

to explain this association; for example, endothelial dysfunction has been posited as a causal mechanism in both OBP dysregulation and dementia [39, 40].

We found no relationship between ASOBPR and atrophy of the insula. The insula is vulnerable to deep watershed ischemia and is involved in autonomic regulation [38, 41]. The earliest dementia-related neuropathological changes may affect the insula [38], therefore neuroimaging concurrent to the measurement of OBP may have been better timed to demonstrate an association. There was no relation-ship between ASOBPR and WMH. This is in line with other studies using neuroimaging to investigate the relationship between OBP and dementia [17], but is perhaps surprising given relationships between OBP, stroke, and cardiovascular disease [31].

Our findings must be interpreted in the context of several limitations. Importantly, although we applied consensus OH criteria, subjects were seated instead of supine and the measurement of OBP at 3 min is lacking. A larger OBP drop would be expected from the supine position and may account for a lack of association with traditional OBP indices and the low prevalence of consensus OH. Optimal timing of the standing BP measurement is contested, however [42], and measurements of standing BP beyond one minute at each annual visit would have allowed investigation of systolic OBP variability [3]. However, a single measurement of standing OBP at one minute is a limitation common to other studies [11, 32]. Future studies using more advanced measures will allow further investigation of the relationship between OBP drops occurring <1 minute (e.g., Initial Orthostatic Hypotension, defined as drop of ≥40 mmHg occurring within 15 seconds of standing associated with symptoms such as dizziness) and cognitive outcomes.

Loss to follow-up and differential participation of more robust older adults may have introduced bias; furthermore, neuroimaging was only available on a subset of those with cognitive adjudication. We note that the association between ASOBPR and CS was robust, remaining significant even when tested in the smaller subsample. This study cannot infer causality based on the determination of CS and MRI data at a single time point. Furthermore, OBP measures contemporaneous to MRI and cognitive adjudication were not available. Neuropathological changes associated with dementia likely begin decades prior to the onset of the clinical syndrome and are progressive [45]. Therefore it is plausible cortical atrophy at the time of MRI would be more advanced in those with earlier onset OBP dysregulation.

Further work is required to determine if a causal relationship exists between OBP and CS. If a causal relationship were to be established, interventions to improve ASOBPR may be important in preserving CS into late old age. Simple conservative strategies are the cornerstone of management of OBP dysregulation, e.g., rationalization of medications; judicious use of antihypertensives; and adequate fluid and salt intake. Examining ASOBPR response may help uncover future CS in the oldest-old. Lower ASOBPR may be on the causal pathway to poorer CS by reducing GMV of brain regions important in autonomic control. Strategies to control ASOBPR may impact future CS possibly by reducing gray matter atrophy in these regions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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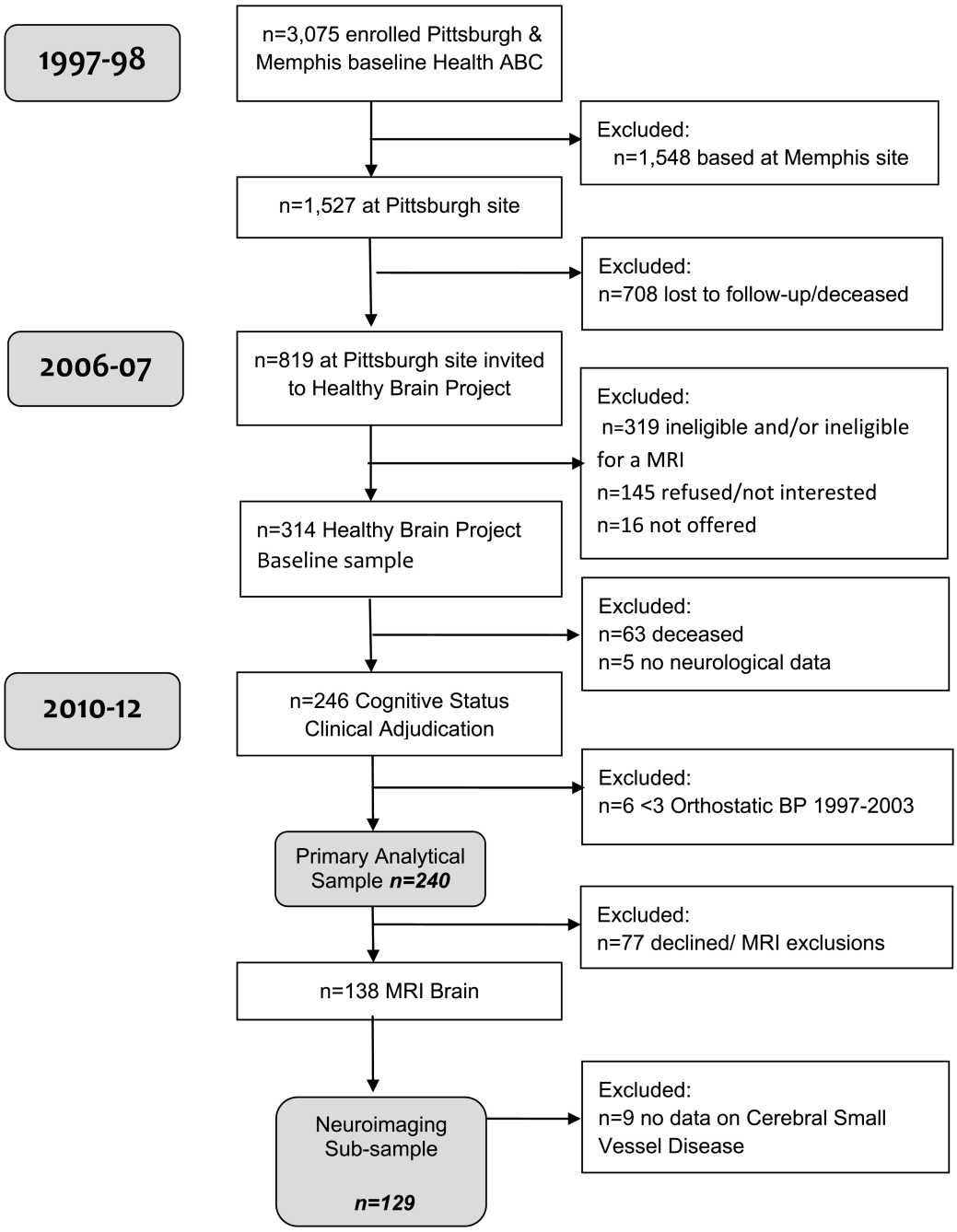

