ORIGINAL ARTICLE

Orthostatic hypotension as a risk factor for longitudinal deterioration of cognitive function in the elderly

M. Zimmermann[a,b], I. Wurster[a,b], S. Lerche[a,b], B. Roeben[a,b], G. Machetanz[a,b], U. Sünkel[a], A.-K. von Thaler[a], G. Eschweiler[b,c], A. J. Fallgatter[b,c], W. Maetzler[d], D. Berg[d] and K. Brockmann[a,b]

[a]*Center of Neurology, Department of Neurodegeneration and Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen;* [b]*German Center for Neurodegenerative Diseases (DZNE), University of Tübingen, Tübingen;* [c]*Department of Psychiatry, University of Tübingen, Tübingen; and* [d]*Department of Neurology, Christian-Albrechts-University of Kiel, Kiel, Germany*

Keywords:
aging, cognitive function, dementia, orthostatic hypotension

Received 31 January 2019
Accepted 22 July 2019

European Journal of Neurology 2020, **27:** 160–167

doi:10.1111/ene.14050

Background and purpose: Orthostatic hypotension is frequent with aging with a prevalence of 20%–30% in people aged 65 or older and is considered to increase the risk for coronary events, strokes and dementia. Our objective was to characterize the association of orthostatic hypotension and cognitive function longitudinally over 6 years in a large cohort of the elderly aged over 50 years.

Methods: In all, 495 participants were assessed longitudinally with the Schellong test and comprehensive cognitive testing using the extended CERAD neuropsychological test battery at baseline and after 6 years. In a subgroup of 92 participants, cerebral magnetic resonance imaging was evaluated for white matter changes using a modified version of the Fazekas score.

Results: The prevalence of orthostatic hypotension increases with aging reaching up to 30% in participants aged >70 years. Participants with orthostatic hypotension presented with a higher vascular burden index (1.03 vs. 0.69, $P \leq 0.001$), tended to have a higher prevalence of cerebral white matter hyperintensities (91.7% vs. 68.8%, $P = 0.091$) and showed a faster deterioration in executive and memory function (Trail Making Test B 95 vs. 87 s, $P \leq 0.001$; word list learning sum −0.53 vs. 0.38, $P = 0.002$) compared to participants without orthostatic hypotension.

Conclusion: Orthostatic hypotension seems to be associated with cognitive decline longitudinally.

Introduction

Orthostatic hypotension (OH) is defined as a reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 min of standing [1]. The prevalence of OH increases with aging [2] with about 20%–30% of people aged 65 or older being affected [3]. Reasons for OH are, amongst others, a reduced baroreceptor sensitivity, a reduced activity of the sympathetic nervous system [4], aortic stiffness [5] and cardiovascular diseases or other conditions causing a decrease in cardiac output. Several studies report a bidirectional interaction of OH with multimorbidity in elderly people comprising hypertension, coronary heart disease and a higher risk for strokes [6], promoting cognitive dysfunction, falls and all-cause mortality [7–9]. The effect of OH on cognitive function remains contradictory in the literature depending on the age group, test battery (screening tool versus comprehensive multi-domain testing), covariates and study design. Several cross-sectional studies showed either no association with global cognitive function [3,10,11] or a significant association in terms of global cognitive decline [2,4,12–14]. In a long-term analysis of the Rotterdam study, Wolters *et al.* reported a higher risk of Alzheimer's disease and vascular dementia in participants with OH [15].

Correspondence: M. Zimmermann, Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen, Hoppe Seyler-Strasse 3, 72076 Tübingen, Germany (tel.: +49-7071-2980172; fax: +49-7071-294617; e-mail: milan.zimmermann@med.uni-tuebingen.de).

EUROPEAN JOURNAL OF NEUROLOGY

The pathogenic model of the interaction between OH and cognitive decline highlights episodes of cerebral hypoperfusion during orthostatic reactions [2], especially in interaction with an impaired autoregulation [4], causing cerebral small vessel disease [16] mainly in subcortical, frontal and prefrontal areas. Thus, it is to be expected that alertness, the ability to concentrate and executive function in particular are affected in patients with OH [17]. Following this concept, the aim was to evaluate the impact of OH on all domains of cognitive function over time in interaction with aging and cardiovascular risk profiles in a longitudinal study of the elderly aged over 50 in a 6-year interval.

