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Orthostatic hypotension, cognition and structural brain imaging in hemodynamically impaired patients

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ABSTRACT

Background: Orthostatic hypotension (OH) is associated with an increased risk of dementia, potentially attributable to cerebral hypoperfusion. We investigated which patterns and characteristics of OH are related to cognition or to potentially underlying structural brain injury in hemodynamically impaired patients and healthy reference participants.

Methods: Participants with carotid occlusive disease or heart failure, and reference participants from the Heart-Brain Connection Study underwent OH measurements, neuropsychological assessment and brain MRI. We analyzed the association between OH, global cognitive functioning, white matter hyperintensity (WMH) volume and brain parenchymal fraction with linear regression. We stratified by participant group, severity and duration of OH, chronotropic incompetence and presence of orthostatic symptoms.

Results: Of 337 participants (mean age 67.3 ± 8.8 years, 118 (35.0%) women), 113 (33.5%) had OH. Overall, presence of OH was not associated with cognitive functioning (β: −0.12 [−0.24–0.00]), but we did observe worse cognitive functioning in those with severe OH (≥ 30/15 mmHg; β: −0.18 [−0.34 to −0.02]) and clinically manifest OH (β: −0.30 [−0.52 to −0.08]). These associations did not differ significantly by OH duration or chronotropic incompetence, and were similar between patient groups and reference participants. Similarly, both severe OH and clinically manifest OH were associated with a lower brain parenchymal fraction, and severe OH also with a somewhat higher WMH volume.

Conclusions: Severe OH and clinically manifest OH are associated with worse cognitive functioning. This supports the notion that specific patterns and characteristics of OH determine its impact on brain health.

Abbrevations: CI, confidence interval; COD, carotid occlusive disease; DBP, diastolic blood pressure; FDR, false discovery rate; FLAIR, fluid-attenuated inversion recovery images; HF, heart failure; MRI, magnetic resonance imaging; OH, orthostatic hypotension; SBP, systolic blood pressure; WMH, white matter hyperintensity.

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1. Introduction

Orthostatic hypotension (OH) is a common, often asymptomatic phenomenon, characterized by a drop in blood pressure upon postural change [1,2]. Among cognitively healthy individuals, OH is associated with cognitive decline and an increased risk of dementia [3]. The prevalence of OH in patients with dementia is approximately two times higher than in adults without dementia [4]. OH might causally contribute to cognitive impairment through episodic decreases in cerebral perfusion, but the association could also reflect shared risk factors, such as hypertension, or reverse causation due to autonomic failure in patients with subclinical neurodegenerative disease [1].

Possible effects of OH on brain health may differ by various OH characteristics that affect cerebral perfusion [5,6]. Prior studies found that associations with cognitive decline differed both by magnitude (i.e. severity) [7–11] and duration of the orthostatic blood pressure drop (i.e. early versus delayed or prolonged drops after postural change) [12–14]. Delayed or prolonged OH, but not early OH, have been related to an increased risk of cognitive decline as compared with no OH [12–14]. Similarly, concomitant chronotropic incompetence (i.e. failure to sufficiently increase the heart rate) and the presence of orthostatic symptoms have been suggested to increase the risk of cognitive decline in some studies [11,15], but not in others [10,11,16]. As of yet, no published studies have combined these various aspects of OH in a single study.

Patients with conditions that by themselves may compromise cerebral hemodynamics could be more prone to develop clinical sequelae of OH. Patients with carotid occlusive disease (COD) or heart failure (HF) may experience difficulty maintaining adequate cerebral perfusion after a sudden decrease in blood pressure, presumably as a result of exhausted cerebral vasoreactivity [17,18]. There is only one study that has investigated the clinical sequelae of OH in these hemodynamically compromised patients [11].

We investigated different patterns and characteristics of OH and determined their association with cognition, white matter hyperintensity (WMH) volume and cerebral atrophy in patients with COD, patients with HF and healthy participants. We hypothesized that detrimental effects of OH are predominantly observed in situations with presumed increased or prolonged cerebral hypoperfusion.

