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ORIGINAL ARTICLE

Association of regional white matter hyperintensities with hypertension and cognition in the population-based 1000BRAINS study

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Abstract

Background: White matter hyperintensities of presumed vascular origin (WMH) are frequent in cerebral magnetic resonance imaging of older people. They are promoted by vascular risk factors, especially hypertension, and are associated with cognitive deficits at the group level. It has been suggested that not only the severity, but also the location, of lesions might critically influence cognitive deficits and represent different pathologies.

Methods: In 560 participants (65.2 ± 7.5 years, 51.4% males) of the population-based 1000BRAINS study, we analyzed the association of regional WMH using Fazekas scoring separately for cerebral lobes, with hypertension and cognition.

Results: WMH most often affected the frontal lobe (83.7% score > 0), followed by the parietal (75.8%), temporal (32.7%), and occipital lobe (7.3%). Higher Fazekas scores in the frontal, parietal, and temporal lobe were associated with higher blood pressure and antihypertensive treatment in unadjusted ordinal regression models and in models adjusted for age, sex, and vascular risk factors (e.g., age- and sex-adjusted odds ratio = 1.14, 95% confidence interval = 1.03–1.25 for the association of frontal lobe WMH Fazekas score with systolic blood pressure [SBP] [per 10 mm Hg]; 1.13 [1.02–1.23] for the association of parietal lobe score with SBP; 1.72 [1.19–2.48] for the association of temporal lobe score with antihypertensive medications). In linear regressions, higher frontal lobe scores were

associated with lower performance in executive function and non-verbal memory, and higher parietal lobe scores were associated with lower performance in executive function, verbal-, and non-verbal memory.

Conclusions: Hypertension promotes WMH in the frontal, parietal, and temporal lobe. WMH in the frontal and parietal lobe are associated with reduced executive function and memory.

KEYWORDS
arterial hypertension, cerebral small vessel disease, cohort studies, Fazekas scale, magnetic resonance imaging

INTRODUCTION

White matter hyperintensities of presumed vascular origin (WMH) [1] are frequently observed in cerebral magnetic resonance imaging (MRI) of older people [2, 3]. Previous studies most often found evidence for total WMH burden worsening cognitive function at the group level [4]. At the individual level, however, clinico-radiological discrepancies are observed with some individuals showing preserved cognitive function despite high total WMH burden and others suffering from severe cognitive impairment despite only moderate WMH burden [5]. As one possible reason for these discrepancies, it was suggested that besides the severity, the location of WMH might be an important determinant of cognitive impairment [6, 7]. For example, small lesions in the thalamus can strongly affect cognition [8], while widely distributed deep WMH can remain clinically silent [9]. In addition to being followed by different cognitive consequences, different locations of WMH might be influenced by different pathomechanisms. Periventricular WMH (PVH) have been shown to be more susceptible to the harmful influence of hypertension than deep WMH (DWMH) [10]. The reason for the latter might be due to watershed areas of blood circulation being around the ventricles where the tissue is supplied by long, narrow end arteries/arterioles that render local oxygen supply insufficient in case of dysregulated blood pressure (BP) [11]. A recent analysis of data from the population-based Northern Manhattan Study (NOMAS), which distinguished between PVH and DWMH and differentiated DWMH into cerebral lobes, suggested that in addition to the periventricular area, the frontal and parietal lobe may also be highly susceptible to hypertensive damage. Unfortunately, relations with cognition were not analyzed [12]. In a clinical cohort of older patients with lacunar infarcts, demented patients showed more severe WMH in the frontal lobe compared to non-demented patients, with WMH in the frontal lobe being significantly associated with systolic (SBP) and diastolic blood pressure (DBP) as well as dementia severity [13]. Since such studies assessing associations between hypertension, regional distribution of WMH, and cognitive performance were lacking in population-based samples, we analyzed the distribution of DWMH in the cerebral lobes with a modified version [14, 15] of the Fazekas scale [16] and their association with BP, its treatment, and treatment efficacy as well as cognitive performance in different domains in the population-based 1000BRAINS study [17].

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 aging [17]. The 1000BRAINS sample is drawn from the 10-year follow-up of the Heinz Nixdorf Recall study [18] including participants aged ≥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) and the mean value of the second and third of three measurements taken ≥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 [19]. Treatment efficacy was defined based on the combination of BP categories [20] and antihypertensive treatment as follows: (i) untreated BP <120/<80 mm Hg, (ii) untreated SBP 120–139 or DBP 80–89 mm Hg, (iii) untreated BP ≥ 140 or ≥90 mm Hg, (iv) treated BP < 120/<80 mm Hg, (v) treated SBP 120–139 or DBP 80–89 mm Hg, and (vi) treated BP ≥ 140 or ≥ 90 mm Hg.

MRI was carried out on a 3 Tesla MR scanner (Tim-TRIO, Siemens Medical Systems) using a 32-channel head coil. A modified Fazekas scoring of WMH [14, 15] was perfomed by two independent raters using the T2-weighted structural brain images

(fluid-attenuated inversion recovery [FLAIR] scanned with: TR = 9 s, TE = 100 ms, FoV = 220×220 mm^2, flip angle = 150°, voxel resolution = 0.9×0.9×4 mm^3, 25 slices). DWMH were scored separately for each cerebral lobe using established neuroanatomical landmarks [14, 15]. Scores ranged from 0 to 3 according to severity of DWMH (0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, 3 = large confluent) [16]. Interrater agreement was moderate to substantial for the frontal (Cohens kappa = 0.59) and parietal (0.62) lobe, and fair to moderate for the temporal (0.47) and occipital (0.30) lobe. In case of interrater disagreement, the raters met to reach a consent.

Covariates (demographics, cardiovascular and central nervous system disease, vascular risk factors) were assessed as described previously [3]. Cognition was assessed with a comprehensive battery of neuropsychological tests as described previously [17]. Raw scores of each tests were *z*-transformed separately for participants aged <55 and ≥55 years; scores for tests where higher values indicated worse performance were inverted. Cognitive domains were created using the mean *z*-score of respective tests as follows:

(i) Verbal memory: Verbaler Gedächtnistest (learning of a 15-word list in five trials, delayed recall of these 15 words)
(ii) Non-verbal memory: Benton-Test (free recall of 20 figures)
(iii) 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, Color-Word-Test interference condition, Visual pattern, Problem solving
(iv) Attention/speed of processing: Trail Making Test A, Color-Word-Test card 2, Digit-Span forward, Block-Tapping-Test forward
(v) Language: Boston Naming Test, Color-Word-Test card 1.

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

Cognitive testing and MRI were performed at the research centre Jülich. BP, its treatment, and covariates were assessed at the Heinz Nixdorf Recall study centre Essen. The time interval between the study visits in Jülich and in Essen ranged from 2 days to 3 years; the median (Q1;Q3) was 9 (5; 20) weeks.

Statistical analysis

The initial 1000BRAINS cohort comprised 1262 participants aged 18–85 years. To be able to compare the present analysis with our previous analyses of quantitative WHM volume and traditional PVH and DWMH Fazekas scoring, we used the same sample including only participants aged ≥50 years without cardiovascular and central nervous system disease as described previously (n = 560) [3, 10]. Continuous data are presented as mean ± standard deviation (SD) for normally distributed and median (Q1, Q3) for non-normally distributed data, categorical data are shown as frequencies (%). Group differences (Fazekas score) were analyzed by one-way ANOVAs with Games–Howell post-hoc tests for continuous data and by Chi-square or Fisher's exact tests for categorical data. Bivariate correlations between WMH volume and Fazekas score were calculated with Spearman's rho correlation. The associations of SBP, DBP, antihypertensive medications, and treatment efficacy with WMH Fazekas score were analyzed with univariable and multivariable ordinal and multinomial regressions, presenting odds ratios (OR) with 95% confidence intervals (CI) and variance explained by the model (McFadden's adjusted pseudo R^2). The assocations of Fazekas score with cognitive performance were analyzed with univariable and multivariable linear regressions, presenting unstandardized regression weights (β) with 95% CI and variance explained by the model (adjusted R^2). Multivariable regressions were adjusted for confounders identified by direct acyclic graphs (DAGs) as described previously [3]. Since DAGs revealed age, sex, education, alcohol consumption, smoking status, apolipoprotein E genotype (APOE) status, and depression as minimal sufficient adjustment set, and APOE status was not measured in the MultiGenerationStudy, the latter variables without APOE status were adjusted for (fully adjusted model). In sensitivity analyses, time between the assessment of cognition/WMH and the assessment of the remaining parameters (in weeks) was additionally adjusted for. Furthermore, to test for interactions with age and sex, multiplicative interaction terms were added to the regression models. Cases with missing values [3] were excluded from analyses listwise. All statistical analyses were performed using SPSS 22 for Windows (IBM Corporation). All statistical tests were two-tailed, to correct for multiple comparisons, p values < 0.001 were considered significant.