Methods

Study population

The TREND study (Tübingen Risk Evaluation for Neurodegenerative Diseases) is a prospective longitudinal study initiated in 2009 with biennial assessments of elderly participants aged between 50 and 80 years without neurodegenerative diseases.

The study was performed at the Department of Neurology and the Department of Psychiatry of the University Hospital Tübingen, Germany. A large assessment battery with mainly quantitative, unobtrusive measurements for repeated objective application was designed. For more details about the TREND study see https://www.trend-studie.de/. Study data were collected and managed using REDCap electronic data capture tools hosted at University of Tübingen [18].

Cohorts for the present analysis

Overall cohort. Only the subgroup of 495 participants who fully completed longitudinal assessments over 6 years were included in the present analyses.

Orthostatic function was assessed using the Schellong test with repeated blood pressure measurements during lying and at 30, 90, 150 and 210 s of active standing. The maximum change in blood pressure at one of the active standing time points was used for the definition of OH. OH was defined as a decrease of more than 20 mmHg in systolic and/or more than 10 mmHg in diastolic blood pressure [19].

Cognitive function was tested using the standardized German version of the extended CERAD-Plus neuropsychological battery [20]. The battery contains the following subtests: semantic and phonematic verbal fluency tasks, Boston Naming Test, Mini Mental State Examination, word list learning, word list recall, word list recognition, figure drawing, figure recall and the Trail Making Tests A and B. The subtests of the CERAD-Plus battery were grouped into four domains: executive function, memory, language and visuospatial abilities.

Nested cohort. To directly overcome the effect of age and sex and evaluate whether results from the overall cohort analyses remain robust a matching approach (nested cohort) was performed to make sure that OH is independently associated with cognitive decline. For the nested cohort 1:1 matching was performed ($n = 86$) with identical means in age at examination (64.26 years) and sex (female 50%). Of 87 participants with OH (OH+ participants), only 86 participants could be matched with 86 participants without OH (OH− participants) as there was no matching partner for the 87th OH+ participant identical in age and sex.

Magnetic resonance imaging cohort. In a subgroup of 92 participants (OH+ $n = 12$; OH− $n = 80$), cerebral 3 T magnetic resonance imaging (MRI) was performed between 2005 and 2017. MRI acquisition was recommended and performed as medical routine during follow-up for the following reasons: headache, dizziness, subjective memory impairment.

T2 or fluid attenuated inversion recovery weighted images were officially evaluated by a trained radiologist and rated according to Fazekas [21] by a neurologist trained in the interpretation of MRI scans. There was just one rater. We used the grading for white matter hyperintensities according to Prins and Scheltens [22]: Fazekas 0, no white matter hyperintensities; Fazekas 1, focal or punctuate lesions (single lesions ≤9 mm or grouped lesions <20 mm); Fazekas 2, beginning confluent lesions (single lesions 10–20 mm, grouped lesions >20 mm in any diameter, no more than connecting bridges between individual lesions); Fazekas 3, confluent lesion (single lesions or confluent areas of hyperintensity ≥20 mm in any diameter).

Statistics

IBM® SPSS® 22.0 software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM corp) was used for statistical analysis. For cognitive variables, Δ values between baseline and follow-up after 6 years were calculated in order to assess changes over time.

Overall cohort

To compare cognitive-associated longitudinal Δ values between OH+ participants versus OH− participants ANCOVA was used with the covariates age, years of education, sex and the cardiovascular risk factors hypertension, arteriosclerosis, diabetes mellitus, smoking (pack years ≥ 15) and obesity (body mass index ≥ 30), which were assessed in a structured interview. A vascular burden index defined as the sum of

these cardiovascular risk factors was calculated [23]. The prevalence of mild cognitive impairment (MCI) between OH+ and OH− participants was also compared using the chi-squared test. In this context, MCI was categorized into amnestic MCI single and multiple domain as well as non-amnestic MCI single and multiple domain [24]. The non-amnestic MCI included the domains language (phonematic and semantic verbal fluency, Boston Naming Test), executive function (Trail Making Test B) and visuospatial abilities (figure drawing). The amnestic MCI included the memory domain (word list recall, figure recall). For the definition of MCI, standard deviations of −1 as well as −1.5 were explored.

