

Periventricular rather than deep white matter hyperintensities mediate effects of hypertension on cognitive performance in the population-based 1000BRAINS study

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Objectives: White matter hyperintensities (WMH) of presumed vascular origin are frequent in cerebral MRI of older people. They represent a sign of small vessel disease, are promoted by arterial hypertension, and relate to cognitive deficits. The interdependence of blood pressure and its treatment, WMH, and cognitive performance has not systematically been studied in population-based studies.

Methods: Consequently, we analysed the interdependence of SBP, DBP, and antihypertensive medications, as well as BP/treatment category, with WMH and cognitive performance in 560 participants of the population-based 1000BRAINS study.

Results: BP, its treatment, and BP/treatment category were moderately associated with cognitive performance (e.g. unadjusted $\beta = -0.10$, 95%CI = -0.19 to -0.02 for the association of SBP (per standard deviation of 17.2 mmHg) with global cognition (per standard deviation of 0.5 z score)). The harmful effect of BP on cognition was strongly mediated by periventricular hyperintensities (PVH), which were significantly associated with both SBP ($\beta = 0.24$, 95% CI = 0.14 – 0.34 (per 1-point-increase in Fazekas score)) and global cognition ($\beta = -0.22$, 95%CI = -0.32 to -0.13). Thus, PVH mediated as much as 52% of the effects of SBP on cognitive performance. Mediation was less strong for deep white matter hyperintensities (DWMH, 16%), which showed less association with SBP ($\beta = 0.14$, 95% CI = 0.05 – 0.24) and global cognition ($\beta = -0.12$, 95% CI = -0.21 to -0.03). Regarding different cognitive domains, PVH most strongly mediated effects of SBP on nonverbal memory (94%) and executive function (81%).

Conclusion: Our results indicate that PVH may predispose to cognitive impairment associated with hypertension, especially in the domains of nonverbal memory and executive function.

Graphical Abstract: <http://links.lww.com/HJH/C102>

Keywords: antihypertensive agents, arterial hypertension, blood pressure, cerebral small vessel disease, cohort studies, Fazekas scale, MRI, mediation analysis

Abbreviations: BP, blood pressure; DWMH, deep white matter hyperintensities; PVH, periventricular hyperintensities; WMH, white matter hyperintensities

INTRODUCTION

White matter hyperintensities (WMH) of presumed vascular origin [1] are frequent in cerebral MRI of older people [2,3], and interpreted as a sign of small vessel disease (SVD) [4]. Although SVD is regarded as a common cause of cognitive impairment and dementia, its pathophysiology has not fully been elucidated yet [5,6]. Previous studies in general population and patient cohorts demonstrated that next to age, hypertension represents the most important risk factor for WMH [7,8] and cognitive impairment [9] with strict blood pressure (BP) control preventing progression of WMH [10] and cognitive decline [11]. These studies, however, did not look at BP/treatment categories (normotension without antihypertensive treatment, treated to normotension, untreated hypertension, hypertension despite treatment), but analysed hypertension defined as high blood pressure or presence of antihypertensive treatment, included only patients receiving antihypertensive

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treatment [9–12], or patients without a need for antihypertensive treatment [13]. Consequently, there is a lack of data comparing patients with untreated hypertension to those with treated hypertension. In research settings with large sample sizes, WMH is mostly assessed quantitatively using automatic volumetric image analysis [3]. In the clinical setting, WMH is preferentially assessed semiquantitatively using visual rating scales [14], because their application is fast for individual patients and possible for images obtained on computerized tomography (CT) or MRI scanners. Among visual rating scales, the Fazekas scale [15] is used most often given its simplicity, reliability, and validity [14]. Fazekas scores are assigned separately for periventricular hyperintensities (PVH) and subcortical (also called deep white matter) hyperintensities (DWMH). There is an ongoing debate whether PVH and DWMH reflect different pathophysiological processes that have different cognitive consequences or just represent different stages of vascular disease, starting in the periventricular and progressing to the subcortical regions [4,16,17]. In the population-based 1000BRAINS study, we analysed the association of BP, its treatment, and BP/treatment category with WMH load using Fazekas score and also assessed the direct and indirect (via WMH) relationships of high BP with cognitive performance in the domains of verbal and nonverbal memory, executive function, language, and attention/speed of processing.

METHODS

Study cohort

1000BRAINS is a longitudinal cohort study at the Institute of Neuroscience and Medicine, Research Centre Jülich, Germany designed to study variability in brain structure, function, and connectivity during ageing [18]. The 1000BRAINS sample is drawn from the 10-year follow-up of the Heinz Nixdorf Recall study [19], including participants at least 55 years at baseline and their spouses and children (sampled from the MultiGenerationStudy). The study was approved by the ethical committee of the University Duisburg-Essen, Germany. All participants gave written informed consent. For the present analysis, we used the baseline data of the 1000BRAINS study cohort.

Measures

BP was measured with an automated oscillometric device (Omron 705-CP; Omron, Mannheim, Germany) and the mean value of the second and third of three measurements taken at least 2 min apart was used. Participants were asked to bring all the medications they had been taking during the previous week. Medications were coded according to the Anatomical Therapeutic Chemical Classification Index (ATC). Antihypertensive medications were coded according to the KORA study definition [20]. BP/treatment category was defined based on the combination of BP category and antihypertensive treatment as follows: untreated SBP/DBP less than 120 mmHg/less than 80 mmHg, untreated SBP 120–139 mmHg or DBP 80 to 89 mmHg, untreated SBP at least 140 mmHg or DBP at least 90 mmHg, treated SBP/DBP less than 120 mmHg/less than 80 mmHg, treated SBP 120 to 139 mmHg or DBP 80–89 mmHg, and treated SBP at least 140 mmHg or DBP at least 90 mmHg.