RESULTS

Study cohort

Our study cohort of 560 participants had an age range of 50–85 years with a mean ± SD of 65.2 ± 7.5 years, and 51.4% were males. 89.3% had some kind of DWMH (Fazekas score > 0, independent of lobe). When DWMH were stratified according to cerebral lobes (Table 1), more than 4 of 5 participants had DWMH affecting the frontal lobe (83.7% score > 0). The parietal lobe was slightly less often affected with about 3 of 4 participants exhibiting DWMH in the parietal lobe (75.8%). DWMH affected the temporal lobe in about 1 of 3 participants (32.7%) but were rare in the occipital lobe with fewer than 1 of 10 participants exhibiting WMH (7.3%). That WMH mostly affect the frontal and parietal lobe is also supported by the higher correlation with automatically determined total WMH volume [3] (r = 0.51 for frontal, r = 0.61 for parietal lobe) compared with temporal (r = 0.41) and occipital lobe Fazekas score (r = 0.18). DWMH affecting only the frontal lobe were seen in 11.1% of all participants, and only the parietal was affected in 4.8%

TABLE 1 Characteristics of the study cohort stratified by modified (scored separately for the cerebral lobes) deep white matter hyperintensities (DWMH) Fazekas score.

Study cohort characteristics	Frontal lobe DWMH Fazekas score				Parietal lobe DWMH Fazekas score			
	0, *N* = 91	1, *N* = 282	2, *N* = 141	3, *N* = 46	0, *N* = 135	1, *N* = 266	2, *N* = 123	3, *N* = 35
Age (years)	62.0 ± 6.8	64.6 ± 7.1	67.2 ± 7.4*	69.4 ± 7.6*†	62.3 ± 6.8	64.6 ± 7.2	68.5 ± 7.2*†	69.6 ± 6.7*†
Male sex, *n* (%)	50 (54.9)	148 (52.5)	71 (50.4)	19 (41.3)	76 (56.3)	128 (48.1)	65 (52.8)	19 (54.3)
Education according to ISCED-1997 (years, median [Q1, Q3])	16.3 (13.0, 17.3)	13.0 (13.0, 16.8)	13.0 (13.0, 16.5)	13.0 (13.0; 16.5)	16.0 (13.0, 17.3)	13.0 (13.0, 16.5)	13.0 (13.0, 16.5)	13.0 (13.0; 16.5)
SBP (mm Hg)	124.9 ± 16.9	127.9 ± 16.9	130.4 ± 17.5	134.3 ± 19.0	126.3 ± 18.2	127.6 ± 16.9	130.7 ± 16.1	138.0 ± 18.2
DBP (mm Hg)	75.2 ± 9.2	76.2 ± 9.4	75.9 ± 10.6	78.5 ± 10.3	76.0 ± 9.3	75.8 ± 9.8	75.8 ± 10.1	80.3 ± 9.7
Antihypertensive medications, *n* (%)	22 (24.2)	103 (36.5)	66 (46.8)	23 (50.0)	33 (24.4)	100 (37.6)	63 (51.2)*	17 (48.6)
Antihypertensive treatment efficacy							*	*
Untreated SBP <120 and DBP < 80 mm Hg, *n* (%)	26 (28.5)	54 (19.1)	27 (19.2)	5 (10.9)	36 (26.7)	56 (21.1)	18 (14.6)	2 (5.7)
Untreated SBP 120–139 or DBP 80–89 mm Hg, *n* (%)	32 (35.2)	90 (31.9)	25 (17.7)	12 (26.1)	50 (37.0)	74 (27.8)	24 (19.6)	11 (31.4)
Untreated SBP ≥140 or DBP ≥90 mm Hg, *n* (%)	11 (12.1)	35 (12.4)	23 (16.3)	6 (13.0)	16 (11.9)	36 (13.5)	18 (14.6)	5 (14.3)
Treated SBP <120 and DBP < 80 mm Hg, *n* (%)	6 (6.6)	32 (11.3)	20 (14.2)	4 (8.7)	9 (6.7)	33 (12.4)	16 (13.0)	3 (8.6)
Treated SBP 120–139 or DBP 80–89 mm Hg, *n* (%)	11 (12.0)	40 (14.2)	23 (16.3)	7 (15.2)	13 (9.6)	36 (13.5)	29 (23.6)	3 (8.6)
Treated SBP ≥140 or DBP ≥ 90 mm Hg, *n* (%)	5 (5.4)	31 (11.1)	23 (16.3)	12 (26.1)	11 (8.1)	31 (11.7)	18 (14.6)	11 (31.4)
Total cholesterol (mg/dL)	223.3 ± 39.2	219.8 ± 35.4	216.3 ± 40.4	228.5 ± 41.4	216.6 ± 37.7	221.8 ± 37.3	218.4 ± 38.2	229.3 ± 41.8
LDL cholesterol (mg/dL)	132.0 ± 32.6	133.3 ± 31.4	128.5 ± 32.5	137.1 ± 35.5	129.7 ± 31.9	133.4 ± 32.2	130.8 ± 31.1	137.8 ± 38.6
HDL cholesterol (mg/dL)	65.6 ± 18.7	64.5 ± 16.9	62.3 ± 17.4	66.8 ± 18.1	63.3 ± 16.3	65.5 ± 18.3	61.7 ± 16.7	68.3 ± 17.4
Lipid-lowering medications, *n* (%)	14 (15.4)	41 (14.5)	31 (22.0)	8 (17.4)	18 (13.3)	44 (16.5)	24 (19.5)	8 (22.9)
HbA1c (%)	5.63 ± 0.52	5.73 ± 0.43	5.90 ± 0.62*	5.86 ± 0.48	5.71 ± 0.52	5.74 ± 0.46	5.90 ± 0.59	5.82 ± 0.47

(Continues)

TABLE 1 (Continued)

Study cohort characteristics	Frontal lobe DWMH Fazekas score				Parietal lobe DWMH Fazekas score			
	0, *N* = 91	1, *N* = 282	2, *N* = 141	3, *N* = 46	0, *N* = 135	1, *N* = 266	2, *N* = 123	3, *N* = 35
Antidiabetic medications, *n* (%)	3 (3.3)	15 (5.3)	13 (9.2)	4 (8.7)	6 (4.4)	16 (6.0)	10 (8.1)	3 (8.6)
Smoking status								
Never smoked, *n* (%)	40 (44.0)	137 (48.6)	63 (44.7)	21 (45.7)	66 (48.9)	125 (47.0)	57 (46.4)	13 (37.1)
Former smoker, *n* (%)	41 (45.0)	119 (42.2)	58 (41.1)	19 (41.3)	46 (34.1)	118 (44.4)	55 (44.7)	17 (48.6)
Current smoking, *n* (%)	10 (11.0)	26 (9.2)	20 (14.2)	6 (13.0)	23 (17.0)	23 (8.6)	11 (8.9)	5 (14.3)
BMI (kg/m^2)	26.8 ± 3.7	27.5 ± 4.2	27.4 ± 4.2	27.1 ± 3.3	26.6 ± 4.0	27.4 ± 4.3	27.8 ± 4.0	27.1 ± 2.3
Alcohol consumption (g/week, median [Q1, Q3])	52.4 (0.0, 112.0)	59.6 (7.71, 39.0)	25.0 (0.0, 99.3)†	17.3 (0.0, 119.1)†	61.4 (2.81, 29.5)	46.1 (1.51, 33.2)	25.2 (0.0, 86.0)	50.0 (0.0, 183.8)
Depression (score, median [Q1, Q3])	4.0 (3.0, 8.0)	4.5 (2.0, 8.0)	5.0 (2.0, 9.0)	5.0 (3.0, 9.0)	4.0 (2.0, 7.0)	5.0 (2.0, 8.0)	5.0 (2.0, 9.0)	5.5 (3.0, 9.0)
APOE-ε4, *n* (%)	8 (13.6)	50 (26.5)	21 (23.1)	8 (21.6)	19 (22.9)	42 (23.6)	20 (23.5)	6 (20.7)
WMH volume (cm^3, median [Q1, Q3])	3.15 (2.14, 4.30)	4.15 (2.80, 6.09)*	6.54 (4.20, 10.36)*†	18.38 (10.14, 25.86)*†‡	2.93 (2.03, 4.22)	4.24 (3.03, 6.09)	8.08 (5.38, 11.77)*†	22.78 (14.78, 28.77)*†‡
WMH volume/white matter volume (%, median [Q1, Q3])	0.63 (0.46, 0.91)	0.88 (0.60, 1.24)*	1.42 (0.94, 2.15)*†	3.87 (2.31, 5.57)*†‡	0.62 (0.45, 0.92)	0.91 (0.63, 1.25)	1.79 (1.15, 2.65)*†	4.72 (3.04, 6.33)*†‡
Global cognition (*z*-score)	0.12 ± 0.56	0.09 ± 0.50	−0.06 ± 0.57	−0.15 ± 0.58	0.12 ± 0.53	0.09 ± 0.53	−0.11 ± 0.56*†	−0.15 ± 0.46
Verbal memory (*z*-score)	0.06 ± 0.99	0.07 ± 0.88	−0.14 ± 0.94	−0.14 ± 1.04	0.09 ± 0.94	0.06 ± 0.86	−0.16 ± 1.02	−0.27 ± 0.95
Non-verbal memory (*z*-score)	0.29 ± 0.94	0.05 ± 0.97	−0.16 ± 0.99	−0.39 ± 1.14*	0.19 ± 0.98	0.05 ± 0.95	−0.22 ± 1.04*	−0.39 ± 1.12*
Executive function (*z*-score)	0.15 ± 0.61	0.07 ± 0.58	−0.09 ± 0.65*	−0.22 ± 0.62*	0.13 ± 0.59	0.08 ± 0.61	−0.16 ± 0.61*	−0.22 ± 0.53*
Language (*z*-score)	0.00 ± 0.83	0.09 ± 0.71	−0.16 ± 0.84†	−0.10 ± 0.92	0.05 ± 0.78	0.04 ± 0.77	−0.11 ± 0.79	−0.11 ± 0.94
Attention/speed of processing (*z*-score)	0.08 ± 0.62	0.03 ± 0.62	−0.04 ± 0.62	−0.16 ± 1.05	0.10 ± 0.60	0.02 ± 0.63	−0.08 ± 0.63	−0.20 ± 1.10