Fig. 1.
Study flow diagram.

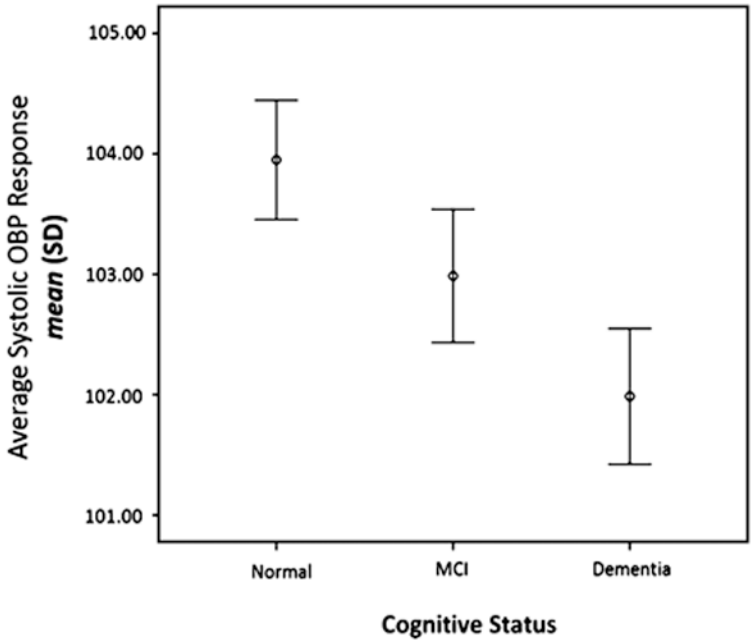

Fig. 2.

Unadjusted average systolic OBP response (averaged across three to four repeated annual observations from 1997–1998 until 2002–2003 with higher values reflecting higher standing BP relative to seated BP) against later cognitive status (2010–2012). OBP, orthostatic BP; MCI, mild cognitive impairment; SD, standard deviation.