MRI was carried out on a 3 Tesla MR scanner (Tim-TRIO, Siemens Medical Systems, Erlangen, Germany) using a 32-channel head coil. The T2-weighted structural brain images [fluid-attenuated inversion recovery (FLAIR) scanned with: repetition time (TR)=9 s, echo time (TE)=100 ms, FoV=220 × 220 mm², flip angle=150°, voxel resolution=0.9 × 0.9 × 4 mm³, 25 slices] [18] were used for Fazekas scoring of WMH [15]. In detail, images were scored by two independent raters who were blinded to further participant data. WMH were categorized into PVH and DWMH and assigned a grade from 0 to 3 according to severity (PVH: 0, absence; 1, ‘caps’ or pencil-thin lining; 2, smooth ‘halo’; and 3, irregular, extending into the deep white matter; DWMH: 0, absence; 1, punctate foci; 2, beginning confluence of foci; and 3, large confluent). A moderate interrater agreement was achieved (Cohens kappa=0.58 for PVH and 0.56 for DWMH). In case of interrater disagreement, the raters met to reach a consent.

History of stroke, coronary heart disease (myocardial infarction or coronary intervention), and peripheral artery disease, cardiac arrhythmias or heart failure, Parkinson’s disease, traumatic brain injury, brain tumour, brain aneurysm, multiple sclerosis, dementia, or alcohol abuse, was assessed with a standardized interview performed by a physician. Strokes and coronary events occurring after the baseline examination of the Heinz Nixdorf Recall study were validated by a blinded endpoint committee. Total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol were measured with standardized enzymatic methods using the ADVIA 1650 system (Siemens Healthcare Diagnostics, Eschborn, Germany). Glycated haemoglobin (HbA1c) was measured using immunonephelometry at 340/700 nm (BNII nephelometer; Dade-Behring, Deerfield, Illinois, USA). Participants were classified as diabetic if fasting glucose greater than 126 mg/dl, nonfasting glucose greater than 200 mg/dl, physician diagnosis of diabetes, or antidiabetic medications. BMI (kg/m²) was calculated from standardized height and weight measurements. Education and smoking were assessed in a standardized computer-assisted personal interview. Education was classified according to the International Standard Classification of Education (ISCED) [21] as total years of formal education, combining school and vocational training. Smoking was categorized based on smoking status (current, former, never) with current smoking defined as current daily or occasional smoking [22]. Depression and alcohol consumption were assessed via self-report paper-and-pencil questionnaire. Depression was assessed with the Centre for Epidemiological Studies Depression Scale (CES-D) [23]. Alcohol consumption was assessed as pure alcohol intake per week in grams [24]. Apolipoprotein-E (APOE) genotypes were investigated using Cardio-Metabochip BeadArrays (Illumina, San Diego, California, USA). Genotypes of two single-nucleotide polymorphisms (SNPs, rs7412 and rs429358) that distinguish between the three APOE alleles (ε2, ε3, and ε4) were extracted from the whole Metabochip data set [25]. For further analyses, APOE genotypes were categorized into APOE-ε4 carriers vs. non-carriers. Lipid-lowering medications included all medications with ATC code C10 and antidiabetic medications all medications with ATC code A10. Cognition was

assessed with a comprehensive battery of neuropsychological tests as described previously [18]. Raw scores of each test were z -transformed separately for participants less than 55 and at least 55 years; scores for tests where higher values indicated worse performance were inverted. Five cognitive domains were created using the mean z score of respective tests based on established neuropsychological handbooks [26,27] as follows:

1. Verbal memory: Verbaler Gedächtnistest (learning of a 15 words list in five trials, delayed recall of this 15 words)
2. Nonverbal memory: Benton-Test (free recall of 20 figures)
3. Executive function: Block-Tapping-Test backwards, Digit-Span backwards, Verbal fluency [phonematic verbal fluency (B, G-R) and Semantic fluency test (occupation, sports-fruits)], Figural fluency test, Trail-making test B, Colour-word-test interference condition, Visual pattern, Problem solving
4. Language: Boston Naming Test, Color-word-test card 1
5. Attention/speed of processing: Trail-making test A, Color-word-test card 2, Digit-Span forward, Block-Tapping-Test forward

Global cognition was defined as mean z score of all tests.

Statistical analysis

The initial 1000BRAINS cohort constituted 1262 participants 18–85 years. To be able to compare the quantitative WMH volume results described in Gronewold *et al.* [3] with the results of Fazekas scoring, we again considered participants at least 50 years for the present analysis ($n = 1007$) because of low prevalence of WMH and vascular risk factors as well as possibly different disease processes in younger persons. We again excluded possible causes of WMH other than risk factor exposure via exclusion of participants with cardiovascular and central nervous system disease ($n = 757$ remaining). One hundred and ninety-six participants were excluded because of missing or incomplete MR data, another participant was excluded because of insufficient image quality for the quantitative WMH volume analysis described in Gronewold *et al.* [3] leaving 560 participants as basis for the present analysis.

Continuous data are presented as mean \pm SD for normally distributed and median (Q1,Q3) for nonnormally distributed data, categorical data are shown as frequencies (%). Group differences (BP/treatment category, Fazekas score), were analysed by one-way ANOVAs with Games–Howell post hoc tests for continuous data and by chi-square tests for categorical data. Bivariate correlations between WMH volume and Fazekas score and between BP and Fazekas score were calculated with Spearman's Rho correlation. The associations of SBP, DBP, antihypertensive medications, and BP/treatment category with WMH Fazekas score were analysed with univariable and multivariable ordinal regressions, presenting odds ratios (OR) with 95% CI and variance explained by the model (McFadden's adjusted pseudo R^2). The associations of Fazekas score with cognitive performance and the