Study cohort characteristics	Temporal lobe DWMH Fazekas score				Occipital lobe DWMH Fazekas score			
	0, *N* = 376	1, *N* = 162	2, *N* = 15	3, *N* = 6	0, *N* = 518	1, *N* = 32	2, *N* = 8	3, *N* = 1
Age (years)	64.6 ± 7.4	66.7 ± 7.4	65.1 ± 7.7	66.3 ± 7.9	65.1 ± 7.4	66.3 ± 8.1	67.8 ± 8.7	74.0
Male sex, *n* (%)	200 (53.2)	77 (47.5)	6 (40.0)	5 (83.3)	265 (51.2)	17 (53.1)	5 (62.5)	1 (100)

TABLE 1 (Continued)

Study cohort characteristics	Temporal lobe DWMH Fazekas score				Occipital lobe DWMH Fazekas score			
	0, *N* = 376	1, *N* = 162	2, *N* = 15	3, *N* = 6	0, *N* = 518	1, *N* = 32	2, *N* = 8	3, *N* = 1
Education according to ISCED-1997 (years, median [Q1, Q3])	16.0 (13.0, 17.0)	13.0 (13.0, 16.5)	13.0 (13.0, 16.5)	13.0 (12.3; 16.9)	13.0 (13.0, 17.0)	13.0 (13.0, 16.5)	13.0 (13.0, 15.6)	13.0
SBP (mm Hg)	127.7 ± 17.3	130.1 ± 16.7	129.3 ± 19.8	143.5 ± 25.3	128.5 ± 17.4	130.7 ± 17.2	128.7 ± 11.3	129.0
DBP (mm Hg)	76.0 ± 9.7	76.1 ± 9.8	78.3 ± 11.6	81.8 ± 5.4	76.1 ± 9.7	76.8 ± 11.2	75.9 ± 7.2	81.0
Antihypertensive medications, *n* (%)	124 (33.0)	80 (49.4)	8 (53.3)	1 (16.7)	197 (38.0)	13 (40.6)	3 (37.5)	0 (0.0)
Antihypertensive treatment efficacy								
Untreated SBP <120 and DBP < 80 mm Hg, *n* (%)	84 (22.3)	25 (15.4)	3 (20.0)	0 (0.0)	105 (20.3)	6 (18.8)	1 (12.5)	0 (0.0)
Untreated SBP 120–139 or DBP 80–89 mm Hg, *n* (%)	119 (31.6)	33 (20.4)	3 (20.0)	4 (66.6)	146 (28.2)	9 (28.1)	3 (37.5)	1 (100.0)
Untreated SBP ≥140 or DBP ≥ 90 mm Hg, *n* (%)	49 (13.0)	24 (14.8)	1 (6.7)	1 (16.7)	70 (13.5)	4 (12.5)	1 (12.5)	0 (0.0)
Treated SBP <120 and DBP < 80 mm Hg, *n* (%)	34 (9.0)	24 (14.8)	3 (20.0)	0 (0.0)	58 (11.2)	2 (6.2)	1 (12.5)	0 (0.0)
Treated SBP 120–139 or DBP 80–89 mm Hg, *n* (%)	50 (13.2)	29 (17.9)	2 (13.3)	0 (0.0)	76 (14.7)	4 (12.5)	1 (12.5)	0 (0.0)
Treated SBP ≥140 or DBP≥90 mm Hg, *n* (%)	40 (10.6)	27 (16.7)	3 (20.0)	1 (16.7)	63 (12.1)	7 (21.9)	1 (12.5)	0 (0.0)
Total cholesterol (mg/dL)	220.2 ± 38.4	219.2 ± 36.6	232.0 ± 40.3	225.0 ± 38.2	220.2 ± 37.9	219.2 ± 37.6	223.9 ± 40.8	244
LDL cholesterol (mg/dL)	133.0 ± 32.4	128.9 ± 39.5	145.7 ± 43.3	137.2 ± 39.8	132.1 ± 32.2	129.3 ± 33.0	145.4 ± 36.5	168
HDL cholesterol (mg/dL)	64.3 ± 16.9	63.8 ± 18.4	68.1 ± 21.4	69.0 ± 10.7	64.3 ± 17.6	66.9 ± 16.5	55.1 ± 14.0	57
Lipid-lowering medications, *n* (%)	59 (15.7)	33 (20.4)	1 (6.7)	1 (16.7)	88 (17.0)	5 (15.6)	1 (12.5)	0 (0.0)
HbA1c (%)	5.73 ± 0.49	5.87 ± 0.57*	5.57 ± 0.41	5.75 ± 0.18	5.77 ± 0.52	5.83 ± 0.48	5.85 ± 0.49	5.60
Antidiabetic medications, *n* (%)	19 (5.1)	15 (9.3)	1 (6.7)	0 (0.0)	30 (5.8)	4 (12.5)	1 (12.5)	0 (0.0)

(Continues)

TABLE 1 (Continued)

Study cohort characteristics	Temporal lobe DWMH Fazekas score				Occipital lobe DWMH Fazekas score			
	0, *N* = 376	1, *N* = 162	2, *N* = 15	3, *N* = 6	0, *N* = 518	1, *N* = 32	2, *N* = 8	3, *N* = 1
Smoking status								
Never smoked, *n* (%)	176 (46.8)	76 (46.9)	5 (33.3)	4 (66.7)	243 (46.9)	12 (37.5)	5 (62.5)	1 (100.0)
Former smoker, *n* (%)	156 (41.5)	71 (43.8)	7 (46.7)	2 (33.3)	218 (42.1)	15 (46.9)	3 (37.5)	0 (0.0)
Current smoking, *n* (%)	44 (11.7)	15 (9.3)	3 (20.0)	0 (0.0)	57 (11.0)	5 (15.6)	0 (0.0)	0 (0.0)
BMI (kg/m^2)	27.2 ± 4.1	27.7 ± 4.2	26.7 ± 3.7	27.8 ± 1.3	27.3 ± 4.1	26.9 ± 3.9	29.1 ± 4.8	26.7
Alcohol consumption (g/week, median [Q1, Q3])	55.6 (0.0, 128.6)	39.7 (0.0, 119.1)	2.8 (0.0, 79.4)	99.3 (39.32, 21.7)	41.7 (0.0, 119.1)	66.7 (6.61, 75.3)	29.2 (0.0, 63.0)	52.4
Depression (score, median [Q1, Q3])	5.0 (2.0, 8.0)	5.0 (3.0, 8.0)	5.0 (2.5, 9.5)	5.0 (2.0, 11.0)	5.0 (2.0, 8.0)	4.0 (2.5, 9.0)	4.8 (1.0, 12.0)	9.0
APOE-ε4, *n* (%)	52 (20.3)	33 (31.7)	2 (18.2)	0 (0.0)	75 (21.9)	9 (36.0)	3 (50.0)	0 (0.0)
WMH volume (cm^3, median [Q1, Q3])	3.96 (2.64, 5.78)	6.52 (4.32, 10.71)*	17.17 (8.08, 31.82)	30.04 (23.06, 47.93)	4.43 (2.97, 7.08)	8.13 (3.68, 14.17)*	15.94 (8.38, 22.58)*	23.2
WMH volume/white matter volume (%, median [Q1, Q3])	0.85 (0.56, 1.23)	1.41 (0.92, 2.51)*	3.11 (1.86, 7.36)	5.27 (4.97, 9.34)	0.95 (0.62, 1.55)	1.51 (0.76, 2.83)*	2.88 (1.87, 6.02)*	5.25
Global cognition (*z*-score)	0.08 ± 0.52	−0.05 ± 0.58	−0.10 ± 0.55	0.17 ± 0.10	0.05 ± 0.54	0.01 ± 0.50	−0.46 ± 0.81	−0.09 ± 0.00
Verbal memory (*z*-score)	0.03 ± 0.93	−0.07 ± 0.92	0.08 ± 1.08	−0.43 ± 0.79	0.02 ± 0.94	−0.10 ± 0.81	−0.50 ± 0.89	−1.00 ± 0.00
Non-verbal memory (*z*-score)	0.08 ± 0.96	−0.18 ± 1.04*	−0.09 ± 0.77	−0.24 ± 1.97	0.92 ± 0.98	−0.23 ± 1.29	−0.10 ± 1.36	−0.06 ± 0.00
Executive function (*z*-score)	0.07 ± 0.59	−0.09 ± 0.66*	−0.17 ± 0.57	0.13 ± 0.54	0.03 ± 0.61	−0.09 ± 0.63	−0.48 ± 0.81	0.07 ± 0.00
Language (*z*-score)	0.06 ± 0.73	−0.12 ± 0.84	0.13 ± 0.75	−0.57 ± 1.71	0.02 ± 0.78	−0.05 ± 0.81	−0.60 ± 1.08	−0.58 ± 0.00
Attention/speed of processing (*z*-score)	0.05 ± 0.59	−0.08 ± 0.67	−0.15 ± 0.59	−0.65 ± 2.58	0.01 ± 0.66	0.04 ± 0.64	−0.41 ± 0.83	0.14 ± 0.00

Note: Data are mean ± standard deviation unless otherwise indicated. One DWMH Fazekas score each is missing for the parietal, temporal, and occipital lobe. *$p < 0.001$ compared with 0. †$< p < 0.001$ compared with 1. ‡$< p < 0.001$ compared with 2.