Nested cohort

To compare cognitive-associated longitudinal Δ values between OH+ versus OH− participants the non-parametric Mann–Whitney *U* test was used.

MRI cohort

The age at baseline examination between OH+ and OH− participants was compared using the non-parametric Mann–Whitney *U* test. For comparison of the vascular burden index between the two groups, univariate analysis of variance was used. The prevalence of white matter hyperintensities grading 0–3 according to the revised Fazekas score by Prins and Scheltens was compared using the chi-squared test. Multivariate regression analysis including age, sex, years of education, OH status, Δ systolic and diastolic blood pressure, baseline CERAD sum score, Beck Depression Inventory score, cardiovascular risk factors and Fazekas grading (Fazekas grading 0 or 1 = 0, Fazekas grading 2 or 3 = 1) was performed to evaluate the association with cognitive function over time measured by the Δ CERAD sum score.

Results

Orthostatic hypotension and age

Eighty-seven participants of the cohort of 495 (17.6%) presented with OH at baseline with an increase of prevalence with aging (age group 51–55 years 9.8%, 56–60 years 16.9%, 61–65 years 17.2%, 66–70 years 17.3%, 71–75 years 28.1%, 76–80 years 30.8%) (Fig. 1). Consequently, the OH+ cohort was older than the OH− cohort (OH+ 64.4 years, OH− 62.4 years, $P = 0.015$). There were no significant differences in sex and years of education.

Orthostatic hypotension and cognitive function

Overall cohort

Compared to the OH− cohort, the OH+ cohort presented with worse cognitive performance measured by higher Δ values between baseline and follow-up in the overall CERAD sum score ($P \leq 0.001$) (Fig. 2) as well as in the executive function and memory domains. For single test results per domain and per time point see Table 1.

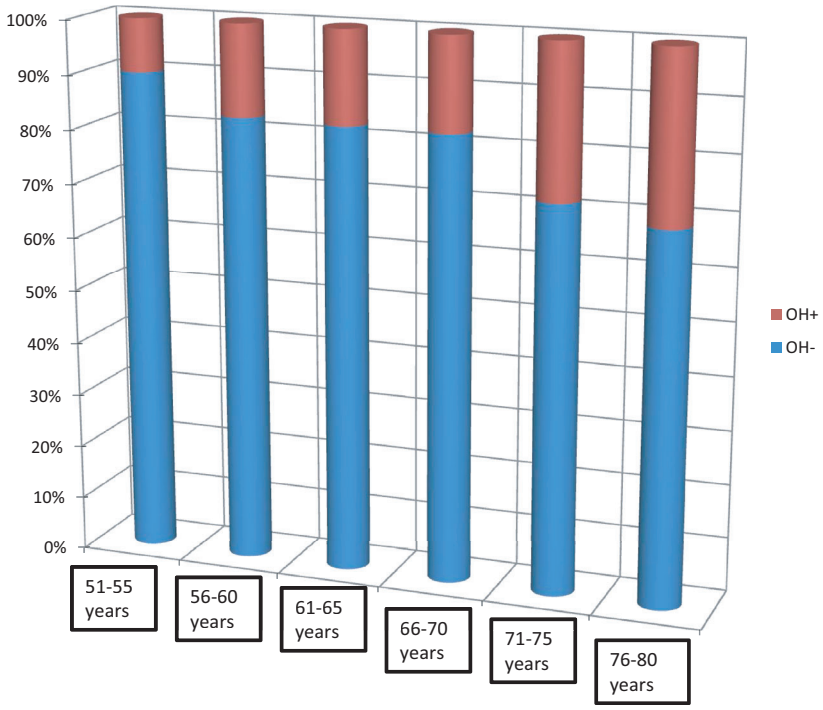

Figure 1 Prevalence of orthostatic hypotension stratified by age in the overall cohort. [Colour figure can be viewed at wileyonlinelibrary.com]