2. Materials and methods

2.1. Study population

This study is part of the Heart-Brain Connection Study, which is a multicenter, prospective, observational study that aims to determine the relation between various cardiovascular and hemodynamic factors and cognitive impairment [19]. Participants were included between 2014 and 2019 in four university medical centers in The Netherlands. The cohort consists of 566 participants aged >50 years with a diagnosis of vascular cognitive impairment ($N = 166$), COD ($N = 109$) or HF ($N = 162$), as well as 129 reference participants without these conditions. All participants had to be independent in activities of daily life and were able to undergo neuropsychological assessment and magnetic resonance imaging (MRI) scanning. Individuals were excluded based on clinical evidence of a neurodegenerative disease other than vascular cognitive impairment or Alzheimer's disease.

For the present study, we included patients with COD or HF and reference participants who had undergone a complete OH measurement, neuropsychological assessment and brain MRI at baseline (Fig. 1).

Participants with COD had a complete occlusion of the internal carotid artery as visible with ultrasound, computed tomography angiography, MR angiography or digital subtraction angiography. HF was diagnosed according to the European Cardiology Society guidelines of 2016, irrespective of left ventricular ejection fraction [20], with a stable situation for at least 6 months. Reference participants were either spouses of patients or volunteers recruited through advertisements without a diagnosis of vascular cognitive impairment, COD or HF.

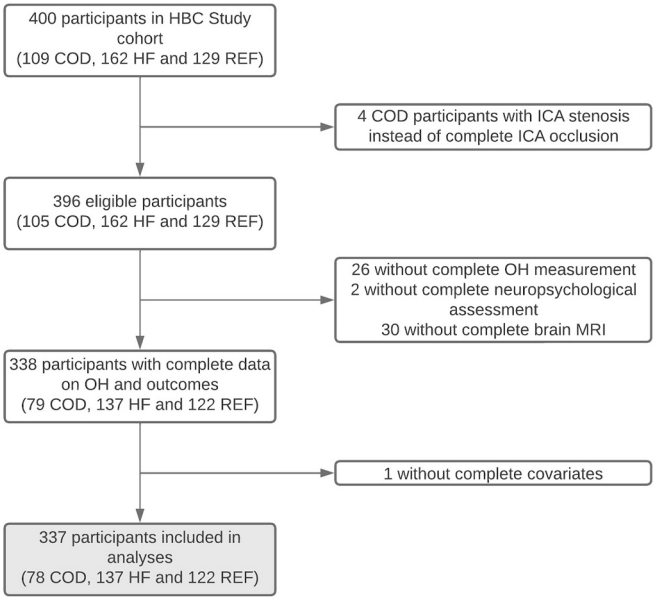

Fig. 1. Flowchart of the study inclusion. COD: carotid occlusive disease; HBC: Heart-Brain Connection; HF: heart failure; ICA: internal carotid artery; MRI: magnetic resonance imaging; OH: orthostatic hypotension; REF: reference participants.

2.2. Ethics statement

The Heart-Brain Connection Study was approved by the medical ethics committee of the Leiden University Medical Center, The Netherlands. Local medical ethics committees of the other sites approved the local implementation of the study. The study was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.3. Orthostatic hypotension measurement and symptoms

Blood pressures were measured during the baseline study visit with an electronic, automated sphygmomanometer. We asked the participants to sit in an upright position for five minutes, after which the blood pressure was measured on both the left and right arm. The cuff of the sphygmomanometer was then placed on the arm with the highest blood pressure. Next, the participants were instructed to lay in a supine position for five minutes, after which the blood pressure was measured once in the supine position. We subsequently asked the participants to immediately change from the supine to the upright standing position in which the researcher supported the arm at heart level. We then measured the blood pressure three times consecutively, approximately at 0 s, 45 s and 90 s after standing, in the upright standing position on the same arm. After these measurements, the participants were asked whether they experienced any complaints related to postural change (i.e. light-headedness, dizziness, blurred vision, or a near fall). These orthostatic symptoms during the OH measurement were classified as present or absent.

OH was defined as ≥20 mmHg decrease in systolic blood pressure (SBP) or ≥10 mmHg decrease in diastolic blood pressure (DBP) after standing in any of the measurements [2]. The change in SBP and DBP was calculated as the lowest blood pressure in the upright standing position minus the blood pressure in the supine position, to preserve the direction of the effect. This change in blood pressure was then categorized into mild OH (a decrease of 20–29 mmHg SBP or 10–14 mmHg DBP) or severe OH (a decrease of ≥30 mmHg SBP or ≥15 mmHg DBP).