Abbreviations: APOE, apolipoprotein E genotype; BMI, body mass index; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensities; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; WMH, white matter hyperintensities.

while only one participant had only temporal lobe and none of the participants only occipital lobe DWMH. When looking at combinations, the highest percentage of participants had DWMH in the frontal and parietal lobe (37.0%); other combinations were less frequent (frontal and temporal: 1.1%; frontal and occipital: 0.7%; frontal, parietal, and temporal: 27.5%; frontal, parietal, temporal, and occipital: 3.4%; parietal and temporal: 0.2%; parietal and occipital: 0.2%; parietal, temporal, and occipital: 0%; temporal and occipital: 0.2%). Presence of frontal and parietal lobe DWMH was significantly related ($X^2(1, N = 559) = 114.7$, $p < 0.001$), and frontal and parietal DWMH score was also significantly correlated ($r = 0.63$, $p < 0.001$). As already observed for WMH volume [3], WMH load quantified by Fazekas score did not significantly differ between men and women but significantly increased with age in the frontal and parietal lobe (Table 1).

Association of BP, its treatment, and treatment efficacy with DWMH in different cerebral lobes → pathophysiology of regional WMH

Descriptive statistics showed increasing DWMH Fazekas scores for the frontal and parietal lobe with increasing BP, increasing treatment frequency, and decreasing treatment efficacy (Table 1, Figure 1). In the unadjusted ordinal regression model, higher SBP was significantly ($p < 0.001$) associated with higher DWMH Fazekas scores for the frontal and parietal lobe (OR = 1.16 per 10 mm Hg, 95% CI = 1.06–1.27 and 1.17 [1.07–1.28], respectively, Table 2). In models adjusted for age and sex as well as in fully adjusted models, associations remained significant at the uncorrected significance level ($p < 0.05$, e.g., fully adjusted OR 1.13 [1.02–1.25] for frontal and 1.11 [1.01–1.19] for parietal lobe DWMH score, Table 2). Participants with higher frontal and parietal lobe Fazekas score also had higher DBP with results however not reaching the corrected statistical significance level (Tables 1 and 2; Figure 2). Prevalence of antihypertensive medications as indicator of mostly long-term hypertension was significantly associated with higher DWMH Fazekas scores for all cerebral lobes except for the occipital lobe in the undjusted model; associations remained significant at the uncorrected significance level ($p < 0.05$, e.g., fully adjusted OR 1.55 [1.11–2.20] for frontal, 1.62 [1.15–2.27] for parietal, 1.86 [1.26–2.72] for temporal, and 1.06 [0.53–2.12] for occipital lobe DWMH score, Table 2; Figure 2). When looking at treated and untreated participants separately, associations between SBP and DWMH scores were slightly stronger in treated than in untreated participants for all cerebral lobes (e.g., crude OR = 1.19 per 10 mm Hg, 95% CI = 1.03–1.38 compared with 1.12 [1.00–1.25] for the frontal lobe). Similarly, the analysis of treatment efficacy showed that especially poorly controlled hypertension was significantly associated with higher DWMH scores reaching statistical significance for all cerebral lobes except for the occipital lobe in the unadjusted model, with associations remaining significant at the uncorrected significance level ($p < 0.05$) in adjusted models (Table 2; Figure 2). Results of ordinal regressions were confirmed by multinomial regressions (Tables S1–S4). Interaction terms of age and sex with BP, its treatment, and treatment efficacy did not reach statistical significance for all cerebral lobes (data not shown). Additionally, adding the time between the assessment of WMH and the assessment of BP, its treatment, and the remaining parameters to all regression models did not change the results to a major extent (data not shown).

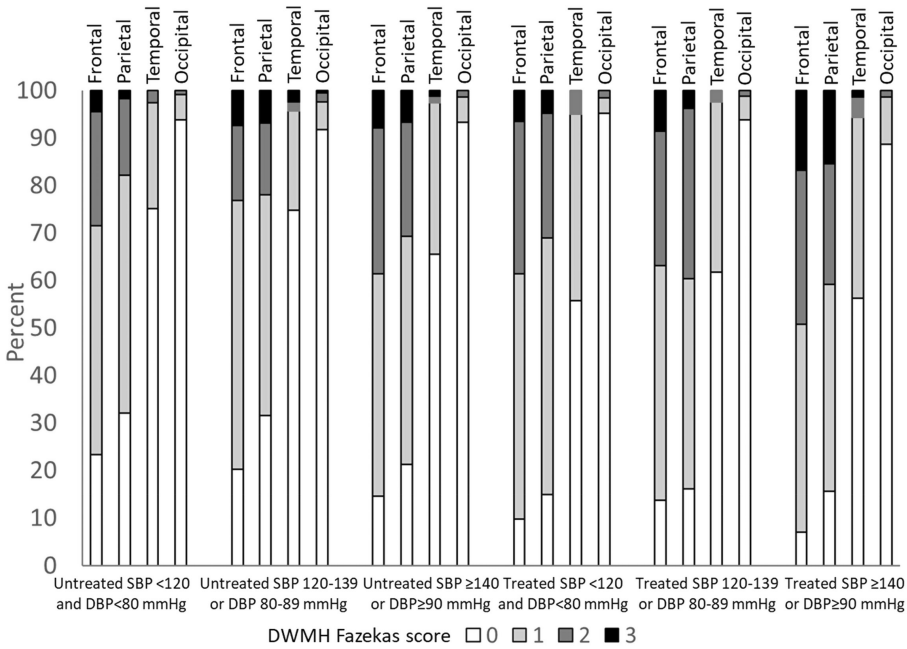

FIGURE 1 Classification of white matter hyperintensities according to modified (scored separately for the cerebral lobes) deep white matter hyperintensities (DWMH) Fazekas score, stratified by antihypertensive treatment efficacy. Data are shown as percentage.

TABLE 2 Association of (A) blood pressure and its treatment and (B) treatment efficacy with modified (scored separately for the cerebral lobes) deep white matter hyperintensities Fazekas score.