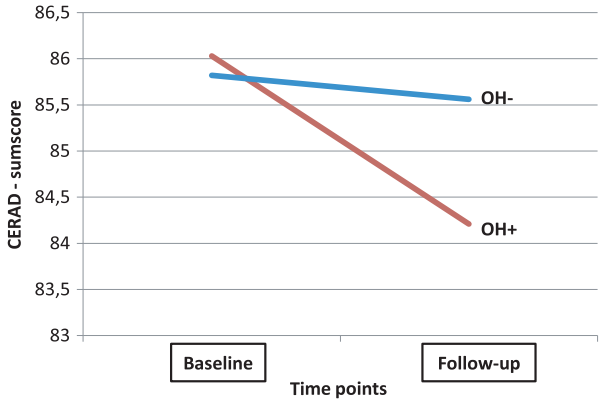

Figure 2 Deterioration of cognitive function of OH+ participants versus OH− participants in the CERAD sum score. [Colour figure can be viewed at wileyonlinelibrary.com]

Linear regression analysis revealed Δ systolic blood pressure and male sex to be associated with worse Δ values of the CERAD sum score (Table S1). There were no significant differences between the prevalence of MCI at follow-up examination between OH+ and OH− (Table S2).

Nested cohort

Participants with OH presented with worse cognitive performance between baseline and follow-up in the domain memory function (word list learning 2, $P = 0.001$; word list learning sum, $P = 0.021$; figure recall sum, $P = 0.039$) as measured by higher Δ values.

Factors associated with orthostatic hypotension

Overall cohort

Participants with OH presented with a higher vascular burden index (OH+ 1.03, OH− 0.69, $P \leq 0.001$) and a

Table 1 Results of cognitive testing amongst participants of the overall cohort with (OH+) and without (OH−) orthostatic hypotension over the 6-year interval

	OH+ (n = 87)		OH− (n = 408)			Δ-baseline – follow-up		
	Baseline	Follow-up	Baseline	Follow-up	P value baseline	OH+	OH−	P value Δ
Age at time point (years)	64	70	62	68	**0.015**	–	–	–
Sex (male)	51.%		46%		0.259	–	–	–
Years of education	14		15		0.400	–	–	–
CERAD sum score	86.03	84.21	85.82	85.56	**≤0.001**	−1.83	−0.25	**≤0.001**
MMSE	28.91	28.41	28.88	28.56	**≤0.001**	−0.49	−0.33	0.169
Memory								
Word list learning 1	5.55	5.62	5.58	5.83	**≤0.001**	0.07	0.26	**0.014**
Word list learning 2	7.59	7.17	7.37	7.53	**≤0.001**	−0.41	0.16	**0.031**
Word list learning 3	8.44	8.25	8.50	8.45	**≤0.001**	−0.18	−0.04	0.107
Word list learning sum	21.57	21.05	21.44	21.81	**≤0.001**	−0.53	0.38	**0.002**
Word list intrusion sum	0.54	0.60	0.48	0.62	**0.043**	0.06	0.14	0.919
Word list recall	7.56	7.33	7.69	7.57	**≤0.001**	−0.23	−0.12	**0.014**
Word list recall intrusion	0.17	0.24	0.16	0.21	0.198	0.07	0.05	0.936
Word list recognition correct yes	9.78	9.75	9.82	9.77	0.080	−0.03	−0.04	0.133
Word list recognition correct no	9.98	9.79	9.97	10.13	0.117	−0.18	0.16	0.499
Word list discriminability	98.79	97.70	98.96	98.33	0.074	−1.09	−0.59	**0.002**
Figure recall sum	9.57	9.14	9.36	9.40	**≤0.001**	−0.44	0.04	0.244
Visuospatial abilities								
Figure drawing sum	10.31	10.15	10.36	10.28	**0.009**	−0.16	−0.08	0.924
Language								
Phonematic verbal fluency	19.05	15.50	18.49	14.98	**≤0.001**	−3.22	−3.58	0.507
Semantic verbal fluency	25.38	24.25	24.94	23.97	**≤0.001**	−1.13	−0.91	0.703
Boston naming test	14.52	14.53	14.63	14.54	**≤0.001**	0.01	−0.09	0.692
Executive function								
Trail making test A	37.69	40.35	35.38	37.50	**≤0.001**	2.65	2.17	**0.006**
Trail making test B	94.35	95.17	83.97	86.54	**≤0.001**	0.82	3.33	**≤0.001**
Trail making test B – A	56.65	54.82	48.65	48.52	**≤0.001**	−1.83	0.82	**0.040**
Trail making test B:A	2.69	2.44	2.48	2.38	**0.043**	−0.25	−0.10	0.753
Neuropsychiatric symptoms								
Beck Depression Inventory	7.89	6.52	7.33	6.70	0.590	−1.36	−0.62	0.352