The duration of OH was classified as either early OH when a participant only matched the criteria for OH immediately after changing from the supine to the upright standing position, or delayed or prolonged OH when a participant matched the criteria for OH at 45 or 90 s after standing, irrespective of the first measurement. The change in heart rate was calculated as the highest heart rate in the upright standing position minus the heart rate in the supine position. Chronotropic incompetence was defined as a heart rate response below the 25th percentile of the study population (heart rate increase of $\leq$7 beats/min).

2.4. Neuropsychological assessment

Participants underwent a standardized neuropsychological assessment that has been described previously [19]. Four major cognitive domains were assessed: memory (total immediate recall, delayed recall and recognition score of the Rey Auditory Verbal Learning Test and part A of the Visual Association Test) [21,22], language (Visual Association Test naming and 1-min animal fluency) [22–24], attention-psychomotor speed (Trail Making Test part A, mean of card I and II of the Stroop Color Word Test, Letter Digit Substitution Test, Digit Span forward) [25–28] and executive functioning (Trail Making Test B/A index, Stroop Color Word Test interference (card III / ((card I + card II) / 2)) and Digit Span backward) [25,26,28]. Individual cognitive test scores were converted into z-scores based on the scores of the reference participants. The z-scores for each cognitive domain were calculated as the average z-scores in that domain. The mean of these four domain scores represented the z-score for global cognitive function.

2.5. Brain imaging acquisition and processing

Brain MRI was performed on a 3 T Philips Ingenia, Philips Achieva or Philips Gemini scanner (Philips, Best, The Netherlands), consisting of T1-weighted images (resolution 1x1x1 mm^3, magnetization-prepared rapid acquisition gradient echo, repetition time 8.2 ms, echo time 4.5 ms, shot interval 3000 ms, flip angle 8°, inversion delay 990 ms) and fluid-attenuated inversion recovery images (FLAIR; resolution 1.11x1.11x1.11 mm^3, repetition time 4800 ms, echo time 313 ms, inversion time 1650 ms, turbo spin-echo factor 182) [19]. Brain infarcts were rated according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria [29]. Infarcts were subsequently manually segmented and masked out of the scans before further segmentation to increase the accuracy of the measured volumes. Total brain volume and WMH volume were then measured with a brain tissue and WMH segmentation method (Quantib BV, Rotterdam, The Netherlands), which was applied to the T1-weighted and FLAIR images [30]. WMH volumes were expressed as percentages of total intracranial volume. The brain parenchymal fraction, calculated by dividing the total brain volume by the total intracranial volume, was chosen as a measure for cerebral atrophy.

2.6. Medical history and cardiovascular risk factors

During a structured interview, the medical history, the presence of cardiovascular risk factors and the use of medication were recorded. Diabetes mellitus was defined as a self-reported history of diabetes or the use of antidiabetic drugs. We defined a history of cerebrovascular or cardiovascular disease, other than the diseases meant in the participant groups, by a self-reported history of ischemic stroke, transient ischemic attack, myocardial infarction or peripheral arterial disease. Body mass index was calculated with the length and weight that were measured during the baseline study visit. Baseline blood pressure was the mean of the two measurements in the seated position before performing the OH measurements.

2.7. Statistical analysis

Of all 338 eligible participants, 337 participants (99.7%) had complete data at baseline (Fig. 1). We proceeded with complete case analyses.

We computed natural log transformed WMH volumes to obtain a roughly normal distribution of the data. The brain parenchymal fraction did not require transformation. Both WMH volume and brain parenchymal fraction were subsequently standardized into z-scores to facilitate comparison, also with the z-scores for global cognitive functioning.

First, we determined the association between the presence of OH and global cognitive function with linear regression. In addition to crude associations, we adjusted in multivariable models for age, sex, years of education, seated SBP, use of blood pressure lowering medication and diabetes mellitus. Confounders were chosen based upon known associations in literature.

Next, we determined the associations between OH and WMH volume and between OH and the brain parenchymal fraction. Similar to the cognition models, we used multivariable linear regression adjusting for age, sex, seated SBP, use of blood pressure lowering medication and diabetes mellitus.