	Frontal lobe DWMH Fazekas score			Parietal lobe DWMH Fazekas score		
Blood pressure, its treatment and treatment efficacy	**OR (95% CI) crude**	**OR (95% CI) adjusted age, sex**	**OR (95% CI) fully adjusted**	**OR (95% CI) crude**	**OR (95% CI) adjusted age, sex**	**OR (95% CI) fully adjusted**
(A)						
SBP (per 10 mm Hg)	$R^2 = 0.008$ 1.16 (1.06–1.27)	$R^2 = 0.041$ 1.14 (1.03–1.25)	$R^2 = 0.044$ 1.13 (1.02–1.25)	$R^2 = 0.008$ 1.17 (1.07–1.28)	$R^2 = 0.048$ 1.13 (1.02–1.23)	$R^2 = 0.048$ 1.11 (1.01–1.22)
DBP (per 5 mm Hg)	$R^2 = 0.001$ 1.05 (0.97–1.14)	$R^2 = 0.041$ 1.12 (1.03–1.21)	$R^2 = 0.043$ 1.11 (1.02–1.21)	$R^2 = 0.001$ 1.04 (0.96–1.13)	$R^2 = 0.048$ 1.11 (1.01–1.20)	$R^2 = 0.048$ 1.09 (1.01–1.19)
Antihypertensive medications (yes vs. no)	$R^2 = 0.011$ 1.88 (1.36–2.61)	$R^2 = 0.041$ 1.49 (1.07–2.08)	$R^2 = 0.044$ 1.55 (1.11–2.20)	$R^2 = 0.015$ 2.12 (1.52–2.92)	$R^2 = 0.050$ 1.67 (1.19–2.32)	$R^2 = 0.050$ 1.62 (1.15–2.27)
(B)	$R^2 = 0.018$	$R^2 = 0.045$	$R^2 = 0.048$	$R^2 = 0.020$	$R^2 = 0.053$	$R^2 = 0.052$
Untreated SBP <120 and DBP < 80 mm Hg	Reference	Reference	Reference	Reference	Reference	Reference
Untreated SBP 120–139 or DBP 80–89 mm Hg	0.97 (0.61–1.54)	0.98 (0.61–1.58)	1.02 (0.63–1.65)	1.16 (0.74–1.84)	1.11 (0.69–1.77)	1.08 (0.67–1.75)
Untreated SBP ≥140 or DBP≥90 mm Hg	1.70 (0.98–2.97)	1.40 (0.79–2.51)	1.32 (0.73–2.39)	1.88 (1.08–3.25)	1.42 (0.79–2.51)	1.26 (0.70–2.25)
Treated SBP <120 and DBP < 80 mm Hg	1.86 (1.03–3.35)	1.34 (0.73–2.44)	1.40 (0.76–2.59)	2.18 (1.21–3.90)	1.49 (0.82–2.75)	1.39 (0.76–2.59)
Treated SBP 120–139 or DBP 80–89 mm Hg	1.68 (0.98–2.89)	1.34 (0.76–2.34)	1.40 (0.79–2.48)	2.56 (1.49–4.39)	1.90 (1.08–3.32)	1.82 (1.04–3.22)
Treated SBP ≥140 or DBP ≥ 90 mm Hg	3.03 (1.72–5.31)	2.41 (1.34–4.31)	2.46 (1.35–4.44)	3.16 (1.80–5.53)	2.34 (1.31–4.18)	2.14 (1.17–3.86)
	Temporal lobe DWMH Fazekas score			**Occipital lobe DWMH Fazekas score**		
Blood pressure, its treatment and treatment efficacy	**OR (95% CI) crude**	**OR (95% CI) adjusted age, sex**	**OR (95% CI) fully adjusted**	**OR (95% CI) crude**	**OR (95% CI) adjusted age, sex**	**OR (95% CI) fully adjusted**
(A)						
SBP (per 10 mm Hg)	$R^2 = 0.004$ 1.11 (0.99–1.22)	$R^2 = 0.014$ 1.09 (0.98–1.22)	$R^2 = 0.016$ 1.07 (0.96–1.19)	$R^2 = 0.001$ 1.06 (0.89–1.27)	$R^2 = 0.007$ 1.02 (0.85–1.23)	$R^2 = 0.020$ 0.99 (0.82–1.21)
DBP (per 5 mm Hg)	$R^2 = 0.001$ 1.03 (0.94–1.13)	$R^2 = 0.013$ 1.06 (0.97–1.17)	$R^2 = 0.016$ 1.05 (0.96–1.16)	$R^2 = 0.001$ 1.03 (0.88–1.21)	$R^2 = 0.007$ 1.03 (0.88–1.22)	$R^2 = 0.020$ 1.01 (0.85–1.21)
Antihypertensive medications (yes vs. no)	$R^2 = 0.014$ 1.88 (1.31–2.66)	$R^2 = 0.020$ 1.72 (1.19–2.48)	$R^2 = 0.027$ 1.86 (1.26–2.72)	$R^2 = 0.001$ 1.04 (0.54–1.99)	$R^2 = 0.007$ 0.92 (0.47–1.80)	$R^2 = 0.020$ 1.06 (0.53–2.12)
(B)	$R^2 = 0.017$	$R^2 = 0.023$	$R^2 = 0.028$	$R^2 = 0.007$	$R^2 = 0.014$	$R^2 = 0.029$
Untreated SBP <120 and DBP < 80 mm Hg	Reference	Reference	Reference	Reference	Reference	Reference
Untreated SBP 120–139 or DBP 80–89 mm Hg	1.03 (0.59–1.80)	1.09 (0.62–1.93)	1.01 (0.57–1.80)	1.35 (0.52–3.53)	1.23 (0.46–3.29)	1.07 (0.39–2.92)
Untreated SBP ≥140 or DBP ≥ 90 mm Hg	1.57 (0.83–2.94)	1.54 (0.79–2.97)	1.27 (0.64–2.51)	1.07 (0.33–3.53)	0.89 (0.26–3.00)	0.64 (0.17–2.41)
Treated SBP <120 and DBP < 80 mm Hg	2.34 (1.21–4.48)	2.16 (1.09–4.22)	2.18 (1.09–4.31)	0.79 (0.20–3.16)	0.63 (0.15–2.61)	0.63 (0.15–2.64)
Treated SBP 120–139 or DBP 80–89 mm Hg	1.80 (0.97–3.32)	1.73 (0.91–3.29)	1.70 (0.89–3.25)	0.99 (0.30–3.25)	0.81 (0.24–2.75)	0.81 (0.24–2.80)
Treated SBP ≥140 or DBP ≥ 90 mm Hg	2.32 (1.23–4.35)	2.20 (1.15–4.22)	2.18 (1.12–4.22)	1.90 (0.65–5.47)	1.52 (0.50–4.57)	1.51 (0.49–4.66)

Note: Fully adjusted = age, alcohol consumption, depression score, education, sex, smoking status.

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensities; OR, odds ratio in ordinal regression; SBP, systolic blood pressure.

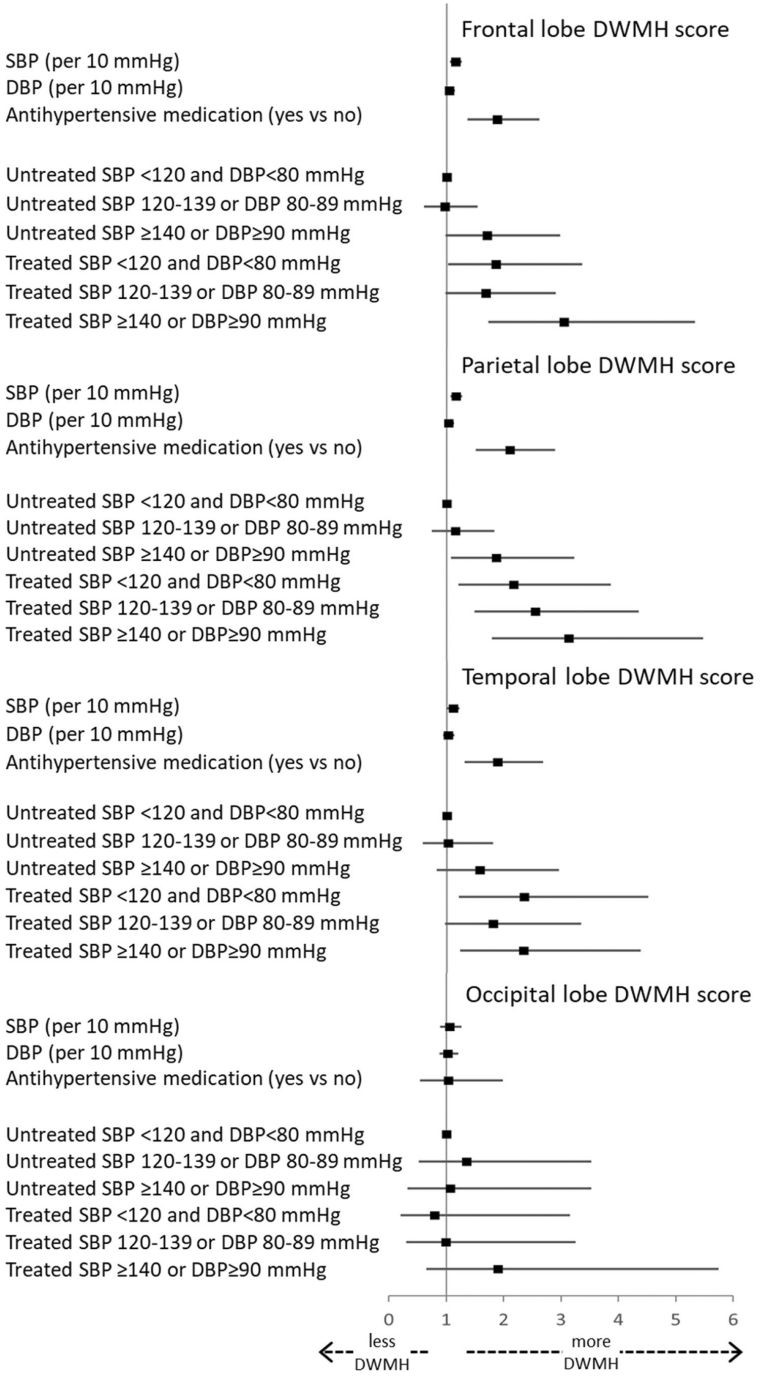

FIGURE 2 Association of blood pressure, its treatment, and treatment efficacy with modified (scored separately for the cerebral lobes) deep white matter hyperintensities (DWMH) Fazekas score. Forest plot shows odds ratios with 95% confidence intervals from unadjusted ordinal regressions. DBP, diastolic blood pressure; SBP, systolic blood pressure.

Association of DWMH in different cerebral lobes with cognitive performance in different domains → clinical consequences of regional WMH

522 participants of the study cohort (93.2%) had complete cognition data. Descriptive statistics showed decreasing performance in global cognition, the summary measure of all neuropsychological tests, and in the domains for executive function and non-verbal memory with increasing DWMH Fazekas scores in the frontal and parietal lobe (Table 1, Figure 3). In the unadjusted linear regression model, global cognition, executive function, and non-verbal memory were significantly associated with frontal and parietal lobe DWMH (Table 3; Figure 4). For the other cognitive domains (verbal memory, language, attention/speed of processing), results did not reach the corrected statistical significance level (Table 3; Figure 4). Associations between DWMH scores and cognition were markedly reduced in adjusted models (Table 3). Since a high percentage of participants exhibited both frontal and parietal DWMH (37.0%), we checked whether adding the other region DWMH improved explanation of cognitive performance. When using hierarchical linear regression models, we observed that adding parietal DWMH score to frontal DWMH score moderately to slightly improved model performance (increase in R^2 by 0.011, $p = 0.110$ for global cognition in the unadjusted model; increase in R^2 by 0.013, $p = 0.063$ for

