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White matter hyperintensity burden, education and cognition in hospitalised patients with cerebral small vessel disease imaging markers: a cross-sectional study of 199 patients

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Research Article

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Abstract

Background

In cerebral small vessel disease (CSVD), white matter hyperintensities (WMH) are associated with cognitive impairment. At the Fazekas visual scale, whether periventricular (PV) and deep (DW) components carry distinguishable information, and how much of the association is independent of education, remain unclear.

Methods

In 199 consecutive patients with CSVD imaging markers (2024–2025), 112 completed the Montreal Cognitive Assessment (MoCA). The primary analysis was a prespecified linear model of MoCA score on Fazekas score, age and education. Secondary analyses comprised component contrasts, competing models with minimum detectable effects (MDE), tests of non-linearity, and domain analyses with false discovery rate (FDR) control under three specifications.

Results

Fazekas score was independently associated with MoCA (β = −0.75, 95% CI − 1.23 to − 0.28; *P* = 0.002). PV and DW were each associated alone (− 1.76 and − 1.09) but did not differ (*P* = 0.13); the minimum detectable DW effect equalled the PV estimate. Microbleeds and circulating markers showed no independent association. Severe grades scored 3.70 points lower (*P* < 0.001), but categorical and linear models did not differ (*P* = 0.08). Visuospatial and orientation domains met the FDR threshold in all three specifications; language was inconsistent. Education explained more variance than WMH (R^2 0.24 versus 0.05) and added little to discrimination (area under the curve 0.74 to 0.75).

Conclusions

WMH burden was independently but modestly associated with cognition; component specificity was not resolvable and education was the dominant correlate. Fazekas grading should inform follow-up intensity rather than decide who needs assessment.

1 Introduction

1.1 Clinical context and the questions that remain

Cerebral small vessel disease (CSVD) is the commonest vascular substrate of stroke, vascular cognitive impairment and age-related cognitive decline. Its MRI marker, white matter hyperintensities (WMH), is extremely common in older people [1], and a heavier burden is associated with faster cognitive decline

and a higher risk of dementia [2]; longitudinal cohorts further show that WMH progression itself predicts incident dementia or mild cognitive impairment [3]. Yet a gap persists between the research literature and the decisions taken at the bedside. Clinical reports of WMH burden rely on inexpensive tools such as the Fazekas visual scale rather than on volumetric quantification or diffusion tensor imaging. When a patient is admitted with a report reading "Fazekas 2–3" and a complete set of laboratory results, the questions that matter are: is this patient's cognition at risk, which part of the lesion burden matters, and how much does it matter?

1.2 First gap: can the components be distinguished?

A knowledge-gap statement in the field of vascular cognitive impairment concluded that whether dividing WMH into periventricular (PV) and deep (DW) components carries independent clinical meaning remains unresolved [4]. Existing evidence tends to favour the PV component: in the population-based 1000BRAINS study, 52% of the association between hypertension and cognition was mediated by PV hyperintensity, against 16% for DW [5]; studies of WMH spatial distribution suggest that the components correspond to different comorbidity profiles and pathological mechanisms [6]; and the periventricular region, a region of terminal venous drainage, shows an association between hyperintensity and venous collagenosis that further supports mechanistic differences between the components [7]. This evidence, however, derives largely from cognitively normal or community populations and rests mostly on volumetric quantification rather than visual grading.

One premise is easily overlooked: distinguishing the components requires measurement resolution. Studies relating the Fazekas grade to WMH volume show that the volumetric transition between adjacent grades is not uniform [8], and the burden captured by Fazekas grading also correlates with Alzheimer-type pathology (amyloid) at the population level [9], suggesting that the grade carries mixed aetiological information rather than a purely vascular burden. If the two components are highly collinear on visual grading, then a joint model showing "PV significant, DW not" may reflect the redistribution of explanatory weight between collinear variables rather than a biological difference. This possibility has rarely been tested formally within a single study.

1.3 Second gap: the place of education

The second gap is simpler but bears more heavily on clinical interpretation. The Montreal Cognitive Assessment (MoCA) is highly sensitive to education [10,11], and patients admitted with CSVD tend to have limited schooling. When a study reports that WMH is "independent of education", this usually means only that education was entered as a linear covariate; it does not mean that WMH carries weight comparable to education in clinical decisions. **Independent association and dominant association are different propositions.** If education accounts for most of the explainable variance, the incremental value of "looking at the Fazekas grade" over "asking about schooling" needs to be quantified explicitly.

1.4 Candidate competing markers

Beyond imaging markers, a series of circulating markers has been proposed to relate to CSVD or to its cognitive consequences: subclinical hypothyroidism has been associated with enlarged perivascular spaces and with overall CSVD burden [12]; data from hospitalised Chinese populations suggest an association between free thyroxine (FT4) and WMH severity [13]; and Mendelian randomisation suggests a causal link between thyroid function and white matter microstructural damage [14]. These markers have rarely been placed in direct competition with WMH and cerebral microbleeds (CMB) in the same patients and within the same model, and evidence is lacking on whether they add information once MRI has been reviewed.

1.5 The present study

This study addressed four questions in 199 hospitalised patients with CSVD imaging markers: (1) is WMH burden independently associated with cognition? (2) within a single modelling framework, which of the PV/DW components, CMB and circulating markers carries the cognitive signal, with the difference between components formally tested and the effects that each null result could exclude reported? (3) what shape does the association take? and (4) where does the association stand relative to educational background? A single primary outcome was prespecified, domain analyses were corrected for multiple testing and repeated under three specifications, and the minimum detectable effect was reported for every null finding. The study is reported in accordance with STROBE [15].