The analyses were then repeated after stratification for (1) participant group, i.e. COD, HF or reference participants, and (2) OH pattern and characteristics, i.e. severity and timing of blood pressure drops, presence of chronotropic incompetence and presence of orthostatic symptoms as described in the methods section on the OH measurement (subsection 2.3).

Finally, we conducted two sensitivity analyses. We repeated all analyses and adjusted for supine SBP instead of seated SBP to determine the potential impact of supine hypertension. We also repeated the analyses with the brain parenchymal fraction in participants without cortical infarcts to account for the potential influence of cortical infarcts on the measured brain parenchymal fraction.

A false discovery rate (FDR) correction was applied in the stratified analyses to account for multiple testing. We considered a FDR-corrected p-value <0.05 to be statistically significant. Analyses were performed using R version 4.0.3 (package ggplot2 3.3.5).

3. Results

Mean age of the 337 participants was 67.3 $\pm$ 8.8 years and 118 (35.0%) were female. Prevalence of OH was 33.5% in the overall population, higher in participants with COD (46.2%) and HF (33.6%) than in reference participants (25.4%). Baseline characteristics for the total sample as well as divided by OH status are displayed in Table 1 and characteristics according to participant group are displayed in Supplementary Table 1.

3.1. Cognitive functioning

Overall, the presence of OH was not significantly related to global cognitive function (adjusted β: −0.12, 95% confidence interval (CI): −0.24–0.00) (Table 2). Associations were larger in patients with COD and in reference participants than in patients with HF, but this difference was not statistically significant (p-interaction = 0.070) (Table 2). The attenuation after adjustment for confounders in the HF group was mostly caused by age.

Participants with severe OH did perform worse on cognitive assessment than participants without OH (adjusted β: −0.18, 95% CI: −0.34 to −0.02) (Fig. 2 and Supplementary Table 2). Participants with clinically manifest OH also had poorer cognitive function than participants without OH and without orthostatic symptoms (adjusted β: −0.30, 95% CI: −0.52 to −0.08), which remained significant after FDR-correction. There were no significant differences in cognition between early and delayed or prolonged OH, nor between the presence or absence of chronotropic incompetence.

Table 1
Baseline characteristics of the participants.

Characteristic	Entire cohort	With OH	Without OH
	N = 337	*N* = 113	*N* = 224
Female	118 (35.0)	31 (27.4)	87 (38.8)
Age, years	67.3 ± 8.8	68.8 ± 9.0	66.6 ± 8.6
Participant group			
Carotid occlusive disease	78 (23.1)	36 (31.9)	42 (18.8)
Heart failure	137 (40.7)	46 (40.7)	91 (40.6)
Reference participants	122 (36.2)	31 (27.4)	91 (40.6)
OH characteristics			
OH present	113 (33.5)	113 (100.0)	0 (0.0)
Decrease in SBP, mmHg	-12 (-20 – -4)	-24 (-30 – -20)	-8 (-13 – 0)
Decrease in DBP, mmHg	-3 (-7 – 2)	-10 (-13 – -4)	0 (-4 – 3)
Duration of OH			
Early OH	34 (10.1)	34 (30.1)	0 (0.0)
Delayed or prolonged OH	79 (23.4)	79 (69.9)	0 (0.0)
Increase in heart rate, beats/min	11 (7–16)	10 (7–17)	11 (7–16)
Orthostatic symptoms during the OH measurement	64 (19.0)	23 (20.4)	41 (18.3)
Vascular risk factors and medical history			
Current smoking	53 (15.7)	26 (23.0)	27 (12.1)
Seated SBP, mmHg	140.3 ± 19.8	144.6 ± 19.7	138.1 ± 19.4
Seated DBP, mmHg	79.3 ± 11.0	80.1 ± 11.6	78.8 ± 10.6
Supine SBP, mmHg	136.7 ± 19.6	144.8 ± 20.6	132.7 ± 17.8
Supine DBP, mmHg	77.9 ± 10.6	81.3 ± 11.6	76.3 ± 9.6
LDL-cholesterol, mmol/l	2.8 ± 1.0	2.8 ± 1.1	2.8 ± 1.0
Diabetes mellitus	53 (15.7)	25 (22.1)	28 (12.5)
Body mass index, kg/m^2	26.8 ± 4.0	26.8 ± 4.3	26.7 ± 3.8
History of cerebrovascular or cardiovascular disease	167 (49.6)	69 (61.1)	98 (43.8)
Medication			
Antihypertensive medication	228 (67.7)	82 (72.6)	146 (65.2)
Lipid lowering medication	186 (55.2)	73 (64.6)	113 (50.4)
Cognitive function			
MMSE, score	29 (28–30)	29 (27–30)	29 (28–30)
Global cognitive function, z-score	-0.20 (-0.64 – 0.15)	-0.35 (-0.82 – 0.05)	-0.13 (-0.56 – 0.19)
MRI characteristics			
Cortical infarcts	75 (22.3)	33 (29.2)	42 (18.8)
Subcortical infarcts	3 (0.9)	2 (1.8)	1 (0.4)
Lacunes	97 (28.8)	40 (35.4)	57 (25.4)
WMH volume, % of ICV	0.08 (0.03–0.22)	0.09 (0.03–0.33)	0.07 (0.02–0.17)
WMH Fazekas grade 2–3	82 (24.3)	36 (31.9)	46 (20.5)
Brain parenchymal fraction, ratio	0.79 ± 0.03	0.78 ± 0.04	0.79 ± 0.03