Table 1

Description of the sample by cognitive status

N	Total Sample 240	Normal 100	MCI 80	Dementia 60	*p*
Cumulative Orthostatic Blood Pressure Parameters[a]					
ASOBPR, %, *mean* (SD)	103.14 (4.86)	103.95 (4.96)	102.99 (4.95)	101.99 (4.37)	0.043
Consensus Orthostatic Hypotension, *n* (%)	25 (10.42)	11 (11.00)	8 (10.00)	6 (10.00)	0.969
Delta SBP, mmHg, mean (SD)	–4.00 (6.43)	–4.97 (6.61)	–3.70 (6.44)	–2.79 (5.94)	0.101
Slope of trajectory of ASOBPR, %, *mean* (SD)	–0.08 (2.09)	–0.24 (2.23)	–0.01 (1.91)	0.09 (2.10)	0.600
Seated SBP, mmHg, mean (SD)	135.63 (14.88)	132.82 (15.84)	136.66 (13.76)	138.96 (14.00)	0.030
Standing SBP, mmHg, mean (SD)	139.63 (15.93)	137.78 (16.69)	140.35 (13.93)	141.74 (17.00)	0.278
Cumulative Seated Systolic Blood Pressure Parameters[b]					
Average Seated SBP, mmHg, mean (SD)	134.00 (12.65)	131.54 (13.13)	135.18 (11.73)	136.50 (12.50)	0.032
Slope of trajectory of Seated SBP, mmHg, mean (SD)	–0.63 (0.80)	–0.58 (0.86)	0.62 (0.67)	–0.73 (0.85)	0.518
Demographics[c]					
Age, *mean* (SD)	72.30 (2.60)	72.47 (2.46)	72.55 (2.58)	73.27 (2.80)	0.142
Female *n* (%)	142 (59.17)	53 (53.00)	49 (61.25)	40 (66.67)	0.211
Black race *n* (%)	90 (37.50)	27 (27.00)	37 (46.25)	26 (43.33)	0.017
Medications[b]					
Antihypertensive Treatment, % visits, *mean* (SD)	61.91 (35.5)	59.5 (35.49)	69.90 (32.76)	55.28 (37.49)	0.036
Antidepressant Treatment, % visits, *mean* (SD)	8.09 (19.96)	8.58 (21.17)	6.77 (18.76)	9.03 (19.67)	0.601
Co-morbid disease[b]					
Cardiovascular disease *n* (%)	56 (23.33)	22 (22.00)	21 (26.25)	13 (21.67)	0.751
Stroke *n* (%)	14 (5.83)	0 (0.00)	10 (12.50)	4 (6.67)	0.002
Hypertension *n* (%)	203 (84.58)	78 (78.00)	72 (90.00)	53 (88.33)	0.056
Diabetes *n* (%)	58 (24.17)	25 (25.00)	15 (18.75)	18 (30.00)	0.296
Other risk factors					
Body Mass Index[c], kg/m2, *mean* (SD)	27.46 (4.49)	26.90 (4.65)	28.12 (4.23)	27.52 (4.49)	0.193
Smoking[c], pack year, *mean* (SD)	13.14 (24.85)	11.92 (22.26)	14.95 (27.29)	12.75 (25.79)	0.713
Weekly Alcohol Consumption[c], *n* (%)					

N	Total Sample 240	Normal 100	MCI 80	Dementia 60	*p*
<1 drink per week	93 (38.75)	28 (28.00)	35 (43.75)	30 (50.00)	0.030
1–7 drinks per week	120 (50)	59 (59.00)	39 (48.75)	22 (36.67)	
Daily	27 (11.25)	13 (13)	6 (7.5)	8 (13.33)	

p values are from ANOVA for normally distributed continuous variables, Kruskal-Wallis for non-normal and χ^2 for categorical variables; ASOBPR, Average Systolic OBP Response; SD, standard deviation; %, Percentage; mmHg, millimeters of mercury; SBP, systolic blood pressure; DBP, diastolic blood pressure; OBP, orthostatic blood pressure; Weekly Alcohol Consumption, 1–7 alcoholic drinks per week.

[a]Calculated from three-to-four annual observations 1997–2003 seated SBP to standing.

[b]From study entry to time of MRI (1997–98 until 2010–12).

[c]Recorded at study entry (1997–98).