2 Methods

2.1 Study design and participants

This was a single-centre cross-sectional study. Consecutive patients admitted with neurological symptoms between September 2024 and August 2025 who had CSVD imaging markers on brain MRI were enrolled. Of 200 records, one duplicate entry (the same patient) was identified on review and removed, leaving 199 patients for analysis.

Inclusion criteria were: (1) age ≥ 18 years; (2) CSVD imaging markers on brain MRI, defined as WMH (total Fazekas score 0–6), CMB or lacunes; and (3) admission for neurological symptoms.

Exclusion criteria were: (1) large-artery or cardioembolic stroke; (2) a previous diagnosis of dementia, or severe aphasia or visual impairment precluding cognitive testing; (3) severe cardiac, hepatic or renal insufficiency, or malignancy; and (4) thyroid-related medication before thyroid function testing.

Neuropsychological assessment was introduced during the study period and completed in 112 patients (enrolment sequence 1–112); the remaining 87 patients were not assessed. Cognitive analyses are therefore based on n = 112, and the baseline characteristics of the two groups are compared in Table 1. Missingness was not treated as random, and neither imputation nor propensity-score weighting was applied. The flow of participants is shown in Fig. 1.

2.2 Ethics

The study was performed in accordance with the Declaration of Helsinki. The Ethics Committee of the Second Affiliated Hospital of Shandong First Medical University confirmed that formal ethics approval and written informed consent were not required, because this was a retrospective analysis of routinely collected, anonymised clinical data (22 October 2026; no approval number was assigned).

2.3 Clinical and laboratory data

Demographic data (age, sex and educational level) and a history of vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, coronary heart disease, cerebral infarction, intracerebral haemorrhage, smoking and alcohol use) were collected. Educational level was mapped to years of schooling as follows: illiterate 0, primary 6, junior high 9, senior high 12, junior college 15, vocational college 15, university 16 and bachelor 16 years (Supplementary Table S4).

Fasting venous blood was collected after admission. Free triiodothyronine (FT3), FT4 and thyroid-stimulating hormone (TSH) were measured on a Siemens Atellica IM 1600 automated chemiluminescence immunoassay analyser with Siemens original reagents; homocysteine (Hcy), uric acid, glycated haemoglobin (HbA1c), total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) were measured on the routine biochemistry platform of the hospital laboratory.

2.4 MRI acquisition and image assessment

MRI was performed on a GE Discovery 750 3.0 T scanner. Sequences included axial T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) and susceptibility-weighted imaging (SWI) (slice thickness 5 mm, field of view 24 cm; SWI reconstructed slice thickness 1.5 mm). All 199 patients were graded by the primary rater on axial FLAIR images using the Fazekas visual scale [16]: periventricular and deep white matter were each scored from 0 to 3, giving a total score of 0–6.

Thirty patients were selected by stratified random sampling across the full Fazekas range (0–6) and re-graded by a second assessor. The same scoring sheet was used, with the primary rater's scores visible; the assessment was therefore partially blinded.

Weighted kappa with quadratic weights was 0.793 (95% CI 0.611–0.905) for the periventricular score, 0.848 (0.704–0.932) for the deep score and 0.868 (0.744–0.935) for the total score; linear-weighted kappa was 0.675, 0.728 and 0.698, respectively. Exact agreement for the total score was 50%, and the second assessor scored systematically higher (mean difference + 0.40). The second reading was used only to assess agreement; all analyses used the primary rater's scores.

CMB were assessed on SWI and counted; they were classified as present or absent, by count category (0 / 1–2 / ≥3) and by location (deep or cortico-subcortical).

Eight patients in the cohort had a total Fazekas score of 0 and no CMB; their inclusion was based on lacunes described in the imaging report. They were retained in the primary analysis and removed in a sensitivity analysis.

2.5 Cognitive assessment

Cognitive assessment was performed on the third day after admission by trained assessors. The MoCA [10] was used to record the total score and seven domain scores (visuospatial/executive, naming, attention, language, abstraction, delayed recall and orientation); the Mini-Mental State Examination (MMSE) was also recorded. Mood was assessed with the GAD-7 [17] and PHQ-9 [18], and functional status with the Barthel Index [19]. The VASCOG criteria [20] provided the diagnostic framework for vascular cognitive impairment.

No age- and education-adjusted normative cut-off was applied to the MoCA; a score below 26 was reported only as a descriptive screen-positive indicator, and all inferences used the continuous total score. In 107 of the 112 patients the recorded total equalled the sum of the seven domain scores; in five it differed by 1–3 points (sensitivity analyses in Section 3.8).

2.6 Statistical analysis

Primary outcome. A single prespecified test was performed: linear regression of total MoCA score on total Fazekas score, age and years of education (n = 112). All other analyses were secondary, supportive or exploratory.

Secondary analyses. (1) *PV/DW decomposition*: PV and DW were entered together and the difference between their coefficients was tested with a Wald test; each component was also entered alone. (2) *Competing models*: CMB (present or absent, count category, deep count and cortical count) and FT3, FT4, TSH, homocysteine, uric acid, HbA1c and LDL-C were added one at a time; for each null result the minimum detectable effect (MDE) was reported as $(t_{0\cdot975} + t_{0\cdot80}) \times SE$, where SE denotes the standard error of the coefficient. (3) *Severity*: dummy variables for mild (0–2), moderate (3–4) and severe (5–6) grades (reference: mild), with a nested *F* test and a quadratic term. (4) *Domains*: the seven MoCA domains with Benjamini–Hochberg false discovery rate (FDR) control ($q < 0.05$), repeated under three covariate specifications (age and years of education; plus sex; education as five categories), reporting only results consistent across all three. (5) *Education*: relative contributions were quantified by independent R^2 and standardised β; patients were stratified by ≤ 9 and > 9 years of education, with within-stratum covariates of Fazekas score and age in the primary specification and a further specification retaining years of education within strata, and an interaction term was tested; additional discriminative ability was expressed as the area under the curve (AUC) for MoCA < 26, with logistic predicted probabilities as the primary metric and linear probability model (LPM) fitted values reported alongside. (6) *Missing data*: baseline characteristics of the two groups were compared; no imputation was performed.