Data are presented as number (percentage) for categorical variables and mean ± standard deviation or median (interquartile range) for continuous variables.
DBP: diastolic blood pressure; ICV: intracranial volume; LDL: low-density lipoprotein; MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging; OH: orthostatic hypotension; SBP: systolic blood pressure; WMH: white matter hyperintensities.

3.2. WMH volume and brain parenchymal fraction

Presence of OH was significantly associated with a lower brain parenchymal fraction (adjusted β −0.26, 95% CI: −0.46 to −0.06), but not a higher WMH volume (adjusted β 0.07, 95% CI: −0.14–0.27) (Table 3). Numerically, associations were again stronger in COD and in reference participants than in those with HF, but differences were not significant (p-interaction = 0.657 for WMH volume, p-interaction = 0.079 for brain parenchymal fraction) (Table 3). The attenuation after adjustment for confounders in the HF group was mostly caused by age.

Similar to associations with cognition, severe OH and clinically manifest OH in particular were associated with a significantly lower brain parenchymal fraction (adjusted β −0.41, 95% CI: −0.68 to −0.14 for severe OH, adjusted β −0.40, 95% CI −0.77 to −0.03 for clinically manifest OH) (Fig. 2 and Supplementary Table 3–4). Participants with severe OH also tended to have a higher WMH volume (adjusted β 0.28, 95% CI: −0.00–0.56). Delayed or prolonged OH was associated with a significantly lower brain parenchymal fraction, but not higher WMH volume, as compared to no OH (adjusted β −0.30, 95% CI: −0.53 to −0.08). The differences in brain parenchymal fraction with OH severity and OH duration remained significant after FDR-correction. Concomitant chronotropic incompetence did not modify the association with WMH volume or brain parenchymal fraction.

3.3. Sensitivity analyses

Effect estimates remained similar when adjusting for supine SBP instead of seated SBP (Supplementary Table 5–7). Exclusion of 75 participants with cortical infarcts resulted in attenuation of the effect estimates for the associations with brain parenchymal fraction

Table 2
Associations between orthostatic hypotension and global cognitive function stratified by participant group.

	Sample size (N)	Crude β (95% CI)	Adjusted β (95% CI)[a]
Overall group	337	−0.23 (−0.37 to −0.08)	−0.12 (−0.24–0.00)
Carotid occlusive disease	78	−0.25 (−0.53–0.03)	−0.19 (−0.44–0.07)
Heart failure	137	−0.12 (−0.35–0.11)	0.02 (−0.18–0.22)
Reference participants	122	−0.15 (−0.36–0.06)	−0.14 (−0.31–0.04)

Associations were already non-significant before false discovery rate correction. False discovery rate correction was not applied in the overall group analyses.
[a] Adjusted for age, sex, years of education, seated systolic blood pressure, use of blood pressure lowering medication and diabetes mellitus.