MMSE, Mini Mental State Examination. For comparison of baseline and Δ values, ANCOVA with the covariates age, years of education, sex and the cardiovascular risk factors hypertension, arteriosclerosis, diabetes mellitus, smoking and obesity was used. Dichotomous data were compared by chi-squared test. Data are given as mean values. *P*-values in bold represent significant differences.

higher prevalence of hypertension (OH+ 51.7%, OH− 34.3%, $P = 0.003$) and obesity (OH+ 19.5%, OH− 9.3%, $P = 0.009$). Moreover, OH+ participants were more likely to take antihypertensive medication (OH+ 59.8%, OH− 40.9%, $P = 0.001$), namely beta-receptor blockers (OH+ 27.6%, OH− 18.2%, $P = 0.036$), AT1-receptor antagonists (OH+ 32.2%, OH− 18.7%, $P = 0.005$) and calcium antagonists (OH+ 14.9%, OH− 7.5%, $P = 0.027$). OH+ participants also had a higher prevalence of intake of platelet inhibitors (OH+ 28.7%, OH− 19.0%, $P = 0.032$). Details are provided in Table 2.

Table 2 Factors associated with orthostatic hypotension in the overall cohort

	OH+	OH−	*P* value
Anticoagulation	6/87 (6.9%)	21/401 (5.2%)	0.345
Platelet inhibition	25/87 (28.7%)	76/401 (19%)	**0.032**
Antihypertensive medication	52/87 (59.8%)	164/401 (40.9%)	**0.001**
Beta-receptor blockers	24/87 (27.6%)	73/401 (18.2%)	**0.036**
ACE inhibitors	18/87 (20.7%)	53/401 (13.2%)	0.056
AT1-receptor antagonists	28/87 (32.2%)	75/401 (18.7%)	**0.005**
Calcium antagonists	13/87 (14.9%)	30/401 (7.5%)	**0.027**
Vasodilators	2/87 (2.3%)	0/401 (0%)	**0.031**
Medication for diabetes	6/87 (6.9%)	20/401 (5%)	0.310
Sum of antihypertensive medication (mean)	1.21	0.71	**≤0.001**
Antidepressant medication	16/87 (18.4%)	50/401 (12.5%)	0.101
Benzodiazepines	0/87 (0%)	6/401 (1.5%)	0.306
Z-drugs	2/87 (2.3%)	6/401 (1.5%)	0.432
Hypertension	45/87 (51.7%)	140/401 (34.3%)	**0.003**
Pack years ≥ 15 years	14/87 (16.1%)	56/387 (13.7%)	0.389
Diabetes	7/87 (8.0%)	20/401 (4.9%)	0.188
Atherosclerosis	7/87 (8.0%)	22/401 (5.4%)	0.245
Obesity	17/87 (19.5%)	38/400 (9.3%)	**0.009**
Vascular burden index (mean)	1.03	0.69	**≤0.001**

For comparison of vascular burden index between OH+ and OH− participants, ANCOVA with the covariates age, years of education and sex was used. Dichotomous data assessing frequencies were compared by chi-squared test. *P*-values in bold represent significant differences.

Nested cohort

Findings from the overall cohort could partly be confirmed in the nested cohort with a higher intake of AT1-receptor antagonists (OH+ 35.0%, OH− 20.6%, $P = 0.014$). There were no significant differences concerning the vascular burden index (OH+ 1.03, OH− 0.74, $P = 0.085$) and the cardiovascular risk factors.