Robustness analyses. Exclusion of 33 patients with acute cerebrovascular events; exclusion of the eight patients with a total Fazekas score of 0; education modelled as an ordinal variable and as five categories; adjustment for sex (n = 110); adjustment for six binary vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking, alcohol use and history of cerebral infarction) in addition to Fazekas score, age and education; leave-one-out analysis; the subgroup with thyroid function within the reference range; and stratification by enrolment period.

Inferential hierarchy. The primary outcome was the only confirmatory test; the family of domain analyses was controlled by Benjamini–Hochberg FDR; all remaining analyses were supportive or descriptive. Tests were two-sided with $\alpha = 0.05$. Analyses were performed in Python 3.12 (statsmodels 0.15.0, SciPy 1.18.1, pandas 3.0.2). A self-contained script recomputes every statistic reported here from the raw data file and checks each against the reported value; all 64 checks pass, and the script and data are provided as a separately uploaded code package.

2.7 Reporting standard

The study is reported in accordance with the STROBE statement [15].

3 Results

3.1 Cohort characteristics and enrolment structure

The 199 patients had a mean age of 63.4 years (range 41–79), and 91 of 196 were male (46.4%; sex was missing or recorded abnormally in three patients). The median duration of education was 9 years (IQR 6–12), and 127 of 199 patients (63.8%) had ≤ 9 years of education, including 16 who were illiterate and 52 with primary schooling. Total Fazekas scores spanned the full 0–6 range (0, n = 8; 1, n = 27; 2, n = 67; 3, n = 24; 4, n = 31; 5, n = 10; 6, n = 32). CMB were present in 60 of 199 patients (30.2%).

Presenting symptoms were dizziness in 72 patients (36.2%), acute cerebrovascular disease in 31 (15.6%), headache in 30 (15.1%), posterior circulation ischaemia in 24 (12.1%) and limb numbness in 8 (4.0%); the remainder had transient ischaemic attack, fatigue, peripheral neuropathy or other symptoms. It should be emphasised that non-specific neurological symptoms predominated: only 37 of 199 patients (18.6%) met the definition of an acute vascular event used in this study (acute cerebrovascular disease, acute cerebral infarction, acute ischaemic cerebrovascular disease or transient ischaemic attack). The cohort therefore differs from "symptomatic CSVD" cohorts defined by lacunar stroke or transient ischaemic attack (Section 4.6).

Among the 112 patients who completed the MoCA, mean age was 63.7 ± 7.3 years and 51 of 110 were male; 68 (60.7%) had hypertension, 32 (28.6%) diabetes mellitus and 14 (12.5%) dyslipidaemia, and 33 (29.5%) had had an acute vascular event. Mean MoCA score was 20.5 ± 5.4 (median 21) and mean MMSE score 27.0 ± 3.4; mean total Fazekas score was 2.98 ± 1.77. MoCA < 26 was recorded in 94 of 112

patients (83.9%), a proportion that ranged from 97% to 100% among patients with primary schooling or less and was 17% among those with a college education or above (Section 3.7).

Baseline characteristics of the two groups are compared in Table 1: age 63.7 versus 63.1 years; male 46.4% versus 46.5%; hypertension 60.7% versus 67.8%; diabetes mellitus 28.6% versus 28.7%; years of education 8.7 versus 9.5; total Fazekas score 2.98 versus 3.05; CMB count 1.46 versus 0.85. The groups were similar on most measured variables, but laboratory indices related to assay batch drifted between them (FT4, HbA1c, LDL-C, HDL-C and total cholesterol; Section 4.5). Missingness was handled as structural (Section 2.1).

3.2 Primary outcome: WMH burden is independently associated with cognition

After adjustment for age and years of education, each 1-point increase in total Fazekas score was associated with a 0.75-point lower MoCA score (β = −0.752, 95% CI − 1.225 to − 0.279; *P* = 0.002; n = 112, R^2 = 0.410). The unadjusted analysis pointed in the same direction (Spearman ρ = −0.261; *P* = 0.005). Within the model, years of education contributed + 0.84 points per year (95% CI 0.59 to 1.09; *P* < 0.001) and age − 0.10 points per year (95% CI − 0.22 to 0.02; *P* = 0.102).

The estimate retained its direction and significance across specifications: education modelled as five dummy variables (β = −0.79, 95% CI − 1.27 to − 0.31; *P* = 0.001); education modelled as an ordinal variable (β = −0.76; *P* = 0.002); adjustment for sex (β = −0.83; *P* = 0.001); adjustment for all vascular risk factors (six binary covariates, excluding sex: n = 112, β = −0.92; *P* = 0.0005; with sex, n = 110, β = −0.96; *P* = 0.0005); exclusion of acute cerebrovascular events (β = −0.70, 95% CI − 1.24 to − 0.15; *P* = 0.013; n = 79); and exclusion of patients with a total Fazekas score of 0 (β = −0.65, 95% CI − 1.14 to − 0.16; *P* = 0.010; n = 109). Leave-one-out analysis gave β between − 0.84 and − 0.65, a maximum change of 0.10 from the point estimate, indicating that the primary result does not depend on any single observation (Table 2; Fig. 2a).