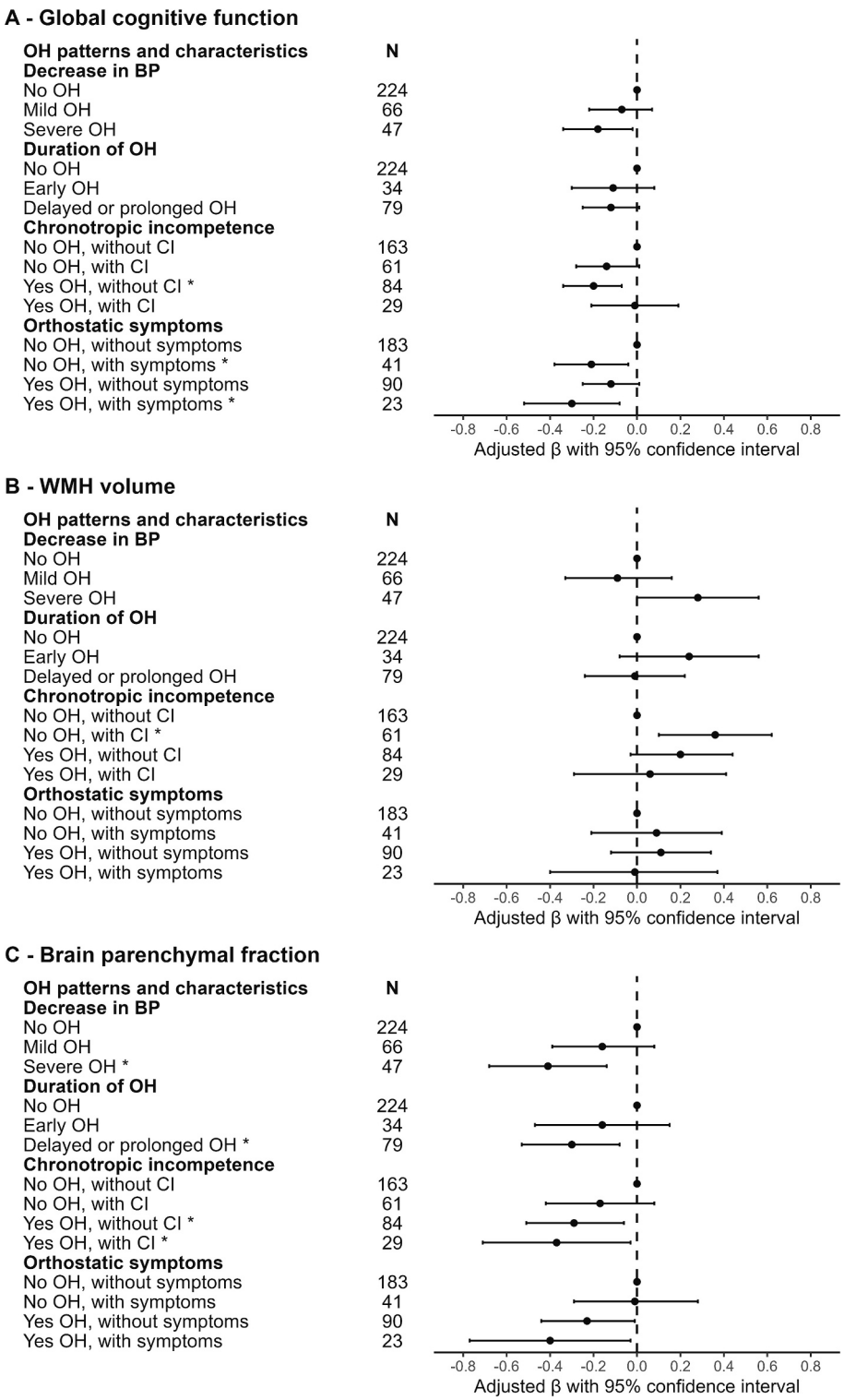

Fig. 2. Patterns and characteristics of orthostatic hypotension in relation to global cognitive function (A), white matter hyperintensity volume (B) and brain parenchymal fraction (C). Regression coefficients from the adjusted models are displayed. Mild OH: a decrease of 20–29 mmHg SBP or 10–14 mmHg DBP. Severe OH: a decrease of ≥30 mmHg SBP or ≥ 15mmHg DBP. Early OH: OH only immediately after standing. Delayed or prolonged OH: OH at 45 or 90 s after standing, irrespective of the first measurement. Chronotropic incompetence: heart rate increase ≤7 beats/min. * indicates $p < 0.05$ after false discovery rate correction. BP: blood pressure; CI: chronotropic incompetence; DBP: diastolic blood pressure; OH: orthostatic hypotension; SBP: systolic blood pressure; WMH: white matter hyperintensities.