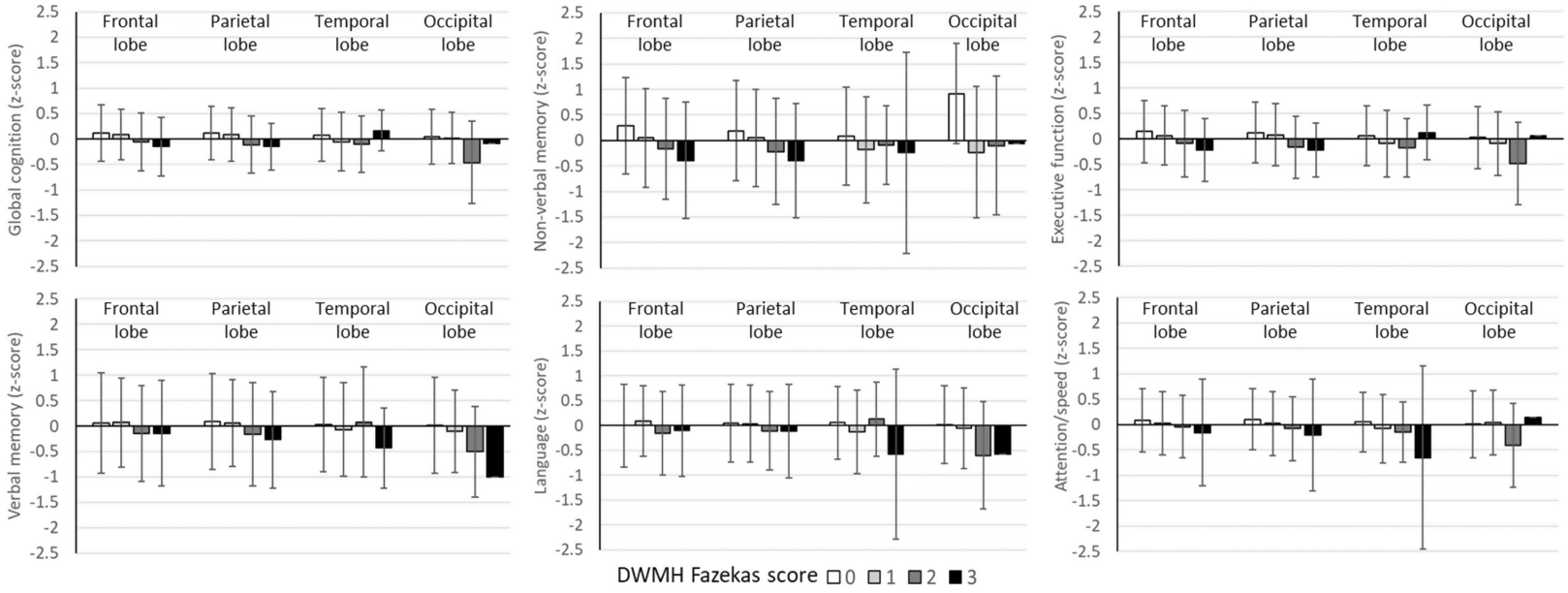

FIGURE 3 Global cognition and cognitive performance in different cognitive domains (*z*-score) stratified by modified (scored separately for the cerebral lobes) deep white matter hyperintensities (DWMH) Fazekas score. Data are shown as mean ± standard deviation.

TABLE 3 Association of modified (scored separately for the cerebral lobes) deep white matter hyperintensities (DWMH) Fazekas scores with global cognition and cognitive performance in different cognitive domains (*z*-score).

	Global cognition			**Verbal memory**		
DWMH Fazekas score	***β* (95% CI) crude**	***β* (95% CI) adjusted age, sex**	***β* (95% CI) fully adjusted**	***β* (95% CI) crude**	***β* (95% CI) adjusted age, sex**	***β* (95% CI) fully adjusted**
Frontal lobe	$R^2 = 0.021$	$R^2 = 0.138$	$R^2 = 0.238$	$R^2 = 0.006$	$R^2 = 0.167$	$R^2 = 0.196$
0	Reference	Reference	Reference	Reference	Reference	Reference
1	−0.03 (−0.16 to 0.10)	0.03 (−0.10 to 0.15)	0.05 (−0.07 to 0.16)	0.02 (−0.20 to 0.24)	0.09 (−0.11 to 0.29)	0.13 (−0.08 to 0.33)
2	−0.18 (−0.33 to −0.04)	−0.06 (−0.20 to 0.08)	−0.04 (−0.17 to 0.09)	−0.19 (−0.44 to 0.05)	−0.06 (−0.28 to 0.18)	−0.03 (−0.26 to 0.20)
3	−0.27 (−0.47 to −0.07)	−0.07 (−0.26 to 0.12)	0.01 (−0.17 to 0.19)	−0.20 (−0.53 to 0.14)	−0.03 (−0.34 to 0.29)	0.05 (−0.27 to 0.37)
Parietal lobe	$R^2 = 0.029$	$R^2 = 0.139$	$R^2 = 0.238$	$R^2 = 0.011$	$R^2 = 0.165$	$R^2 = 0.194$
0	Reference	Reference	Reference	Reference	Reference	Reference
1	−0.03 (−0.14 to 0.08)	0.02 (−0.09 to 0.13)	0.04 (−0.06 to 0.14)	−0.03 (−0.22 to 0.17)	−0.01 (−0.19 to 0.17)	0.04 (−0.14 to 0.22)
2	−0.23 (−0.37 to −0.10)	−0.08 (−0.21 to 0.05)	−0.04 (−0.17 to 0.08)	−0.25 (−0.48 to −0.02)	−0.09 (−0.31 to 0.13)	−0.03 (−0.25 to 0.19)
3	−0.27 (−0.47 to −0.06)	−0.08 (−0.28 to 0.28)	−0.07 (−0.27 to 0.13)	−0.37 (−0.71 to −0.02)	−0.16 (−0.49 to 0.17)	−0.16 (−0.50 to 0.19)
Temporal lobe	$R^2 = 0.008$	$R^2 = 0.139$	$R^2 = 0.236$	$R^2 = 0.001$	$R^2 = 0.164$	$R^2 = 0.192$
0	Reference	Reference	Reference	Reference	Reference	Reference
1	−0.13 (−0.24 to −0.03)	−0.07 (−0.17 to 0.03)	−0.04 (−0.13 to 0.05)	−0.10 (−0.27 to 0.08)	−0.06 (−0.22 to 0.10)	−0.04 (−0.20 to 0.13)
2	−0.18 (−0.47 to 0.11)	−0.15 (−0.42 to 0.12)	0.01 (−0.26 to 0.28)	0.05 (−0.43 to 0.53)	−0.01 (−0.44 to 0.44)	0.07 (−0.40 to 0.53)
3	0.09 (−0.39 to 0.56)	0.08 (−0.36 to 0.53)	0.21 (−0.20 to 0.63)	−0.47 (−1.22 to 0.29)	0.08 (−0.24 to 0.35)	−0.15 (−0.83 to 0.54)
Occipital lobe	$R^2 = 0.008$	$R^2 = 0.144$	$R^2 = 0.235$	$R^2 = 0.002$	$R^2 = 0.165$	$R^2 = 0.192$
0	Reference	Reference	Reference	Reference	Reference	Reference
1	−0.04 (−0.24 to 0.17)	−0.02 (−0.21 to 0.17)	−0.02 (−0.20 to 0.16)	−0.11 (−0.45 to 0.22)	−0.06 (−0.37 to 0.25)	−0.03 (−0.34 to 0.28)
2	−0.51 (−0.89 to −0.14)	−0.44 (−0.79 to −0.09)	−0.12 (−0.50 to 0.26)	−0.52 (−1.17 to 0.13)	−0.37 (−0.91 to 0.23)	−0.18 (−0.86 to 0.50)
3	−0.14 (−1.20 to 0.92)	0.08 (−0.91 to 1.07)	0.32 (−0.60 to 1.24)	−1.02 (−2.85 to 0.80)	−0.46 (−2.21 to 1.22)	−0.27 (−1.92 to 1.39)
	Non-verbal memory			**Executive function**		
DWMH Fazekas score	***β* (95% CI) crude**	***β* (95% CI) adjusted age, sex**	***β* (95% CI) fully adjusted**	***β* (95% CI) crude**	***β* (95% CI) adjusted age, sex**	***β* (95% CI) fully adjusted**
Frontal lobe	$R^2 = 0.029$	$R^2 = 0.150$	$R^2 = 0.237$	$R^2 = 0.025$	$R^2 = 0.129$	$R^2 = 0.247$
0	Reference	Reference	Reference	Reference	Reference	Reference
1	−0.25 (−0.48 to −0.01)	−0.12 (−0.34 to 0.11)	−0.07 (−0.28 to 0.14)	−0.08 (−0.22 to 0.07)	−0.01 (−0.15 to 0.13)	0.01 (−0.12 to 0.13)
2	−0.46 (−0.72 to −0.19)	−0.21 (−0.46 to 0.04)	−0.16 (−0.41 to 0.08)	−0.23 (−0.39 to −0.07)	−0.09 (−0.25 to 0.06)	−0.08 (−0.22 to 0.07)
3	−0.68 (−1.04 to −0.33)	−0.30 (−0.64 to 0.05)	−0.21 (−0.54 to 0.13)	−0.36 (−0.58 to −0.14)	−0.15 (−0.36 to 0.07)	−0.07 (−0.27 to 0.13)
Parietal lobe	$R^2 = 0.025$	$R^2 = 0.146$	$R^2 = 0.238$	$R^2 = 0.035$	$R^2 = 0.134$	$R^2 = 0.252$
0	Reference	Reference	Reference	Reference	Reference	Reference

(Continues)

TABLE 3 (Continued)