3.3 Decomposition: the point estimate favours the periventricular component, but the two cannot be distinguished

Table 4
Periventricular and deep white matter coefficients entered alone and together

Model	PV	DW
Each entered alone (adjusted for age and education)	−1.76 (− 2.76 to − 0.77), *P* = 0.0006	**−1.09 (− 1.92 to − 0.26), P = 0.011**
Entered together	−2.07 (− 3.83 to − 0.31), *P* = 0.022	**+ 0.31 (− 1.13 to + 1.75), P = 0.673**
Incremental R^2 for DW	—	0.001 (*F*(1,107) = 0.18, *P* = 0.673)

Three points must be made together.

(1) DW is not "signal-free". Entered alone, it was significantly associated with cognition (− 1.09; *P* = 0.011), with an effect of the same order as that of PV (− 1.76). Entered together, its coefficient reversed sign (*P* = 0.673); the two components were highly collinear (Pearson *r* = 0.838; partial *r* = 0.824).

(2) The difference between components did not reach statistical significance. A Wald test of the hypothesis that the PV and DW coefficients are equal gave a difference of + 2.38 (SE 1.54; *t* = 1.54; *P* = 0.126). The statement that "the cognitive signal comes from the periventricular region while the deep component is null" therefore does not hold as a claim about the difference between the two.

(3) The design lacked the power to decide. The minimum detectable effect for DW in the joint model was 2.06 points per grade (80% power, α = 0.05), whereas the PV point estimate was 2.07. The study could therefore only have detected a DW effect as large as the PV effect, and the 95% CI for DW (− 1.13 to + 1.75) fully contains its own univariable estimate.

The conclusion is accordingly restricted: at the measurement resolution of the Fazekas visual scale, component specificity cannot be determined. The point estimates suggest a signal weighted toward the periventricular region, but that difference cannot be established statistically. Figure 2b shows the coefficients for the two components entered alone and together, and Table 4 gives the corresponding estimates.

3.4 Competing markers: neither CMB nor circulating markers showed an independent association

CMB (four specifications, each also including total Fazekas score; Table 3): present versus absent β = +0.30 (*P* = 0.737); count category (0 / 1–2 / ≥3, test for linear trend) *P* = 0.755; deep count *P* = 0.932; cortical count *P* = 0.971. Total Fazekas score remained significant in every model containing CMB (*P* ≤ 0.005). CMB were present in 33.9% (38 of 112); the minimum detectable effect for this test was 2.55 points, so the sample could not exclude a moderate-to-small CMB effect.

Circulating markers (each entered together with total Fazekas score; β, 95% CI and MDE in Table 3):

In every model containing a circulating marker, total Fazekas score remained significant ($P \leq 0.005$). The tests differed in information content: for FT4, HbA1c and LDL-C the confidence intervals were so wide that a null result carries almost no information, whereas the narrower intervals for TSH, Hcy and uric acid make their null results relatively more meaningful. Uric acid ($P = 0.055$) and FT3 ($P = 0.078$) were borderline findings that did not survive correction for multiple testing and were not given a biological interpretation.

3.5 Severity: severe grades score lower, but there is no evidence of a threshold pattern

Grouped by total Fazekas score, mean MoCA scores were 21.64 for mild (0–2, n = 59), 21.17 for moderate (3–4, n = 29) and 16.79 for severe (5–6, n = 24) grades (the per-score distribution and the group-versus-prediction comparison are shown in Fig. 3). With the mild group as reference and adjustment for age and education, the moderate group differed by β = −0.28 (95% CI − 2.16 to 1.61; $P = 0.774$) and the severe group by β = −3.70 (95% CI − 5.79 to − 1.61; $P = 0.0006$).

The categorical model did not, however, outperform the linear model: the nested test of the three dummy variables against a single linear term gave $F(1,107) = 3.14$ ($P = 0.079$), and the quadratic term was β = −0.11 ($P = 0.431$). Values predicted by the linear model were 21.80, 20.29 and 17.46, all within 0.9 points of the observed means. The data therefore do not support a "plateau in mild-to-moderate disease followed by an abrupt decline"; the finding is stated as follows: patients with severe grades scored lower, by an amount compatible with the linear trend.

Examination by individual score showed that the signal was concentrated at grade 6: mean MoCA was 16.62 at grade 6 (n = 21) and 18.00 at grade 5 (n = 3); with grades 0–4 as reference, β was − 3.45 at grade 6 ($P = 0.001$) and − 4.49 at grade 5 ($P = 0.068$; n = 3, unstable estimate).

3.6 Cognitive domains: visuospatial and orientation robust, language inconsistent

Under the primary specification (age and years of education) with Benjamini–Hochberg FDR control across the seven domains, visuospatial ($P = 0.013$, $q = 0.039$), orientation ($P = 0.015$, $q = 0.039$) and language ($P = 0.017$, $q = 0.039$) passed; delayed recall was borderline ($P = 0.039$, $q = 0.069$); naming, attention and abstraction showed no signal. Identical q values for three domains are a normal consequence of the monotone Benjamini–Hochberg step and not repeated counting.

After repetition under the three specifications, the visuospatial and orientation domains met the threshold in all three, whereas the language domain did not; the coefficients and q values for all seven domains under each specification are given in Table 2 and Fig. 4.

The domain-level conclusion is therefore narrowed: the visuospatial and orientation domains passed FDR control under all three specifications; the language result depended on the covariate specification

and is not considered robust; delayed recall remained borderline throughout (interpretation in Section 4.4).

3.7 Education is the dominant correlate of cognitive status in this population

This was the most notable finding of the study, and it does not rest on any single model.