(Supplementary Table 8). This was most pronounced within the COD group (adjusted β 0.09, 95% CI: −0.69–0.87), which also decreased in size to only 27 participants after exclusion of those with cortical infarcts.

4. Discussion

In this study, OH was overall not significantly associated with global cognitive function, similar for patients with COD and HF compared to

Table 3
Associations between orthostatic hypotension, white matter hyperintensity volume and brain parenchymal fraction stratified by participant group.

	Sample size (N)	Crude β (95% CI)	Adjusted β (95% CI)[a]
WMH volume			
Overall group	337	0.17 (−0.05–0.40)	0.07 (−0.14–0.27)
Carotid occlusive disease	78	0.16 (−0.28–0.59)	0.10 (−0.31–0.52)
Heart failure	137	0.16 (−0.19–0.51)	−0.04 (−0.35–0.28)
Reference participants	122	0.16 (−0.25–0.56)	0.06 (−0.33–0.44)
Brain parenchymal fraction			
Overall group	337	−0.43 (−0.65 to −0.21)	−0.26 (−0.46 to −0.06)
Carotid occlusive disease	78	−0.49 (−0.93 to −0.04)	−0.43 (−0.84 to −0.02)
Heart failure	137	−0.27 (−0.62–0.08)	−0.05 (−0.36–0.26)
Reference participants	122	−0.23 (−0.56–0.11)	−0.21 (−0.50–0.08)

None of the associations remained significant after false discovery rate correction. False discovery rate correction was not applied in the overall group analyses.
WMH: white matter hyperintensities.
[a] Adjusted for age, sex, seated systolic blood pressure, use of blood pressure lowering medication and diabetes mellitus.

reference participants. Yet, severe OH and clinically manifest OH were associated with worse cognitive function, both coinciding with a lower brain parenchymal fraction. Participants with severe OH also tended to have somewhat higher WMH volumes. Some of these associations were, however, no longer statistically significant after FDR-correction. These findings support the hypothesis that the association between OH and cognitive function may be most profound in situations with presumed increased or prolonged cerebral hypoperfusion.

Most longitudinal population based studies have linked the magnitude of the drops in blood pressure after postural change to incident dementia [7–11]. Although OH was overall not related to cognitive ability in our study, the observed association with more severe blood pressure drops is in line with prior evidence [7–11]. The importance of orthostatic symptoms along with OH remains debated. Symptoms like light-headedness upon standing, which could point towards a more severe orthostatic blood pressure drop, were found to be related to a worse cognitive function. In addition, even symptoms of OH without a relevant drop in blood pressure were related to a worse cognitive function in our study and in one earlier study [15], possibly reflecting a vulnerability to even the smallest blood pressure drops in some individuals. Two other studies found similar risk estimates for OH regardless of concurrent orthostatic symptoms [10,11]. More standardized enquiry about the timing and nature of such symptoms may help to resolve this clinically relevant question.

Of potential explanations for the association between OH and cognitive impairment, mediation by cerebral hypoperfusion and reverse causation due to autonomic dysfunction with neurodegenerative disease have received most attention [1]. Early orthostatic blood pressure drops in particular reduce cerebral perfusion [31], potentially leading to hypoxia, small vessel disease and neuronal injury. In support of this hypothesis, we observed a trend of higher WMH burden and a significantly lower brain parenchymal fraction in patients with severe OH. Severe OH has previously also been related to a lower total brain volume, predominantly driven by atrophy in the medial temporal regions, in both community based samples and in patients with Parkinson's disease or dementia with Lewy bodies [32–34]. However, four prior clinical and population based studies, including 68 to 2265 participants, did not find an association between severe OH and WMH volume [33,35–37]. Moreover, we did not observe clear differences between early and delayed or prolonged OH in our study, with respect to cognitive function or WMH. In contrast to early OH, delayed or prolonged OH and OH with chronotropic incompetence are more indicative of autonomic dysfunction and could therefore reflect reverse causation [5,6]. In our population with predominantly vascular pathology, these OH patterns did not specifically relate to cognition, but delayed or prolonged OH was associated with a lower brain parenchymal fraction, which might point to reverse causation due to subclinical neurodegeneration. Likewise, an earlier study in a memory clinic population also reported a strong association of delayed or prolonged OH with progression from mild cognitive impairment to dementia [13]. Yet, two population based studies, with a lower risk of reverse causation, also described delayed or prolonged OH as an unfavorable OH pattern in terms of cognitive decline [12,14]. Supplementary measurements of cerebral atrophy were unavailable in any of these studies. Notably, these studies monitored for OH during 2–3 min after postural change [12–14], whereas in our study blood pressure was measured three times in approximately 1.5 min. Standardization of the definition of delayed or prolonged OH may aid to harmonize future research efforts. Similarly, the definition of chronotropic incompetence varies substantially among published studies, potentially contributing to the contrasts in their results [10,11,16].