associations of SBP, DBP, antihypertensive medications, and BP/treatment category with cognitive performance were analysed with univariable and multivariable linear regressions, presenting unstandardized regression weights (β) with 95% CI and variance explained by the model (adjusted R^2). As our analysis cohort included related participants (120 spouses, 28 offspring; in total, the analysis sample constituted of 510 different families), we used multilevel regression models, including family identity as level 2 predictor allowing intercept and slopes to randomly vary across families, to check for significant data dependency. Here, we observed no significant effect for the random intercept or slope of our covariates across families and thus reported the results of the ordinary unilevel regression models. Multivariable regressions were adjusted for confounders identified by direct acyclic graphs (DAGs) as described before [3]. As DAGs revealed age, sex, education, alcohol consumption, smoking status, APOE status, and depression as minimal sufficient adjustment set, and APOE status was not measured in the MultiGeneration Study, resulting in 184 additional missing values, the latter variables without APOE status were adjusted for in the main analyses (fully adjusted model). In sensitivity analyses, we also included APOE status in the fully adjusted model (fully adjusted with APOE- $\epsilon 4$) and calculated a model adjusting for established cardiovascular risk factors (age, sex, diabetes, current smoking, HDL, and total cholesterol). Analyses were also conducted stratified by sex (men vs. women), age (<65 vs. ≥ 65 years), and presence of APOE- $\epsilon 4$ genotype (noncarriers vs. carriers). Stratified analyses were not adjusted for the stratification variable. To test the interdependence of hypertension, WMH, and cognition, we applied mediation analysis using LAVAAN package for R [28]. Cognition was used as dependent, SBP as independent, and WMH Fazekas score as mediator variable. We calculated the total effect of SBP on cognition (path c) and the association between SBP and WMH (path a) and between WMH and cognition (path b), which provided the estimates for the direct effect (path c'), which provided the estimates for the direct effect (path c'). The proportion of mediation was determined by dividing the indirect effect (path a \times path b) by the total effect (path c). Total effect represents the sum of the direct and the indirect effect. Cases with missing values [3] were excluded from analyses listwise. All statistical analyses were performed using SPSS 22 for Windows (IBM Corporation, Armonk, New York, USA) except for mediation analyses, which were performed with R (<https://www.R-project.org/> version 4.1.1). All statistical tests were two-tailed, P values less than 0.05 were considered significant.

RESULTS

Study cohort

Our study cohort of 560 participants had an age range of 50–85 years with a mean \pm standard deviation of 65.2 \pm 7.5 years, 51.4% were men). 98.6% had some kind of WMH (PVH or DWMH Fazekas score > 0). When stratified by PVH vs. DWMH, 96.4% had PVH whereas 89.3% had DWMH (Table 1). 9.3% only had PVH and no DWMH, only very few participants (2.1%) exhibited only DWMH and no PVH. As already observed for total WMH volume [3], WMH load quantified by Fazekas score was similar in men and women and increased with age (Table S1, <http://links.lww.com>).

TABLE 1. Characteristics of the study cohort stratified by periventricular and deep white matter hyperintensities Fazekas score

Variable	PVH				DWMH			
	0N = 20	1N = 302	2N = 172	3N = 66	0N = 60	1N = 273	2N = 170	3N = 57
Age (years)	59.8 ± 7.03	63.2 ± 6.6	67.1 ± 7.5 [†]	71.6 ± 5.9 ^{†,‡}	63.7 ± 6.9	66.7 ± 7.3	68.8 ± 7.2 [†]	69.9 ± 7.3 [†]
Male sex [n (%)]	13 (65.0)	158 (52.3)	87 (50.6)	30 (45.5)	33 (55.0)	147 (53.8)	81 (47.6)	27 (47.4)
Education according to ISCED-1997 [years, median (Q1,Q3)]	13.0 (13.0,17.0)	16.0 (13.0,17.0)	13.0 (13.0,17.0)	13.0 (13.0,16.5) [†]	14.8 (13.0,18.0)	13.0 (13.0,17.0)	13.0 (13.0,16.5)	13.0 (13.0,16.5)
SBP (mmHg)	120.9 ± 15.1	125.5 ± 16.3	132.0 ± 17.1 [†]	136.1 ± 19.2 [†]	134.5 ± 24.8	131.3 ± 18.8	132.7 ± 17.0	136.3 ± 17.3 [†]
DBP (mmHg)	70.9 ± 7.9	75.2 ± 9.2	77.6 ± 10.2 [*]	78.2 ± 10.9 [*]	80.9 ± 13.8	77.5 ± 11.1	77.2 ± 10.3	79.1 ± 9.3
Antihypertensive medications [n (%)]	7 (35.0)	92 (30.5)	84 (48.8) [†]	31 (47.0) [†]	13 (21.7)	95 (34.8) [*]	79 (46.5) [†]	27 (47.4) [*]
Total cholesterol (mg/dl)	218.3 ± 33.7	218.7 ± 37.1	222.1 ± 39.1	222.9 ± 39.9	202.8 ± 45.9	221.9 ± 36.8	221.2 ± 39.4	227.8 ± 41.4
LDL cholesterol (mg/dl)	138.0 ± 28.4	131.6 ± 31.3	132.8 ± 33.4	131.4 ± 34.9	110.8 ± 44.2	133.4 ± 36.1	131.1 ± 30.7	136.3 ± 36.1
HDL cholesterol (mg/dl)	58.3 ± 14.9	64.3 ± 17.4	64.1 ± 18.1	66.7 ± 16.7	62.6 ± 16.9	65.0 ± 17.3	62.9 ± 17.5	66.8 ± 18.6
Lipid-lowering medications [n (%)]	2 (10.0)	45 (14.9)	30 (17.4)	17 (25.8)	10 (16.7)	41 (15.0)	32 (18.8)	11 (19.3)
HbA1c (%)	5.56 ± 0.61	5.74 ± 0.49	5.76 ± 0.46	5.97 ± 0.65 ^{†,‡}	5.57 ± 0.45	5.73 ± 0.45	5.88 ± 0.61 [†]	5.83 ± 0.45 [*]
Antidiabetic medications [n (%)]	1 (5.0)	15 (5.0)	12 (7.0)	7 (10.6)	1 (1.7)	15 (5.5)	15 (8.8)	4 (7.0)
Smoking status								
Never smoked [n (%)]	8 (40.0)	142 (47.0)	80 (46.5)	1 (47.0)	29 (48.3)	130 (47.6)	80 (47.1)	22 (38.6)
Former smoker [n (%)]	9 (45.0)	126 (41.7)	74 (43.0)	28 (42.4)	22 (36.7)	119 (43.6)	69 (40.6)	27 (47.4)
Current smoking [n (%)]	3 (15.0)	34 (11.3)	18 (10.5)	7 (10.6)	9 (15.0)	24 (8.8)	21 (12.4)	8 (14.0)
BMI (kg/m ²)	28.1 ± 3.9	27.2 ± 4.4	27.3 ± 3.6	27.5 ± 3.4	26.9 ± 3.9	27.4 ± 4.2	27.4 ± 4.2	27.1 ± 3.2
Alcohol consumption (g/week, median [Q1,Q3])	30.5 (63.5,90.1)	55.6 (1.9,139.0)	39.7 (0.0,119.1)	16.3 (0.0,97.3)	56.5 (0.0,111.8)	61.4 (9.9,140.9)	23.8 (0.0,95.3) [†]	28.2 (0.0,119.1) [†]
Depression (score, median [Q1,Q3])	3.0 (2.0,5.0)	4.0 (2.0,8.0)	5.0 (3.0,9.0) [†]	5.0 (2.0,8.3)	4.0 (3.0,7.8)	4.3 (2.0,8.0)	5.0 (2.0,9.0)	5.0 (3.0,8.6)
APOE-ε4 [n (%)]	1 (25.0)	49 (24.3)	25 (21.4)	12 (22.6)	5 (13.9)	49 (26.8)	21 (18.9)	12 (26.1)
WMH volume (cm ³ , median [Q1,Q3])	1.67 (1.43,2.16)	3.51 (2.52,4.92) [*]	6.48 (4.68,9.28) [†]	17.75 (11.41,23.82) ^{†,‡}	2.69 (1.99,4.11)	3.79 (2.63,5.42) [*]	6.33 (4.21,9.80) [†]	16.85 (9.98,23.96) ^{†,‡}
WMH volume/white matter volume (% , median [Q1,Q3])	0.37 (0.29,0.45)	0.74 (0.55,1.01) [*]	1.42 (1.00,1.90) [†]	3.71 (2.53,5.27) ^{†,‡}	0.58 (0.43,0.88)	0.83 (0.57,1.15) [*]	1.35 (0.93,1.99) [†]	3.68 (2.22,5.21) ^{†,‡}