	Non-verbal memory			Executive function		
DWMH Fazekas score	**β (95% CI) crude**	**β (95% CI) adjusted age, sex**	**β (95% CI) fully adjusted**	**β (95% CI) crude**	**β (95% CI) adjusted age, sex**	**β (95% CI) fully adjusted**
1	−0.13 (−0.34 to 0.07)	−0.01 (−0.21 to 0.18)	0.02 (−0.17 to 0.20)	−0.05 (−0.18 to 0.08)	0.02 (−0.11 to 0.14)	0.03 (−0.09 to 0.14)
2	−0.41 (−0.65 to −0.16)	−0.11 (−0.35 to 0.13)	−0.07 (−0.30 to 0.16)	−0.29 (−0.44 to −0.14)	−0.12 (−0.27 to 0.03)	−0.08 (−0.22 to 0.06)
3	−0.58 (−0.95 to −0.21)	−0.20 (−0.56 to 0.15)	−0.27 (−0.63 to 0.09)	−0.35 (−0.58 to −0.12)	−0.16 (−0.38 to 0.06)	−0.18 (−0.40 to 0.03)
Temporal lobe	$R^2 = 0.009$	$R^2 = 0.148$	$R^2 = 0.237$	$R^2 = 0.012$	$R^2 = 0.132$	$R^2 = 0.246$
0	Reference	Reference	Reference	Reference	Reference	Reference
1	−0.26 (−0.45 to −0.07)	−0.15 (−0.33 to 0.03)	−0.13 (−0.30 to 0.04)	−0.16 (−0.28 to −0.05)	−0.10 (−0.21 to 0.01)	−0.06 (−0.16 to 0.04)
2	−0.17 (−0.71 to 0.36)	−0.08 (−0.58 to 0.41)	0.02 (−0.49 to 0.52)	−0.24 (−0.56 to 0.07)	−0.21 (−0.51 to 0.08)	−0.05 (−0.34 to 0.24)
3	−0.33 (−1.13 to 0.48)	−0.31 (−1.05 to 0.44)	−0.14 (−0.85 to 0.56)	0.06 (−0.48 to 0.60)	0.03 (−0.47 to 0.54)	0.19 (−0.28 to 0.65)
Occipital lobe	$R^2 = 0.001$	$R^2 = 0.146$	$R^2 = 0.237$	$R^2 = 0.007$	$R^2 = 0.134$	$R^2 = 0.246$
0	Reference	Reference	Reference	Reference	Reference	Reference
1	−0.24 (−0.62 to 0.13)	−0.23 (−0.57 to 0.12)	−0.18 (−0.51 to 0.15)	−0.13 (−0.35 to 0.10)	−0.10 (−0.31 to 0.11)	−0.09 (−0.28 to 0.11)
2	−0.12 (−0.82 to 0.58)	−0.01 (−0.66 to 0.64)	0.33 (−0.38 to 1.03)	−0.52 (−0.94 to −0.09)	−0.45 (−0.85 to −0.05)	−0.12 (−0.54 to 0.31)
3	−0.07 (−2.04 to 1.89)	0.26 (−1.57 to 2.08)	0.67 (−1.05 to 2.39)	0.04 (−1.16 to 1.24)	0.24 (−0.88 to 1.36)	0.53 (−0.50 to 1.57)
	Language			**Attention/speed of processing**		
DWMH Fazekas score	**β (95% CI) crude**	**β (95% CI) adjusted age, sex**	**β (95% CI) fully adjusted**	**β (95% CI) crude**	**β (95% CI) adjusted age, sex**	**β (95% CI) fully adjusted**
Frontal lobe	$R^2 = 0.013$	$R^2 = 0.082$	$R^2 = 0.125$	$R^2 = 0.004$	$R^2 = 0.081$	$R^2 = 0.092$
0	Reference	Reference	Reference	Reference	Reference	Reference
1	0.09 (−0.10 to 0.28)	0.17 (−0.02 to 0.35)	0.18 (0.01 to 0.36)	−0.06 (−0.21 to 0.10)	0.02 (−0.14 to 0.17)	0.03 (−0.12 to 0.18)
2	−0.16 (−0.37 to −0.05)	−0.01 (−0.22 to 0.20)	0.01 (−0.20 to 0.21)	−0.12 (−0.30 to 0.05)	0.02 (−0.16 to 0.19)	0.05 (−0.12 to 0.23)
3	−0.10 (−0.38 to 0.18)	0.13 (−0.16 to 0.40)	0.20 (−0.09 to 0.48)	−0.25 (−0.48 to −0.01)	−0.04 (−0.28 to 0.20)	0.02 (−0.22 to 0.25)
Parietal lobe	$R^2 = 0.003$	$R^2 = 0.071$	$R^2 = 0.098$	$R^2 = 0.010$	$R^2 = 0.083$	$R^2 = 0.093$
0	Reference	Reference	Reference	Reference	Reference	Reference
1	−0.01 (−0.17 to 0.16)	0.07 (−0.09 to 0.23)	0.09 (−0.07 to 0.25)	−0.09 (−0.22 to 0.05)	−0.03 (−0.16 to 0.11)	−0.03 (−0.16 to 0.11)
2	−0.16 (−0.36 to 0.03)	0.02 (−0.18 to 0.22)	0.07 (−0.13 to 0.26)	−0.19 (−0.35 to −0.02)	−0.03 (−0.19 to 0.14)	0.01 (−0.16 to 0.16)
3	−0.16 (−0.45 to 0.14)	0.06 (−0.24 to 0.35)	0.06 (−0.24 to 0.35)	−0.30 (−0.55 to −0.05)	−0.11- (0.36 to 0.13)	−0.11 (−0.36 to 0.14)
Temporal lobe	$R^2 = 0.011$	$R^2 = 0.080$	$R^2 = 0.106$	$R^2 = 0.014$	$R^2 = 0.096$	$R^2 = 0.104$
0	Reference	Reference	Reference	Reference	Reference	Reference
1	−0.17 (−0.32 to −0.02)	−0.11 (−0.25 to 0.04)	−0.07 (−0.22 to 0.07)	−0.13 (−0.25 to −0.01)	−0.07 (−0.19 to 0.05)	−0.06 (−0.18 to 0.06)
2	0.07 (−0.33 to 0.48)	0.10 (−0.29 to 0.49)	0.28 (−0.13 to 0.69)	−0.21 (−0.55 to 0.13)	−0.19 (−0.51 to 0.14)	−0.09 (−0.43 to 0.26)
3	−0.63 (−1.26 to 0.01)	−0.61 (−1.22 to 0.01)	−0.51 (−1.10 to 0.09)	−0.70 (−1.24 to −0.17)	−0.66 (−1.19 to −0.16)	−0.64 (−1.14 to −0.14)

TABLE 3 (Continued)

	Language			Attention/speed of processing		
DWMH Fazekas score	**β (95% CI) crude**	**β (95% CI) adjusted age, sex**	**β (95% CI) fully adjusted**	**β (95% CI) crude**	**β (95% CI) adjusted age, sex**	**β (95% CI) fully adjusted**
Occipital lobe	$R^2 = 0.005$	$R^2 = 0.078$	$R^2 = 0.096$	$R^2 = 0.001$	$R^2 = 0.086$	$R^2 = 0.093$
0	Reference	Reference	Reference	Reference	Reference	Reference
1	−0.06 (−0.34 to 0.22)	−0.03 (−0.30 to 0.24)	−0.02 (−0.29 to 0.24)	0.03 (−0.22 to 0.27)	0.05 (−0.18 to 0.28)	0.04 (−0.19 to 0.27)
2	−0.62 (−1.17 to −0.07)	−0.55 (−1.08 to 1.10)	−0.08 (−0.67 to 0.52)	−0.42 (−0.89 to 0.04)	−0.36 (−0.81 to 0.09)	−0.09 (−0.60 to 0.41)
3	−0.59 (−2.14 to 0.95)	−0.39 (−1.88 to 1.10)	−0.19 (−1.65 to 1.28)	0.14 (−1.17 to 1.44)	−0.34 (−0.91 to 1.59)	0.49 (−0.74 to 1.72)

Note: Fully adjusted = age, alcohol consumption, depression score, education, sex, smoking status.

Abbreviations: CI, confidence interval; DWMH, deep white matter hyperintensities; β, unstandardized weight in linear regression.

executive function; increase in R^2 by 0.008, $p = 0.224$ for verbal memory; increase in R^2 by 0.006, $p = 0.368$ for non-verbal memory; increase in R^2 by 0.006, $p = 0.321$ for attention/speed of processing; increase in R^2 by 0.001, $p = 0.919$ for language). Adding frontal to parietal DWMH score increased R^2 by 0.004, $p = 0.536$ for global cognition; by 0.004, $p = 0.487$ for executive function; by 0.003, $p = 0.693$ for verbal memory; by 0.029, $p = 0.137$ for non-verbal memory; by 0.001, $p = 0.966$ for attention/speed of processing; and by 0.011, $p = 0.096$ for language. Additionally, adding the time between the assessment of cognition/WMH and the assessment of the remaining parameters to the fully adjusted regression model did not change the results to a major extent (data not shown).

DISCUSSION

Using data from the population-based 1000BRAINS study, we showed that (i) DWMH were highly frequent in the frontal and parietal, less frequent in the temporal, and rare in the occipital lobe; (ii) higher BP, prevalence of antihypertensive medications, and lower treatment efficacy were significantly associated with higher scores for DWMH in the frontal, parietal, and temporal, but not occipital lobe; and (iii) higher scores for DWMH in the frontal and parietal, but not temporal and occipital lobe were significantly associated with lower performance in executive function and memory.