Insights in the physiology and pathophysiology of OH could benefit from studying the combination of different OH patterns and characteristics in larger, unselected samples. Using for instance cluster analyses to determine latent classes could establish comprehensive patterns of orthostatic blood pressure changes, which also encompass the different heart rate responses and presence of orthostatic symptoms, and their impact on the brain [14]. Additionally, larger samples provide the opportunity to investigate the notion that supine hypertension modifies the association between OH and structural and functional brain injury [38]. In particular when combined with continuous registration of cerebral blood flow during the entire OH measurement, such patterns could provide further insight into the physiological and pathophysiological mechanisms surrounding OH, in patients with and without supine hypertension.

Given the transient drops in cerebral blood flow with OH [1], we hypothesized effects of OH to be stronger in patients with HF or COD, who have more difficulty maintaining adequate cerebral perfusion, than in the reference group. A subgroup analysis of a population based study suggested that the association between OH and dementia risk may be more profound in individuals with HF than in those without HF [11]. We could not replicate this finding in our clinical population of patients with HF, nor did we find stronger associations between OH and cognition in patients with COD. No other published studies have reported on cognition in patients with COD and OH. Overall, even for severe OH associations with cognition were of small magnitude. The lack of profound effects in our patients with COD and HF may be due to compensatory mechanisms for decreases in blood pressure, such as collateral blood supply, or due to the use of blood pressure lowering medication. The participation of these relatively healthier patients with COD and HF may have led to selection bias and subsequently skewed results.

The main strength of our study is that we jointly investigated in a single study the most relevant OH patterns and characteristics among patients with detailed phenotyping along the heart-brain axis. Several limitations need to be taken into account also when interpreting our findings. First, the sample size was too small to investigate OH patterns and characteristics by participant group, although associations with the consensus definition of OH were not significantly different across the

participant groups. For severe OH and clinically manifest OH in particular, larger studies are needed to confirm or refute associations with cognitive function, WMH and cerebral atrophy. Second, blood pressure was measured three times consecutively rather than continuously or at fixed time points, which may have led to small differences in classification of early versus delayed or prolonged OH, compared to earlier studies. Third, the inclusion of relatively healthy participants with COD and HF may have introduced selection bias, which would lead most likely to attenuation of effect estimates in these groups. Finally, examining all the different OH patterns and characteristics might have increased the type I error rate, which we tried to mitigate by applying FDR-correction.

5. Conclusions

Overall, OH was not significantly associated with global cognitive function with similar associations in hemodynamically impaired patients and reference participants. Severe OH or clinically manifest OH could be more strongly associated with cognitive function, cerebral atrophy and WMH volume, but replication in larger cohorts is warranted. These findings support the hypothesis that the impact of OH on brain health may be most profound in situations with presumed increased or prolonged cerebral hypoperfusion.

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CRediT authorship contribution statement

Naomi L.P. Starmans: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Frank J. Wolters:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Anna E. Leeuwis:** Writing – review & editing, Investigation. **Esther E. Bron:** Writing – review & editing, Data curation. **Jeroen de Bresser:** Writing – review & editing, Data curation. **Hans-Peter Brunner-La Rocca:** Writing – review & editing, Investigation. **Julie Staals:** Writing – review & editing, Investigation. **Majon Muller:** Writing – review & editing, Investigation. **Geert Jan Biessels:** Writing – review & editing, Supervision, Investigation, Conceptualization. **L. Jaap Kappelle:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization.

Declaration of competing interest

None.

Data availability

The data used in preparation of this manuscript is available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.123026.

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