Data are mean ± standard deviation unless otherwise indicated. APOE, apolipoprotein E genotype; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WMH, white matter hyperintensities.
^{*} P less than 0.05 compared with Fazekas score 0.
[†] Less than P less than 0.05 compared with Fazekas score 1.
[‡] Less than P less than 0.05 compared with Fazekas score 2.

com/HJH/C55). There was a high correspondence between automatically determined total WMH volume and Fazekas score (Table 1) especially for PVH ($r=0.69$; $r=0.56$ for DWMH).

Association of blood pressure, its treatment, and blood pressure/treatment category with cognition

Five hundred and twenty-two participants of the study cohort (93.2%) had complete cognitive data. When looking at different cognitive domains, 545 (97.3%) participants had complete data for verbal memory, 547 (97.7%) for nonverbal memory, 540 (96.4%) for executive function, 552 (98.6%) for language, and 553 (98.8%) for attention/speed of processing. Global cognition, the summary measure of all neuropsychological tests, decreased with increasing BP with generally worse cognition for treated than untreated participants (Fig. 1, Table S2, <http://links.lww.com/HJH/C55>). Post hoc tests revealed that participants with treated SBP at least 140 mmHg or DBP at least 90 mmHg (-0.09 ± 0.54) significantly differed from participants with untreated SBP less than 120 mmHg and DBP less than 80 mmHg (0.14 ± 0.46 z score). When looking into different cognitive domains (Table S2, <http://links.lww.com/HJH/C55>), associations were strongest for verbal and nonverbal memory. Participants with untreated SBP at least 140 mmHg or DBP at least 90 mmHg (-0.13 ± 0.96), treated SBP 120–139 or DBP 80–89 mmHg (-0.11 ± 0.94) and treated SBP at least 140 mmHg or DBP at least 90 mmHg (-0.32 ± 0.96) had significantly worse verbal memory performance than participants with untreated SBP/DBP less than 120/80 mmHg (0.31 ± 0.87). For nonverbal memory, participants with treated SBP at least 140 mmHg or DBP at least 90 mmHg (-0.29 ± 1.11) showed significantly worse performance than participants with untreated SBP 120–139 or DBP 80–89 mmHg (0.20 ± 0.90).

In linear regressions, associations of SBP, DBP, antihypertensive medications, and BP/treatment category with global cognition were moderate and reduced in multivariable models (Table S3, <http://links.lww.com/HJH/C55>). When looking into cognitive domains, results were similar except for attention/speed of processing, which showed a statistically significant association with SBP [e.g. a decrease of 0.4 z scores (95% CI -0.07 to -0.01) of attention/speed of processing per increase of 10 mmHg in SBP in the fully adjusted model, Tables S4–S8, <http://links.lww.com/HJH/C55>].

In analyses stratified by sex and age, associations were stronger in men than in women and in older (≥ 65 years) than in younger (< 65 years) participants for BP/treatment category; only for SBP, associations were slightly stronger in women than in men (Tables S9–S26, <http://links.lww.com/HJH/C55>).