White matter hyperintensities in cerebral MRI

In the MRI subgroup OH+ and OH− participants were similar in age (OH+ 63.9 years, OH− 62.9 years, $P = 0.880$) and in vascular burden index (OH+ 0.7, OH− 0.8, $P = 0.656$). The prevalence of white matter hyperintensities tended to be higher in OH+ (91.7%) compared to OH− (68.8%) ($P = 0.091$). Specifically, OH+ participants showed less Fazekas 0 scoring whilst the prevalence of Fazekas 1 and 2 scoring was higher compared to the OH− group: Fazekas 0, OH+ 8.3%, OH− 31.3%; Fazekas 1, OH+ 50%, OH− 42.5%; Fazekas 2, OH+ 41.7%, OH− 22.5%; Fazekas 3, OH+ 0%, OH− 3.8%) (Fig. 3).

Regression analysis revealed no association between white matter hyperintensities as assessed by Fazekas scoring with cognitive function over time measured by Δ CERAD scores (beta 0.084, $P = 0.458$).

Discussion

By evaluating OH in relation to cognitive function over time in interaction with aging and cardiovascular risk profiles in a longitudinal study of elderly subjects aged over 50 years it was found that (i) the prevalence of OH increases with aging reaching up to 30% in participants aged >70 years; (ii) OH+ participants present with a higher vascular burden index and higher prevalence of cerebral white matter hyperintensities; and (iii) OH+ participants, especially those with large variability in systolic blood pressure, seem to show a faster deterioration of cognitive function, especially in the executive and memory domains. Further evidence supporting our finding comes from the large Hypertension in the Very Elderly Trial (HYVET) cohort. The cohort consisted of 3121 participants of whom 538 were classified as OH+ and presented with increased risk of cognitive impairment assessed by the Mini Mental State Examination and/or a diagnosis of dementia according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [25]. In a long-term analysis of the Rotterdam study, Wolters *et al.* reported a higher risk of Alzheimer's disease and vascular dementia in participants with OH after 15 years [15]. Interestingly, the risk of both entities was comparable. Unfortunately, no information on the

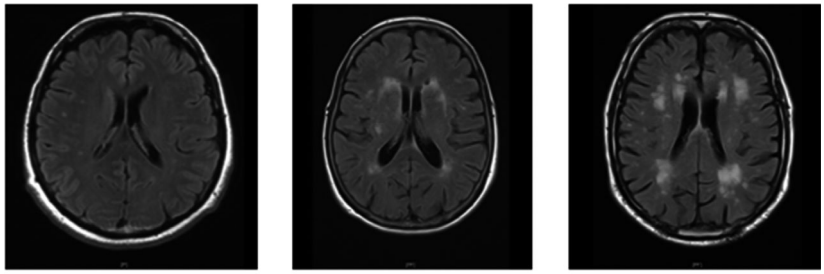

Figure 3 Examples of white matter hyperintensities grading 1–3 according to the revised Fazekas score by Prins and Scheltens in our MRI cohort.

predominantly involved cognitive domains before and at the time of diagnosis has been reported. Whether the amnestic domain (Alzheimer's disease) and executive dysfunction (vascular dementia) were to be found might be conjectured. Although conversion to a manifest disease stage was not observed in our cohort, it was shown that those two domains (amnestic, executive) in particular were impaired. A longer follow-up of our cohort is needed to detect conversion to manifest disease stages. Of note and similar to our analysis a large variability in systolic blood pressure was reported as the most significant determinant of OH [15].

The age-related prevalence of OH with up to 30% in subjects older than 70 years observed in our study is in line with the literature [2,3]. Interestingly, current concepts focus on a bidirectional interaction of OH with multimorbidity in elderly people comprising hypertension, coronary heart disease and a higher risk for strokes [6], promoting cognitive dysfunction, falls and mortality [7–9]. Indeed, participants with OH in the present study showed more pronounced cardiovascular risk profiles and a higher prevalence of white matter hyperintensities in cerebral MRI [26]. Remarkably, some of the factors such as body mass index, hypertension and/or respective antihypertensive medication, diabetes and smoking can potentially be influenced by lifestyle and should be part of medical counseling not only in the context of cardiovascular diseases but also in terms of cognitive function. In this line of evidence, a recent analysis reported bolus water drinking, physical counter maneuvers and abdominal compression to be effective non-pharmacological treatment options in the elderly with OH [27].