(1) Relative contribution (Table 5**).** Standardised β and independent R^2 for each variable in the primary model:

Table 5
Relative contribution of education, Fazekas score and age to the primary model

Variable	Standardised β	Independent R^2	Share of model R^2
Years of education	**+ 0.51**	**0.243**	**59.2%**
Total Fazekas score	−0.25	0.054	13.2%
Age	−0.13	0.015	3.6%

Across the full exposure range, a change in total Fazekas score from 0 to 6 corresponded to a 4.5-point lower MoCA score, whereas 0 to 16 years of education corresponded to a 13.5-point higher score.

(2) The screen-positive rate for MoCA < 26 was determined by the educational composition of the sample (Table 6**).**

Table 6
Screen-positive rate for MoCA < 26 by educational level

Educational level	n	Mean MoCA	Proportion with MoCA < 26
Illiterate	6	12.2	100%
Primary	29	17.4	97%
Junior high	48	21.7	81%
Senior high	23	22.2	87%
College or above	6	27.0	17%

(3) The WMH–cognition association was stronger in the low-education group, but the stratified estimates depend on the covariate set (Table 7**).**

Table 7
Stratified estimates of the Fazekas coefficient by years of education

Stratum	Within-stratum covariates	n	β	*P*
≤ 9 years	Fazekas + age (primary specification)	83	−0.90	0.010
≤ 9 years	Also retaining years of education	83	−0.91	0.004
> 9 years	Fazekas + age (primary specification)	29	−0.26	0.484
> 9 years	Also retaining years of education	29	−0.42	0.193

The interaction term (Fazekas × higher education, the latter coded 1 for > 9 years) was β = +0.66 (*P* = 0.251) under the primary specification and β = +0.53 (*P* = 0.294) when years of education was retained within strata; coding lower education as 1 reverses the sign with the same meaning. Neither specification showed a statistically significant interaction. Retaining education within strata moved the point estimate for the > 9-year group from − 0.26 to − 0.42, reducing the ratio of the two point estimates from 3.5 to 2.2. The conclusion is therefore best stated as "the association was stronger in the low-education group" rather than "the association was present only in the low-education group". With only 29 patients in the higher-education subgroup, the sample is sufficient neither to claim nor to exclude effect modification.

(4) Beyond education and age, the incremental discriminative value of the Fazekas score was small. Areas under the curve for discriminating MoCA < 26, calculated from logistic predicted probabilities, were 0.579 for Fazekas score alone, 0.720 for education alone, 0.738 for age plus education and 0.750 for age plus education plus Fazekas score (increment + 0.012). With fitted values from a linear probability model (LPM) the corresponding values were 0.738 and 0.745 (increment + 0.007). Among patients with ≤ 9 years of education, 73 of 83 (88%) had MoCA < 26 and only 10 were unimpaired, so the discrimination indices are unstable (LPM 0.733 to 0.735; logistic 0.733 to 0.729) and should not be interpreted quantitatively.

3.8 Availability and batch effects of the cognitive assessment

The two groups are compared in Section 3.1 and Table 1. Indices related to assay batch drifted in the same direction between the two segments (FT4 1.17 versus 1.28, *P* < 0.001; HbA1c, LDL-C, HDL-C and total cholesterol likewise), whereas age, Fazekas grade, TSH, FT3, Hcy and uric acid were stable. This pattern is consistent with a change in assay conditions over time, so subgroup analyses involving these indices are confined to the supplementary material and are not interpreted in the main text.

Agreement between total and domain scores. When the total score was recomputed as the sum of the seven domains, the primary estimate was β = −0.80 (95% CI − 1.27 to − 0.34; *P* = 0.0009); after excluding the five patients whose recorded total differed from the sum, β = −0.89 (95% CI − 1.38 to − 0.40; *P* = 0.0005). Direction and significance were unchanged.

4 Discussion

4.1 Principal findings

In 199 hospitalised patients with CSVD imaging markers: (1) the Fazekas grade was independently associated with cognition, although the effect was modest and remained stable after adjustment for education and age, after exclusion of acute events and after exclusion of patients without WMH; (2) at the measurement resolution of the Fazekas scale, the difference between the periventricular and deep components could not be determined — each was associated with cognition, the difference did not reach statistical significance, and the sample was insufficient to detect an effect specific to the deep component; (3) CMB and circulating markers showed no independent association, although the effects that each test could exclude differed; (4) patients with severe grades scored lower, but there was no evidence of a non-linear threshold; (5) the visuospatial and orientation domains were robustly affected; and (6) **education was the dominant correlate of cognitive status in this population, with an independent explanatory variance about 4.5 times that of the Fazekas score**.

4.2 Why component specificity cannot be determined in this design

Our handling of this question differs from that of earlier studies and merits separate comment. Previous work has inferred component differences either by modelling PV and DW separately or through mediation analysis [5,6], but such inference rests on two premises: that the two components can be distinguished by the measurement used, and that the sample has sufficient power to detect a difference between them. This study shows that neither premise holds for the Fazekas visual scale. The partial correlation between PV and DW was 0.824 and the DW coefficient reversed sign in the joint model; and the minimum detectable effect (2.06) was almost equal to the PV point estimate (2.07), so that even a DW effect of half the PV magnitude could not have been detected.

The conclusion is therefore confined to the level of information: within the information captured by a routine clinical tool, the point estimate of the cognitive signal favours the periventricular region, but the question of whether the deep component carries independent information requires volumetric quantification, diffusion tensor imaging or a larger sample, and the Fazekas scale does not have that resolution. This does not contradict previous volumetric studies; it indicates that **visual grading cannot carry the burden of component inference**, a conclusion with direct implications for how reports are worded — a Fazekas report should not imply a component difference.