Association of blood pressure, its treatment, and blood pressure/treatment category with white matter hyperintensities

Participants with higher PVH Fazekas scores had higher SBP and DBP, relationships of DWMH with BP were less consistent (Table 1). Prevalence of antihypertensive medications increased with increasing Fazekas score both for PVH and DWMH, especially for scores at least 2 vs. less than 2 (Table 1). When analysing treated and untreated participants separately, associations between BP and Fazekas score were similar in treated (e.g. $r=0.24$ for SBP and PVH; $r=0.14$ for SBP and DWMH) and untreated participants ($r=0.21$ for SBP and PVH; $r=0.12$ for SBP and DWMH). Stratification by BP/treatment category confirmed that Fazekas scores were higher for treated than for untreated participants and increased with increasing BP both for PVH and DWMH with again a stronger association for PVH than DWMH (Fig. 2).

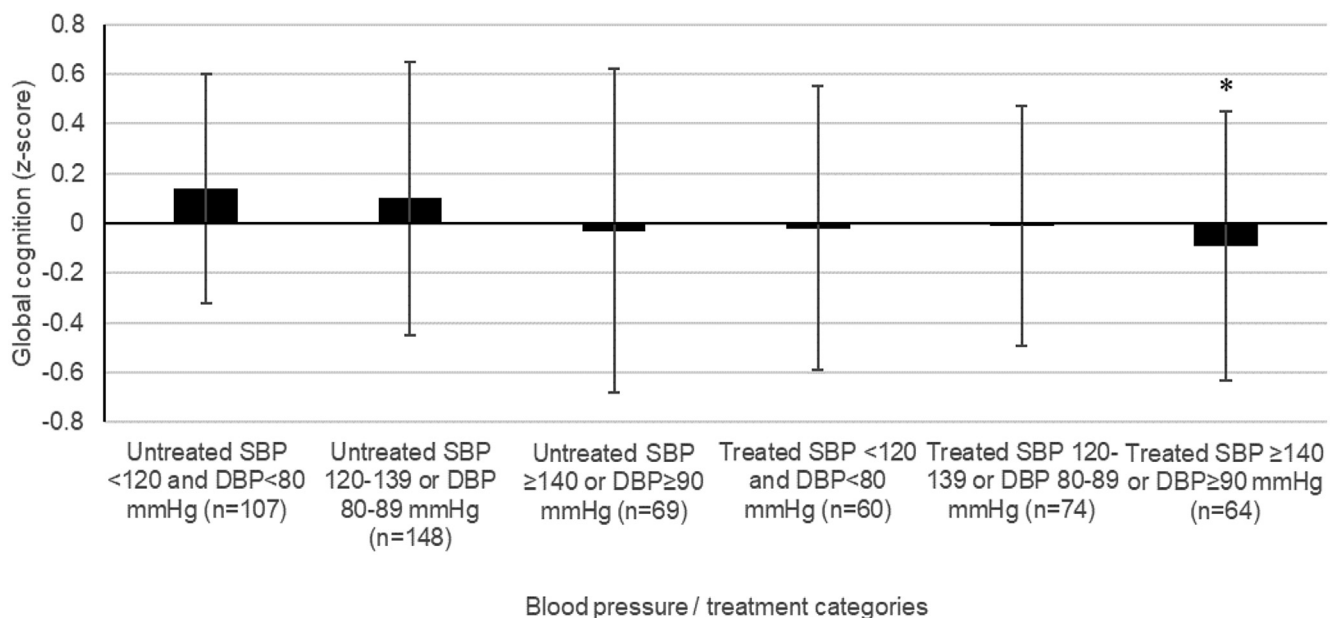


FIGURE 1 Global cognitive performance of the study cohort stratified by blood pressure/treatment category. Data are shown as mean \pm standard deviation. ANOVA results for the overall effect of blood pressure/treatment category on global cognition: $F(5, 516) = 2.49$, $P = 0.031$. * P less than 0.05 compared with no antihypertensives and SBP less than 120 mmHg and DBP less than 80 mmHg.

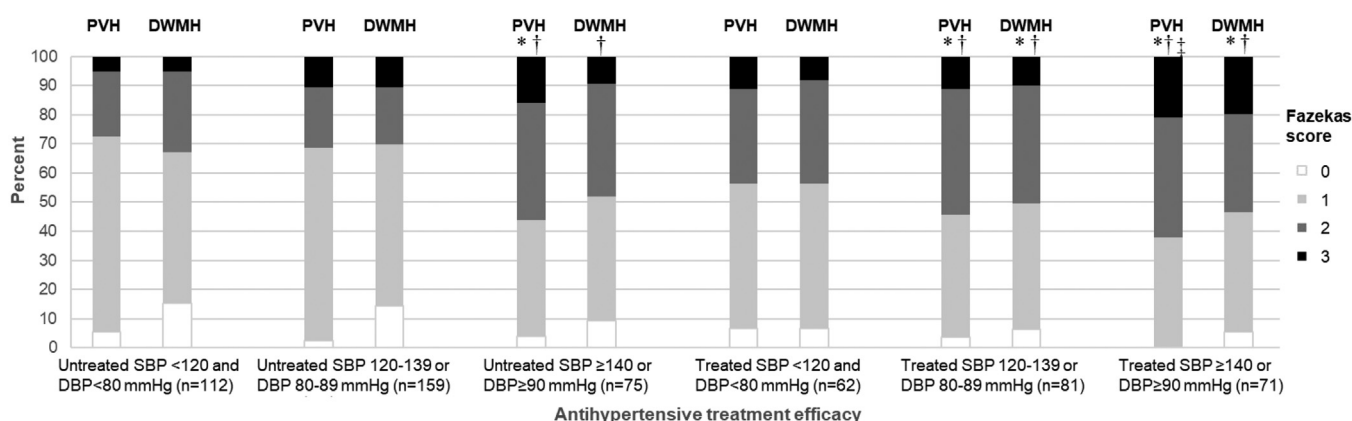


FIGURE 2 Classification of white matter hyperintensities according to Fazekas scoring in the total 1000BRAINS cohort ($n=560$), stratified by blood pressure/treatment category. DWMH, deep white matter hyperintensities; PVH, periventricular hyperintensities. Overall chi-square test for the association of blood pressure/treatment category with PVH: $\chi^2(15, N=560)=48.58, P<0.001$; overall chi-square test for the association of blood pressure/treatment category with DWMH: $\chi^2(15, N=560)=33.39, P=0.004$. * P less than 0.05 compared with no antihypertensives and SBP less than 120 and DBP less than 80 mmHg. † P less than 0.05 compared with no antihypertensives and SBP 120–139 mmHg or DBP 80–89 mmHg. ‡ P less than 0.05 compared with antihypertensives and SBP less than 120 mmHg and DBP less than 80 mmHg.