The association of regional WMH with hypertension and different cognitive functions has not been investigated in population-based studies before. Previous evidence from a small cohort of older patients with multiple lacunar infarcts showed that compared with non-demented patients, demented patients had more severe WMH in the frontal lobe, which were significantly associated with SBP and DBP as well as dementia severity [13]. Regarding the association between hypertension and regional WMH, previous population-based evidence is available only from NOMAS, which had a similar age but slightly more females and in contrast to our cohort had a multi-ethnic composition, a higher mean BP, and higher variability of WMH. Using automatically determined regional WMH volume instead of Fazekas scoring, this study also showed that the frontal lobe was most strongly affected by WMH, followed by the parietal, temporal, and occipital lobe. Regarding the association between hypertension and regional WMH volume, a main drawback of that study was the time lag between the assessment of hypertension and WMH (6 ± 3 years). In sensitivity analyses accounting for potential selection bias by weighting for inverse probability of selection, low DBP (<80 mm Hg) and SBP (<120 mm Hg) were associated with lower WMH volume in the frontal and parietal lobe relative to high DBP (≥90 mm Hg) and SBP (≥140 mm Hg). Temporal and occipital WMH volume was not significantly associated with BP categories [12]. Also in women undergoing hormone treatment participating in the Women's Health Initiative (WHI) Memory Study - Magnetic Resonance Imaging (WHIMS-MRI) trial, WMH volume was highest in the frontal lobe, followed by the parietal lobe and temporal lobe, being low in the occipital lobe.

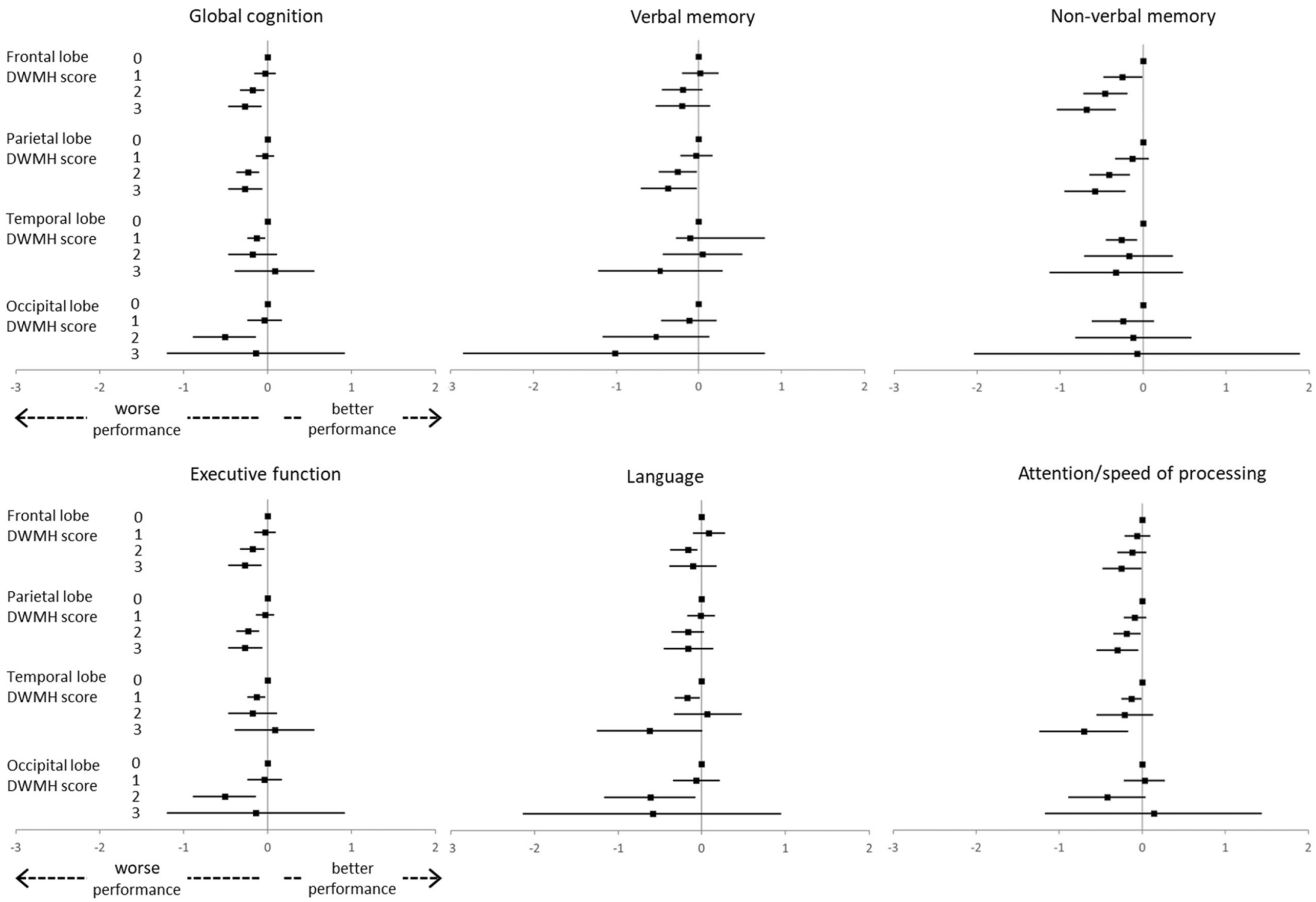

FIGURE 4 Association of modified (scored separately for the cerebral lobes) deep white matter hyperintensities (DWMH) Fazekas scores with global cognition and cognitive performance in different cognitive domains (*z*-score). Forest plot shows unstandardized weights with 95% confidence intervals from linear regressions.

Hypertension (SBP ≥140 mm Hg, or DBP ≥90 mm Hg, or antihypertensive medications) was significantly associated with WMH volume in all cerebral lobes except for the occipital lobe [21]. In a case–control study including hypertensive patients (SBP 160–179 mm Hg or DBP 90–99 mm Hg) and normotensive controls (BP <150/90 mm Hg) aged ≥70 years, WMH, which were quantified with the Scheltens scale, again most often affected the frontal lobe, followed by the parietal, temporal, and occipital lobe. Hypertension was again associated with WMH severity in all lobes except for the occipital lobe [22]. The differential regional susceptibility to hypertensive damage might explain the differential distribution of WMH across cerebral lobes, thus indicating different pathophysiological mechanisms. There is evidence that blood flow is reduced in prefrontal brain areas of older hypertensive patients as a function of the hemodynamic effects of vascular remodeling in long-term hypertension, rendering the frontal lobe especially susceptible to white matter lesions [11].

Previous population-based evidence on the association between regional WMH, which were in contrast to our study determined automatically as WMH volume, and different cognitive functions is to date available from the Leipzig Research Centre for Civilization Diseases (LIFE) study cohort, which is slightly older than our 1000BRAINS cohort. In this study, similar to our observations, WMH in the frontal lobe were associated with executive function and WMH in the parieto-temporal junctions with memory performance [23]. In a small cohort study of older persons including normal, cognitively impaired, and demented subjects, WMH volume was also highest in the frontal lobe, and higher frontal lobe WMH volume was related to lower executive function and lower frontal lobe glucose metabolism. Higher WMH volume, but not lower glucose metabolism in the frontal lobe, was related to lower memory performance [24]. Similar to our study, these previous studies showed subtle associations between regional WMH and cognition. While the LIFE study controlled for age, sex, and education as we did in our analyses [23], the smaller cohort study only reported unadjusted regression analyses [24]. Especially when adjusted for age, associations between DWMH in the frontal and parietal lobe were markedly reduced in our study. Since age represents a non-modifiable risk factor for cognitive decline and WMH increase with increasing age, it represents a reasonable approach to control factors associated with WMH such as hypertension in the aging population. Given the high prevalence of hypertension in the elderly and the increased prevalence of dementia cases, our study underlines that early and effective treatment of hypertension is needed to maintain cognitive brain health. In future longitudinal analyses using multiple MRI, BP, and cognitive measurements, we plan to strengthen the interpretation of the causal relationship between WMH, BP, and cognition. Further, we plan to

analyze the association of WMH location with hypertension and cognition voxel-wise to increase information about WMH location compared with ordinal rating scales like the clinical Fazekas scale.

To conclude, our study provides the first cross-sectional evidence that DWMH in the frontal and parietal lobe is highly frequent and significantly associated with higher BP, prevalence of antihypertensive medications, and lower treatment efficacy, as well as lower performance in executive function and memory in the general population. Our results should stimulate longitudinal observational as well as treatment studies to strengthen our observations.

AUTHOR CONTRIBUTIONS

Janine Gronewold: conceptualization; writing—original draft; formal analysis; visualization. **Martha Jokisch:** data curation; funding acquisition; writing—review & editing. **Sara Schramm:** supervision; project administration; writing—review & editing. **Heiko Himpfen:** writing—review & editing. **Theresa Ginster:** data curation; writing—review & editing. **Isabell Tenhagen:** data curation; writing—review & editing. **Thorsten R. Doeppner:** writing—review & editing. **Christiane Jockwitz:** data curation; writing—review & editing. **Tatiana Miller:** data curation; writing—review & editing. **Nils Lehmann:** writing—review & editing. **Susanne Moebus:** conceptualization; funding acquisition; project administration; supervision; writing—review & editing. **Karl-Heinz Jöckel:** conceptualization; funding acquisition; writing—review & editing; project administration; supervision. **Raimund Erbel:** conceptualization; funding acquisition; writing—review & editing; project administration; supervision. **Svenja Caspers:** conceptualization; funding acquisition; project administration; supervision; writing—review & editing. **Dirk M. Hermann:** writing—review & editing; supervision; project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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