4.3 Why education deserves centre stage

The result most likely to run counter to readers' expectations is that, in a study whose exposure is WMH, education accounted for about 59% of the model variance and WMH for only 13%. We regard this not as confounding that should be downplayed but as a finding to be reported directly, for three reasons.

First, it reflects the real structure of this population. Median education in the cohort was 9 years and 63.8% of patients had ≤ 9 years of schooling. The MoCA is highly sensitive to education [10,11], and in such a population the positive rate at a fixed cut-off (MoCA < 26) is determined mainly by the educational composition (100% among illiterate patients versus 17% among those with a college education or above). Any "prevalence of cognitive impairment" defined by a fixed cut-off measures, in this population, largely education rather than CSVD.

Second, it determines the clinical weight of WMH. Across the full range, the Fazekas score corresponds to a 4.5-point difference in MoCA score whereas education corresponds to 13.5 points; and beyond age and education the Fazekas score adds only 0.012 to the AUC for individual discrimination (0.738 to 0.750). Among patients with ≤ 9 years of education this increment **approaches zero** (LPM + 0.002; logistic − 0.004) — that is, **in a low-education population the incremental value of the Fazekas score for cognitive discrimination is close to none**. This is more specific than a statement of independent association: it indicates that, at the level of decision-making in this population, education has almost absorbed the information that the Fazekas score can provide. Admittedly, 88% of this subgroup already had MoCA < 26 and only 10 patients were unimpaired, so the discrimination indices are themselves unstable and the increments should be read only for their direction.

Third, it explains why the association was concentrated in the low-education group. β was − 0.90 among patients with ≤ 9 years of education and − 0.26 among those with > 9 years. Two explanations are both tenable and cannot be distinguished here: cognitive reserve buffers the cognitive consequences of WMH [21,22,23], or the MoCA measures cognition less precisely and residual confounding is greater in people with limited education. The study cannot separate these, so no causal interpretation is offered.

The clinical translation is direct and contrary to the intuition of "reading the grade": **when identifying cognitive risk, asking how many years of schooling a patient completed yields more information than reading a Fazekas report**. This does not deny the value of imaging but calibrates its position — grading supplies a small increment above education, not the dominant information.

4.4 Domain profile: what robust visuospatial and orientation involvement means

Domain analyses in previous SVD cohorts have centred on slowed processing speed and impaired executive function [24], and the domain profiles of different microvascular aetiologies (cerebral amyloid angiopathy versus hypertension-related microangiopathy) differ reproducibly [25]. Two features of the present results merit discussion.

First, the two domains that survived FDR control were **visuospatial and orientation**, not the "executive/attention" pattern most often reported. Three sources may contribute to this discrepancy: (1) measurement — the MoCA "visuospatial/executive" domain combines alternating trails with figure copying and is not a pure measure of executive function, so the robust visuospatial signal may partly carry an executive component; (2) population — the cohort consisted mainly of patients admitted with

non-specific symptoms and had a low educational composition, unlike community cohorts of older adults [24]; (3) measurement resolution — the total Fazekas score is a coarse index of global white matter burden that carries no network-localising information and cannot readily be mapped onto a specific cognitive domain. We therefore do not interpret "visuospatial and orientation involvement" as a specific domain profile at odds with the literature, but report it as the most stable signal at this measurement resolution.

Second, delayed recall was borderline under all specifications ($q \approx 0.07$). Work on injury to mesocortical pathways indicates that the cognitive and behavioural consequences of SVD are distributed along specific networks rather than uniformly attenuated [26], and deep white matter lesions are likewise associated with behavioural symptoms such as apathy [26,27]. This suggests that approximating "cognition" with a single total score obscures differences at the level of domains and of behaviour. The present study did not assess apathy systematically and the mood scales were recorded only, so no conclusion is drawn about affective symptoms.

The robustness of the domain-level conclusions is further limited by the coarsely ordinal nature of the domain scores (limitation (4) in Section 4.8).

4.5 How null results should be read

This paper reports a number of null results, whose information content differs; they must be treated separately.

The null result for CMB should not be read as "CMB are unrelated to cognition". Large symptomatic SVD cohorts have shown an independent association between CMB and cognitive impairment [28], and a meta-analysis supports this [29]. In the cognitive subgroup of the present study the prevalence of CMB was only 33.9% (30.2% in the full cohort) and the MDE was 2.55 points, so power was clearly insufficient; the result can be stated only as "not detected in this sample".

For circulating markers, the null findings for thyroid function are not fully consistent with previous observational [12,13] or Mendelian randomisation evidence [14]. However, the confidence interval for FT4 (− 5.02 to 4.20) is far wider than its physiological range, so this test carries almost no information and should not be cited as evidence that "thyroid function is unrelated to cognition". The intervals for TSH, Hcy and uric acid were narrower, and their null results are correspondingly more meaningful. The null result for Hcy is also inconsistent with positive associations between related markers and WMH in community cohorts [30], possibly reflecting selection in a symptomatic population.

We suggest that readers interpret these results in terms of the effects that can be excluded rather than in terms of statistical significance, which is why the MDE is reported alongside every null finding.