In unadjusted ordinal regressions, SBP, DBP, and antihypertensive medications were significantly associated with PVH (Table S27, <http://links.lww.com/HJH/C55>). For every 10 mmHg increase in SBP, the predicted odds of having a higher score increased by a factor of 1.32 with a 95% CI of 1.20–1.45. For every increase of 5 mmHg in DBP, the odds of having a higher score increased by 1.17 (95% CI=1.08–1.27). The odds of participants who received antihypertensive medications having a higher PVH score were 1.91 times (95% CI=1.37–2.65) that of participants who did not receive antihypertensive medications. The likelihood of participants with higher SBP and DBP having a higher PVH score remained stable in the multivariable models including different adjustment sets while the association of antihypertensive medication intake with higher PVH score was reduced in multivariable models. Regarding BP/treatment category, participants with untreated SBP at least 140 mmHg or DBP at least 90 mmHg, treated SBP 120–139 mmHg or DBP 80–89 mmHg, and treated SBP at least 140 mmHg or DBP at least 90 mmHg were significantly more likely to have a higher PVH score than participants with untreated SBP/DBP less than 120/80 mmHg in multivariable models [e.g., 2.48 (1.34–4.66), 2.12 (1.15–3.86), and 2.97(1.58–5.53) in the fully adjusted model]. Compared with PVH, BP was less strongly associated with DWMH [e.g. 1.16 (1.06–1.27) for SBP and 1.03 (0.95–1.12) for DBP in the unadjusted model]. Antihypertensive medications were similarly associated with PVH and DWMH [e.g. 1.86 (1.34–2.56) for DWMH in the unadjusted model]. Similar to PVH, associations remained stable in the multivariable models including different adjustment sets for SBP and DBP and were reduced for antihypertensive medication intake. In contrast with PVH, only treated SBP at least 140 mmHg or DBP at least 90 mmHg was associated with a significantly higher likelihood of higher DWMH compared with untreated SBP/DBP less than 120/80 mmHg in multivariable models (e.g. 2.01(1.12–3.67 in the fully adjusted model). In analyses stratified by sex and age, associations were similar in men and women and similar in younger (<65 years) and older (≥ 65 years) participants for PVH (Tables S28/S29, <http://links.lww.com/HJH/C55>). For DWMH, associations

were stronger in women than in men and similar in younger and older participants (Tables S30/S31, <http://links.lww.com/HJH/C55>). Stratification by APOE- $\epsilon 4$ showed that BP, its treatment, and BP/treatment category were significantly associated with PVH and DWMH only in noncarriers but not in carriers (Table S32, <http://links.lww.com/HJH/C55>).

Association of white matter hyperintensities with cognition

Participants with higher PVH Fazekas scores showed lower global cognitive performance, relationships of DWMH with cognition were less consistent (Fig. 3, Table S33, <http://links.lww.com/HJH/C55>). Post hoc tests revealed that participants with PVH score 3 (-0.28 ± 0.59) showed significantly worse global cognition than participants with score 2 (0.01 ± 0.53), 1 (0.12 ± 0.52), or 0 (0.18 ± 0.63). Participants with DWMH score of 3 (-0.13 ± 0.54) and 2 (-0.07 ± 0.57) showed worse performance than participants with DWMH score of 1 (0.14 ± 0.50), but not of DWMH score 0 (0.05 ± 0.55). When looking into different cognitive domains (Table S33, <http://links.lww.com/HJH/C55>), associations between WMH and cognition were strongest for nonverbal memory and executive function with again stronger associations for PVH than DWMH. Also unadjusted linear regressions confirmed a significant negative association of PVH score 3 for global cognition [0.46 (-0.73 to -0.19)] using PVH score of 0 as reference with no significant linear association for DWMH. Associations were reduced in multivariable models (Table S34, <http://links.lww.com/HJH/C55>). Regarding the different cognitive domains, linear regressions confirmed strongest associations of PVH with nonverbal memory and executive function (Tables S35–S39, <http://links.lww.com/HJH/C55>).

Interdependence of hypertension, white matter hyperintensities, and cognition

To characterize the interdependence of hypertension, WMH, and cognition, we subsequently performed mediation analyses. As continuous variables are easier to interpret and depict, we chose SBP, which has been shown to have a