The strength of the study is the longitudinal design including a comprehensive cognitive test battery assessing all cognitive domains in detail.

The limitations of the present study comprise the small sample size especially with regard to the MRI cohort and the visual rating of MRI by just one blinded rater as well as the fact that the MRIs were not generated at one time point.

Taken together, the hypothesis of an association between cardiovascular risk profiles, OH and cognitive decline could be further supported in a large cohort of the elderly over a period of 6 years. Knowledge of such circuits offers windows for medical counseling where lifestyle factors that could potentially be influenced should be addressed.

Acknowledgements

No specific funding was received for the TREND study.

Disclosure of conflicts of interest

Dr Berg has served on scientific advisory boards for UCB/Schwarz Pharma, Lundbeck, Biogen and BIAL; has received funding for travel or speaker honoraria from Lundbeck Inc., Novartis, UCB/Schwarz Pharma, Merck Serono, Biogen, Zambon, AbbVie and BIAL; and has received research support from Janssen, Teva Pharmaceutical Industries Ltd, Solvay Pharmaceuticals Inc./Abbott, Boehringer, UCB, Michael J. Fox Foundation, BMBF, dPV (German Parkinson's disease association), Neuroallianz, DZNE, Center of Integrative Neurosciences and the Damp Foundation. Dr Brockmann has received a research grant from the University of Tübingen (Clinician Scientist) and the German Society of Parkinson's disease (dpv), funding from the Michael J. Fox Foundation and the German Centre for Neurodegenerative Diseases (DZNE, MIGAP), travel grants from the Movement Disorders Society and speaker honoraria from Abbvie, Lundbeck, UCB and Zambon. Dr Eschweiler received research grants from the Innovationsfonds of the Gemeinsamer Bundesausschuss in Germany, the German Ministry for Research and Education and the European Union. Dr Fallgatter received research grants from the German Research Foundation, the German Ministry for Research and Education and the European Union. Gerrit Machetanz receives funding from the Michael J. Fox Foundation. Dr Maetzler

receives or received funding from the European Union, the Michael J. Fox Foundation, Robert Bosch Foundation, Neuroalliance, Lundbeck and Janssen, and holds part of a patent for the assessment of dyskinesias (German patent office, 102015220741.2). He received speaker honoraria from GlaxoSmithKline, Abbvie, Bayer, UCB, Licher MT and Rölke Pharma, and was invited to Advisory Boards of Lundbeck, Market Access & Pricing Strategy GmbH, Abbvie and Biogen. He is co-chair of the MDS Technology Task Force. Dr Zimmermann, Dr Wurster, Dr von Thaler, Ulrike Sünkel and Dr Lerche have nothing to disclose.

Ethics

The study was approved by the Ethics Committee of the Faculty of Medicine at the University of Tübingen, and all participants gave written informed consent.

Data availability statement

Anonymized data can be shared upon request.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Factors associated with cognitive function over time.
Table S2. Prevalence of mild cognitive impairment.