4.6 Cohort characteristics and the boundaries of generalisation

The cohort was admitted predominantly with non-specific neurological symptoms: dizziness in 72 patients (36.2%), headache in 30 (15.1%) and limb numbness in 8 (4.0%); including fatigue, peripheral neuropathy and other such presentations, non-specific symptoms accounted for 115 patients (57.8%). Under the definition of acute vascular events applied throughout (acute cerebrovascular disease, acute cerebral infarction, acute ischaemic cerebrovascular disease and transient ischaemic attack; Section 2.1), only **37 of 199 patients (18.6%)** had an acute event, and a further 24 (12.1%) were diagnosed with posterior circulation ischaemia, which was neither counted as an acute event nor excluded in the sensitivity analysis. This differs from the "symptomatic CSVD" cohorts usually defined by lacunar stroke or transient ischaemic attack. The findings should therefore be understood as describing the relation between WMH and cognition **in patients who present with neurological symptoms and in whom CSVD imaging markers are found incidentally or in passing**. Such patients account for most of routine clinical practice, but the attribution of their cognitive impairment cannot be extrapolated directly to post-stroke cognitive impairment.

In addition, cognitive assessment covered only 112 patients (enrolment sequence 1–112); the remaining 87 were not assessed. The two segments were similar on most measured variables, but missingness was determined by enrolment order and assay batches drifted; for these reasons missingness was not treated as random, and propensity-score weighting was not used as a correction.

4.7 Clinical implications

The findings do not support using the Fazekas grade as a decision rule for whether to initiate cognitive assessment. In this cohort, taking a Fazekas score ≥ 5 as the trigger gave a sensitivity of only 0.22 (73 of the 94 patients with MoCA < 26 would have been missed), whereas patients with MoCA < 26 made up 83.9% of the sample — at such a prevalence, no high-specificity, low-sensitivity imaging cut-off can serve a screening function.

What the data do support is **risk description at the group level and stratification of follow-up intensity**: patients with a Fazekas score of 5–6 had a mean MoCA score about 3.7 points lower and form a group of higher priority for cognitive follow-up; but whether an individual needs assessment should be decided by a cognitive screening instrument rather than by an imaging grade [31]. Where resources permit, applying the MoCA directly to patients admitted with neurological symptoms and CSVD imaging markers is more rational than selecting patients by grade, because grading misses far more patients than it identifies. Such a strategy must, however, also address the high false-positive rate of the MoCA in low-education populations (83.9% of this cohort had MoCA < 26, a substantial part of which was determined by educational composition), so a positive screen should be interpreted in the light of educational background rather than equated directly with cognitive impairment.

The findings also suggest that years of education should be included in the initial assessment of cognitive risk. In resource-limited settings this is a zero-cost variable.

4.8 Limitations

(1) The single-centre cross-sectional design cannot establish causality; the compatibility of "lower scores in the severe group" with a compensatory mechanism is speculative.

(2) Cognitive assessment covered only 112 patients (enrolment sequence 1–112) and is not a random subset; although the two segments had similar baseline characteristics, residual bias from structural missingness cannot be excluded and generalisation requires caution.

(3) The Fazekas visual scale has a ceiling effect and an uneven volumetric transition between grades [8], and it cannot capture volumetric variation within a grade; decomposition of the components is therefore limited.

(4) Cognitive assessment relied on the MoCA alone, and domain scores are coarsely ordinal, so domain-level conclusions have limited robustness. No age- and education-adjusted normative values were applied, and MoCA < 26 served only as a descriptive indicator.

(5) Educational level entered the model as mapped years of schooling and is subject to measurement error; although results were unchanged when education was modelled categorically, residual misclassification cannot be excluded.

(6) Power was insufficient for CMB and for several circulating markers, and null results cannot be interpreted as absence of association.

(7) In patients with acute cerebrovascular events (33 of 112) the WMH may include post-ischaemic change, and assessment on the third day after admission may have been influenced by acute encephalopathy, medication and fatigue; the primary result remained robust after exclusion ($P = 0.013$), but residual heterogeneity cannot be excluded.

(8) PV and DW are highly collinear and the difference between them was not established; distinguishing their independent contributions requires volumetric quantification or a prospective design.

(9) Presenting symptoms were predominantly non-specific and the cohort differs from classic symptomatic CSVD cohorts, so generalisation must be bounded as set out in Section 4.6.

(10) Eight patients had a total Fazekas score of 0 and no CMB; their inclusion was based on lacunes described in the imaging report; lacunes were used only for inclusion and were not analysed as a variable. Excluding these patients did not change the primary result ($P = 0.010$).

(11) Re-grading was not fully blinded: the primary rater's scores and the re-grading column were in the same worksheet, so the second assessor could see the primary scores while re-grading. Independent reading was explicitly requested, the observed agreement was moderate to good, and the disagreement was systematically one-sided (mean difference in total score + 0.40), which does not match the typical pattern of strong anchoring; anchoring cannot, however, be excluded, and **the agreement coefficients**

reported here may be overestimated. Future studies should re-grade using a blank form that does not contain the primary rater's scores.

4.9 Conclusion

In hospitalised patients with CSVD imaging markers, white matter hyperintensity burden was independently but modestly associated with cognition. At the measurement resolution of the Fazekas visual scale, the difference between the periventricular and deep components could not be determined: each was associated with cognition, and this study could not distinguish them. Educational background was the dominant correlate of cognitive status in this population, and beyond age and education the Fazekas grade offered only a small increment in discriminative ability. The Fazekas grade is therefore better used for risk description at the group level and for stratifying follow-up intensity than as an individual screening tool or as the basis for deciding whether to initiate cognitive assessment. In other words, grading is not useless, but its purpose needs to be repositioned: it marks a small increment above educational background and should serve as a guide to the intensity of cognitive follow-up rather than as a substitute for cognitive assessment — imaging grade and cognitive assessment answer different questions, the former indicating who deserves closer follow-up and the latter whether cognition is impaired.

Declarations

Ethics approval and consent to participate.