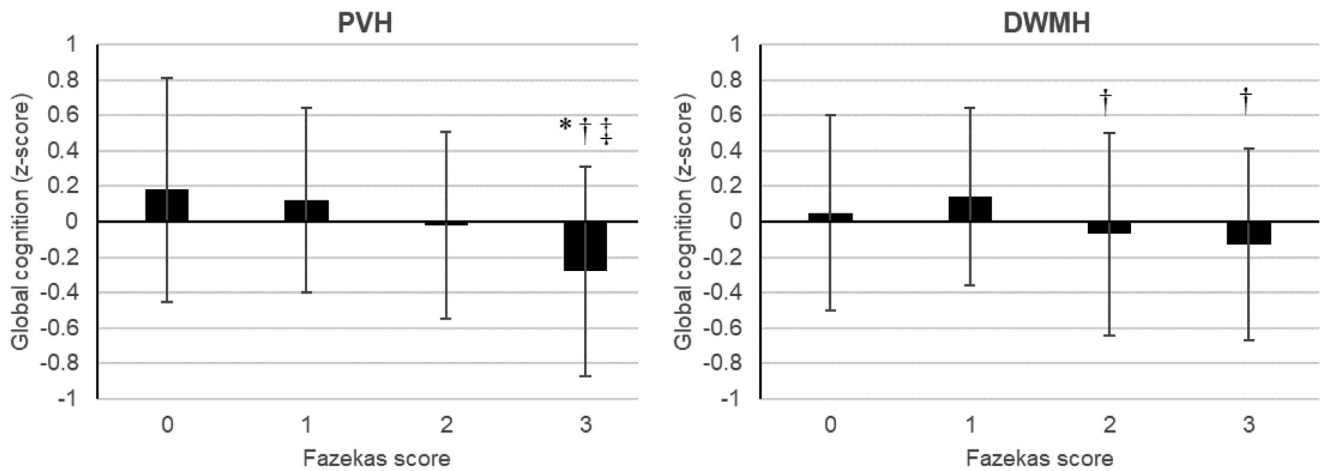


FIGURE 3 Global cognitive performance of the study cohort stratified by Fazekas score. Data are shown as mean \pm standard deviation. DWMH, deep white matter hyperintensities; PVH, periventricular hyperintensities. ANOVA results for the overall effect of Fazekas score on global cognition: PVH: $F(3, 518) = 10.51$, $P < 0.001$; DWMH: $F(3, 518) = 6.75$, $P < 0.001$. * P less than 0.05 compared with Fazekas score 0. † P less than 0.05 compared with Fazekas score 1. ‡ P less than 0.05 compared with Fazekas score 2.

stronger association with WMH and cognition than DBP [6], as independent variable, cognitive performance as dependent variable, and WMH Fazekas score as mediator variable. Mediation analysis showed that a significant proportion of the influence of SBP on global cognition was mediated by PVH (52%) and to a lesser extent by DWMH (16%, Fig. 4). When looking at the different cognitive domains, strongest mediation was observed for nonverbal memory (94% for PVH, 30% for DWMH) and executive function (81% for PVH, 26% of DWMH), whereas the relationship of SBP with cognition was less strongly mediated for the domains of verbal memory (16% for PVH, 4% for DWMH), language (40% for PVH, 25% for DWMH), and attention/speed of processing (3% for PVH, 5% for DWMH, Figures S1/S2, <http://links.lww.com/HJH/C55>).

DISCUSSION

Using data from the population-based 1000BRAINS study, we showed that (1) higher SBP, prevalence of antihypertensive treatment, and higher BP despite treatment showed moderate associations with lower cognitive performance, (2) higher SBP and DBP, prevalence of antihypertensive

treatment, and higher BP despite treatment were significantly associated with higher scores for PVH and to a lesser extent DWMH both in unadjusted models and multivariable models using different adjustment sets, (3) higher scores for PVH and to a lesser extent DWMH, were significantly associated with lower cognitive performance, especially in the domains of nonverbal memory and executive function, and (4) PVH more than DWMH was a relevant mediator of the association between SBP and cognitive performance, especially in the domains of nonverbal memory and executive function.

Studies on the relationship of hypertension with cognition so far yielded inconsistent results in cross-sectional analyses but more consistent results in longitudinal analyses highlighting the importance of midlife hypertension and decreases in blood pressure in later life for cognitive decline and incident dementia in later life [6,9]. In contrast to our study, these studies did not look at BP/treatment categories (normotension without antihypertensive treatment, treated to normotension, untreated hypertension, hypertension despite treatment). Studies analysing the benefits of antihypertensive treatment for the prevention of cognitive decline, including observational studies and RCTs, indicate

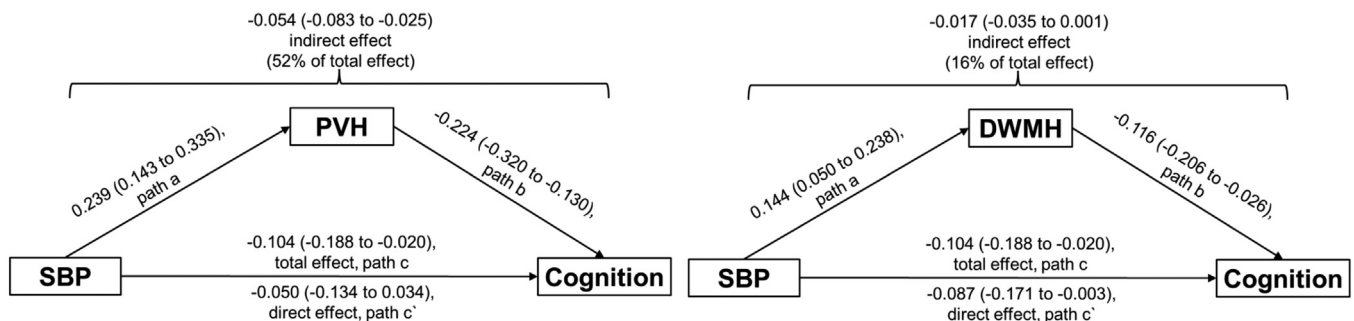


FIGURE 4 Mediation analysis of the interdependence of SBP, periventricular or deep white matter hyperintensities Fazekas score (PVH or DWMH, respectively) and global cognition (cognition). Regression coefficients with 95% confidence intervals are shown, per standard deviation increase for the continuous variables (SBP: 17.2 mmHg, global cognition: 0.5 z score), per increase of 1 point for Fazekas score.

that there remains uncertainty about the benefit of BP lowering and prevention of cognitive decline or dementia [9–13], leading to uncertainty about when to initiate anti-hypertensive therapy and which target blood pressure to achieve [29].