Table 2

Multivariate multinomial regression results comparing Average Systolic OBP Response (ASOBPR)[a] across diagnostic categories of cognitive status[b] (*n* = 240); coefficients of ASOBPR are reported as odds ratios (OR) and 95% confidence intervals (CI)

		Normal Cognition versus MCI		Normal Cognition versus Dementia	
Model	**Variables in the model**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
1	Age, sex, race	0.951 (0.891–1.014)	0.122	0.912 (0.849–0.980)	0.012
2	Model 1 + Longitudinal seated SBP	0.953 (0.893–1.017)	0.144	0.914 (0.850–0.983)	0.016
3	Model 1 + Cardiometabolic conditions	0.971 (0.907–1.039)	0.397	0.919 (0.855–0.988)	0.023
4	Model 1 + Health Behaviors	0.953 (0.892–1.017)	0.145	0.914 (0.848–0.984)	0.017
5	Model 1 + Antidepressants & antihypertensives	0.950 (0.891–1.014)	0.124	0.914 (0.850–0.983)	0.015

Data are Odd Ratios (95% Confidence Intervals) for differences between diagnostic categories of cognitive status. OBP, orthostatic blood pressure; ASOBPR, Average Systolic OBP Response; Longitudinal seated SBP, average seated systolic blood pressure 1997–2012; Cardiometabolic conditions: stroke, coronary heart disease, diabetes; Health behaviors: alcohol consumption, body mass index, physical activity, smoking history.

[a]ASOBPR, percent change in SBP from sitting to stand, averaged across all (three to four) annual observations 1997–2003 with higher values reflecting higher standing SBP relative to seated SBP.

[b]Cognitive Status, i.e., dementia, mild cognitive impairment (MCI), normal cognition adjudicated 2010–2012.

Table 3

Relationship of regional gray matter volumes[a] with average systolic OBP response[b] (*n* = 129)

	Partial Correlation Co-efficient	*p*-value
Dorsolateral Prefrontal Cortex	0.2823	0.0014 ** †
Precuneus	0.1085	0.2283
Lingual Gyrus	0.2751	0.0019 ** †
Cingulate Cortex		
Anterior	0.0919	0.3079
Middle	0.2153	0.0159 *
Posterior	0.1252	0.1642
Insula	0.1272	0.1575
Thalamus	−0.0123	0.8915
Amygdala	0.0491	0.5870
Hippocampus	0.1815	0.0428 *
Parahippocampus	0.1804	0.0441 *
Angular Gyrus	0.0749	0.4063
Suprmarginal Gyrus	−0.0282	0.7546
Frontoinsular Cortex	0.0616	0.4953

Data are partial correlation coefficients adjusted for age, sex, race, and atrophy index. OBP, orthostatic blood pressure.

** $p < 0.01$

* $p < 0.05$;

† Survives Sidak Correction for multiple comparisons (14 comparisons; $p < 0.00366$);

[a] MRI brain 2010–2012; Data shown are for Right Hemispheric Relationships; Left Sided Relationships were not significant.

[b] Average Systolic OBP Response, percent change in SBP from sitting to stand, averaged across all (three to four) annual observations 1997–2003 with higher values reflecting higher standing SBP relative to seated SBP.

Table 4

Multivariate multinomial regression results comparing diagnostic categories of cognitive status[a]. Relationship with Average Systolic OBP Response (ASOBPR)[b] adjusted for MRI[c] parameters (*n* = 129); coefficients of ASOBPR are reported as odds ratios (OR) and 95% confidence intervals (CI)

		Normal Cognition versus MCI		Normal Cognition versus Dementia	
Model	**Variables in the model**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
1	Age, sex, race	0.940 (0.865–1.02)	0.143	0.863 (0.756–0.985)	0.029
2	Model 1 + Cerebral Small Vessel Disease	0.940 (0.865–1.021)	0.144	0.861 (0.754–0.984)	0.028
3	Model 1 + Atrophy Index	0.944 (0.867–1.027)	0.179	0.869 (0.762–0.992)	0.038
4	Model 1 + Atrophy Index & DLPFC GMV	0.939 (0.858–1.028)	0.171	0.833 (0.723–0.958)	0.011
5	Model 1 + Atrophy Index & Lingual Gyrus GMV	0.930 (0.850–1.017)	0.110	0.852 (0.742–0.979)	0.023

Data are Odd Ratios (95% Confidence Intervals) for differences between diagnostic categories of cognitive status. DLPFC, dorsolateral prefrontal cortex; GMV, gray matter volume; OBP, orthostatic blood pressure.

[a]Cognitive Status, i.e., dementia, mild cognitive impairment (MCI), normal cognition adjudicated 2010–2012;

[b]ASOBPR, percent change in SBP from sitting to stand, averaged across all (three to four) annual observations 1997–2003 with higher values reflecting higher standing SBP relative to seated SBP.

[c]MRI brain 2010–2012.