References

1. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology* 1996; **46:** 1470.
2. O'Hare C, McCrory C, O'Connell MD, Kenny RA. Sub-clinical orthostatic hypotension is associated with greater subjective memory impairment in older adults. *Int J Geriatr Psychiatry* 2017; **32:** 429–438.
3. Curreri C, Giantin V, Veronese N, *et al*. Orthostatic changes in blood pressure and cognitive status in the elderly: the Progetto Veneto Anziani study. *Hypertension* 2016; **68:** 427–435.
4. Mehrabian S, Duron E, Labouree F, *et al*. Relationship between orthostatic hypotension and cognitive impairment in the elderly. *J Neurol Sci* 2010; **299:** 45–48.
5. Cooper LL, Himali JJ, Torjesen A, *et al*. Inter-relations of orthostatic blood pressure change, aortic stiffness, and brain structure and function in young adults. *J Am Heart Assoc* 2017; **6**.
6. Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987–1996. *Stroke* 2000; **31:** 2307–2313.
7. Rose KM, Eigenbrodt ML, Biga RL, *et al*. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2006; **114:** 630–636.
8. Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (the Malmo Preventive Project). *Eur Heart J* 2010; **31:** 85–91.
9. Finucane C, O'Connell MD, Donoghue O, Richardson K, Savva GM, Kenny RA. Impaired orthostatic blood pressure recovery is associated with unexplained and injurious falls. *J Am Geriatr Soc* 2017; **65:** 474–482.
10. Foster-Dingley JC, Moonen JEF, de Ruijter W, van der Mast RC, van der Grond J. Orthostatic hypotension in older persons is not associated with cognitive functioning, features of cerebral damage or cerebral blood flow. *J Hypertens* 2018; **36:** 1201–1206.
11. Kuo HK, Jones RN, Milberg WP, *et al*. Effect of blood pressure and diabetes mellitus on cognitive and physical functions in older adults: a longitudinal analysis of the advanced cognitive training for independent and vital elderly cohort. *J Am Geriatr Soc* 2005; **53:** 1154–1161.
12. Bocti C, Pepin F, Tetreault M, *et al*. Orthostatic hypotension associated with executive dysfunction in mild cognitive impairment. *J Neurol Sci* 2017; **382:** 79–83.
13. McNicholas T, Tobin K, Carey D, O'Callaghan S, Kenny RA. Is baseline orthostatic hypotension associated with a decline in global cognitive performance at 4-year follow-up? Data from TILDA (the Irish Longitudinal Study on Ageing). *J Am Heart Assoc* 2018; **7:** e008976.
14. Rawlings AM, Juraschek SP, Heiss G, *et al*. Association of orthostatic hypotension with incident dementia, stroke, and cognitive decline. *Neurology* 2018; **91:** e759–e768.
15. Wolters FJ, Mattace-Raso FU, Koudstaal PJ, Hofman A, Ikram MA, Heart Brain Connection Collaborative Research Group. Orthostatic hypotension and the long-term risk of dementia: a population-based study. *PLoS Med* 2016; **13:** e1002143.
16. Rose KM, Couper D, Eigenbrodt ML, Mosley TH, Sharrett AR, Gottesman RF. Orthostatic hypotension and cognitive function: the Atherosclerosis Risk in Communities Study. *Neuroepidemiology* 2010; **34:** 1–7.
17. Bendini C, Angelini A, Salsi F, *et al*. Relation of neurocardiovascular instability to cognitive, emotional and functional domains. *Arch Gerontol Geriatr* 2007; **44** (Suppl. 1)**:** 69–74.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42:** 377–381.
19. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *J Neurol Sci* 1996; **144:** 218–219.
20. Welsh-Bohmer KA, Mohs RC. Neuropsychological assessment of Alzheimer's disease. *Neurology* 1997; **49**(3 Suppl. 3)**:** S11–S13.

21. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* 1987; **149:** 351–356.
22. Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol* 2015; **11:** 157–165.
23. Heinzel S, Liepelt-Scarfone I, Roeben B, *et al*. A neurodegenerative vascular burden index and the impact on cognition. *Front Aging Neurosci* 2014; **6:** 161.
24. Roberts RO, Geda YE, Knopman DS, *et al*. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology* 2008; **30:** 58–69.
25. Peters R, Anstey KJ, Booth A, *et al*. Orthostatic hypotension and symptomatic subclinical orthostatic hypotension increase risk of cognitive impairment: an integrated evidence review and analysis of a large older adult hypertensive cohort. *Eur Heart J* 2018; **39:** 3135–3143.
26. Longstreth WT Jr, Manolio TA, Arnold A, *et al*. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke* 1996; **27:** 1274–1282.
27. Newton JL, Frith J. The efficacy of nonpharmacologic intervention for orthostatic hypotension associated with aging. *Neurology* 2018; **91:** e652–e656.