The hypothesis whether the relationship of hypertension with cognition is fully or partially mediated through WMH has not been investigated before. WMH has rarely been quantified with the Fazekas scale in previous population-based studies, analysing associations between hypertension, WMH, and cognition. In 321 nondemented, community-dwelling older adults from the Beijing Aging Brain Rejuvenation Initiative Study, higher Fazekas scores were significantly associated with lower performance in working memory and episodic memory. Especially severe WMH load (sum of PVH and DWMH score ≥ 3) was associated with significant cognitive impairment, which matches our observation that participants with Fazekas score 3 showed significantly worse global cognition, nonverbal memory, and executive function than participants with score 0 or score 1 for PVH and DWMH. Associations with BP were not assessed in this study [30]. In a small sample of 177 community-living individuals above 75 years from the population-based Brazilian Pietà study, severe WMH, defined by PVH or DWMH Fazekas score 3, was significantly associated with hypertension, defined by medical history or intake of antihypertensive medication, as well as cognitive impairment, defined as performance below the 25th percentile according to age and educational level in Mini-Mental Status Examination test and Brief Cognitive Screening Battery [31]. In a large sample of 1797 participants from three population-based studies in the Asia Pacific Region, a higher number of markers of small vessel disease (modified Fazekas score, lacunes, and microbleeds) was associated with the presence of hypertension (SBP ≥ 140 mmHg/DBP ≥ 90 mmHg or antihypertensive medications) and lower cognitive performance in Mini Mental Status Examination test and Montreal Cognitive Assessment (MoCA). Fazekas score was not evaluated as separate outcome in this study [32]. Previous population-based studies mostly used automated volumetric WMH measurement or customized visual rating scales for the assessment of WMH load [3] instead of Fazekas scoring even though it is discussed that PVH and DWMH, which are quantified separately with Fazekas scoring, might have different pathomechanisms and cognitive consequences [4,16,33,34].

Evidence on the associations between hypertension, Fazekas scores and cognition mostly comes from patient cohort studies. In 147 patients from a Chinese neurology department exhibiting WMH, higher Fazekas scores were associated with higher BP, lower cognitive performance assessed by MoCA, and lower cerebral blood flow. Associations were significant both for PVH and DWMH with slightly stronger associations for PVH than DWMH like in our analysis [35]. Also, in a cohort of 618 patients with ischemic stroke or transient ischemic attack, hypertension identified in medical records was significantly associated with higher PVH and DWMH in univariable but only with PVH in multivariable analyses adjusted for age and diabetes [7]. Similarly, self-reported hypertension showed a stronger association with PVH than DWMH in 567 patients from a

Chinese neurology department examined because of dizziness and headaches [16]. Even in a cohort of 301 Tibetan patients residing at high altitudes with rather heterogeneous neurological diagnoses, patients with hypertension (BP $\geq 140/90$ mmHg or antihypertensive medications) had significantly higher Fazekas scores than patients without hypertension, however, Fazekas scores were not evaluated separately as PVH and DWMH [36]. Regarding BP/treatment category, especially poorly controlled hypertension was associated with significantly increased WMH, which in contrast to our study was assessed as volume in 189 older hypertensive male patients [37], and confirms our results with WMH quantified using Fazekas score and our previous analysis quantifying WMH as total volume [3].

Using continuous total volume and voxel-wise spatial distribution of WMH, Veldsman *et al.* [17] observed significant interdependencies between vascular risk factors including hypertension, WMH, and cognition in a large sample of 13 680 individuals from the UK Biobank cohort, which matches our observation that WMH was a significant mediator of the negative relationship of high BP with cognitive performance. However, in contrast to our study, cognition was only quantified with a reaction time test, assessing speed of processing because of high number of missing values in other cognitive test variables. Even though not explicitly performing mediation analyses, Guevarra *et al.* [38] confirmed that hypertension, defined by SBP at least 140 mmHg, and WMH, assessed by a modified version of the Fazekas score, were mutually associated risk factors for cognitive impairment, assessed by MoCA in 488 individuals with prodromal or mild dementia. Similarly, Shanguan *et al.* described higher Fazekas scores and lower MoCA scores in hypertensive (BP $\geq 140/90$ mmHg or antihypertensive medications) vs. nonhypertensive patients using a sample of 157 patients exhibiting WMH. MoCA scores were lower in patients with hypertension and high Fazekas score (sum of PVH and DWHM ≥ 3) than in patients with hypertension and low Fazekas score (sum of PVH and DWHM < 3); MoCA scores were lower in patients with hypertension and high Fazekas score than in patients without hypertension and high Fazekas score [39]. We provided population-based evidence that PVH may play an important role in mediating the negative consequences of hypertension on brain structure and function.

There are some limitations that need to be considered. Our 1000BRAINS study sample is representative of the adult general population 50–85 years (mean \pm standard deviation 65.2 ± 7.5 years) living in German industrialized urban areas. Thus, generalizability to other age ranges, ethnicities, or rural areas needs to be shown. BP was only measured on the study visit, whereas the definition and treatment of hypertension should ideally be grounded on multiple measurements of office BP or long-term ambulatory or home BP measurement. In stratified analyses, small sample sizes in some subgroups (e.g. APOE- $\epsilon 4$ carriers, $n = 87$) might have reduced statistical power to detect significant effects. Our results are based on a cross-sectional analysis of baseline data of the 1000BRAINS study cohort; thus, we cannot control the sequence of hypertension, PVH/DWMH and cognitive function. Consequently, as this is a cross-sectional analysis, it is difficult to infer any causative

relationship between BP, WMH, and cognition. Future studies are needed to identify early markers of hypertension-related brain damage, and especially longitudinal analyses are needed to confirm the temporal sequence of hypertension, WMH, and cognitive impairment. Such data will help to prevent negative consequences of hypertension for brain structure and function, such as stroke and dementia. 1000BRAINS is an observational study in which the exposure to hypertension and its treatment is not controlled by the investigator but by the treating physicians and the compliance of the patients, which can lead to the problem of bias and confounding prohibiting causal interpretation. The current gold standard to identify causes of health outcomes is still the RCT. Our results call for additional RCTs with longer follow-ups to investigate whether applying stricter BP control leads to a reduction of WMH and cognitive impairment.

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Conflicts of interest

There are no conflicts of interest.

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