The study was performed in accordance with the Declaration of Helsinki. The Ethics Committee of the Second Affiliated Hospital of Shandong First Medical University confirmed that formal ethics approval and written informed consent were not required for this retrospective analysis of routinely collected, anonymised clinical data (22 October 2026; no approval number was assigned).

Consent for publication.

Not applicable.

Competing interests.

The authors declare that they have no competing interests.

Tables

Tables 1–3 are provided as separate files, each with its title and footnote. Tables 4–7 appear within Section 3.

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Authors' contributions.

XH: Investigation, Data curation, Writing – original draft. MH: Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision, Correspondence. Both authors read and approved the final manuscript.

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Availability of data and materials.

The de-identified dataset and analysis scripts are available from the corresponding author on reasonable request.

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Tables

Tables 1 to 3 are not available with this version.

Figures

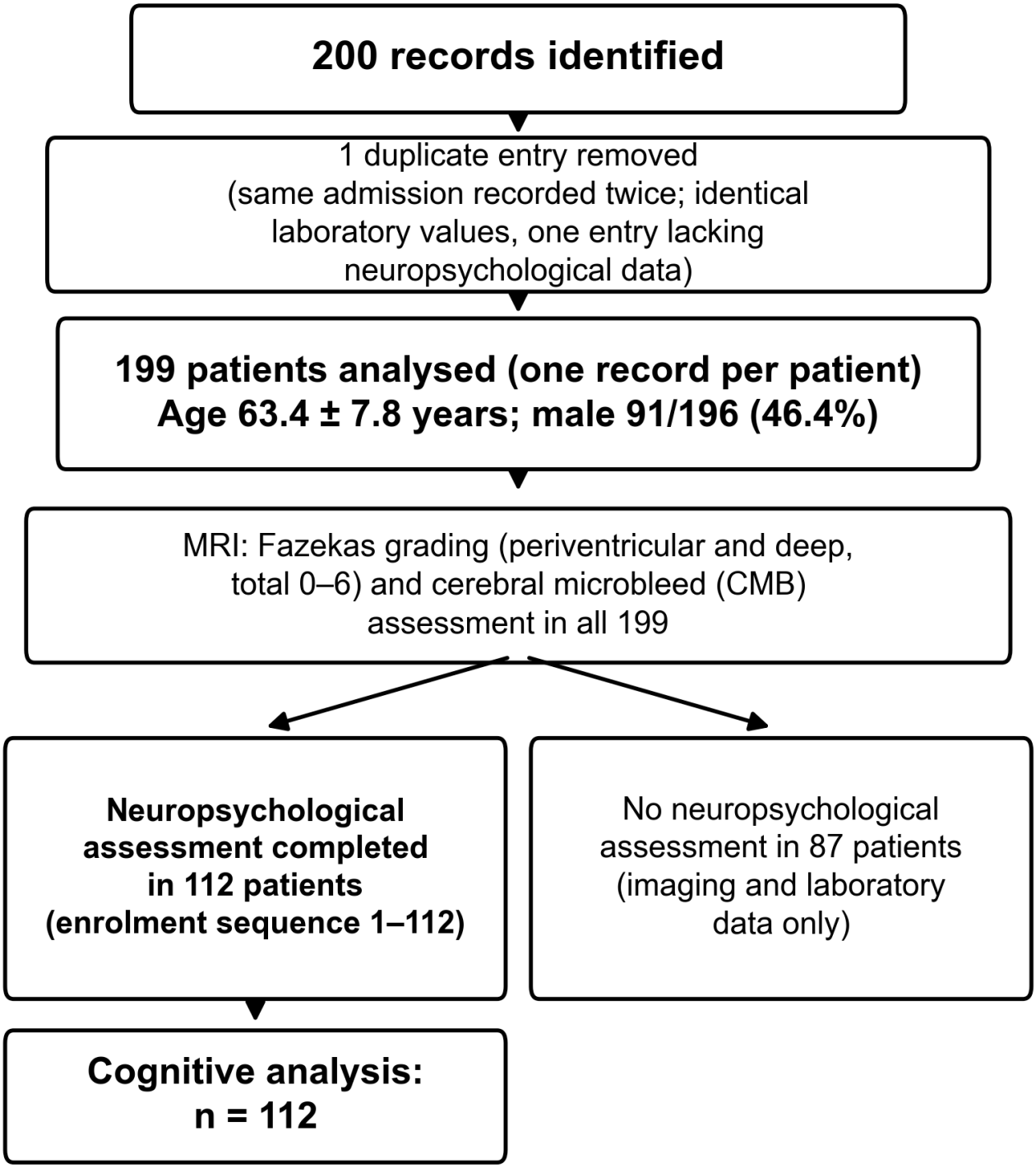


Figure 1

Flow of participants through the study (STROBE). Of 200 records, one was a second entry of the same admission: the two entries had identical age, body mass index, Fazekas grade, cerebral microbleed counts and all laboratory values, differing only in glycated haemoglobin (5.1% vs 5.6%) and in the wording of the diagnosis, and one of them lacked neuropsychological data. That entry was removed, leaving 199 patients with one record each. Neuropsychological assessment was completed in 112

patients (enrolment sequence 1-112); the remaining 87 underwent imaging and laboratory testing only and are not a random subset. Cognitive analyses are therefore based on n = 112. Eight patients had a total Fazekas score of 0 and no cerebral microbleed; their inclusion was based on the imaging report, and removing them did not change the primary estimate (beta = -0.65, P = 0.010). CSVD, cerebral small vessel disease; MRI, magnetic resonance imaging; MoCA, Montreal Cognitive Assessment; CMB, cerebral microbleed.

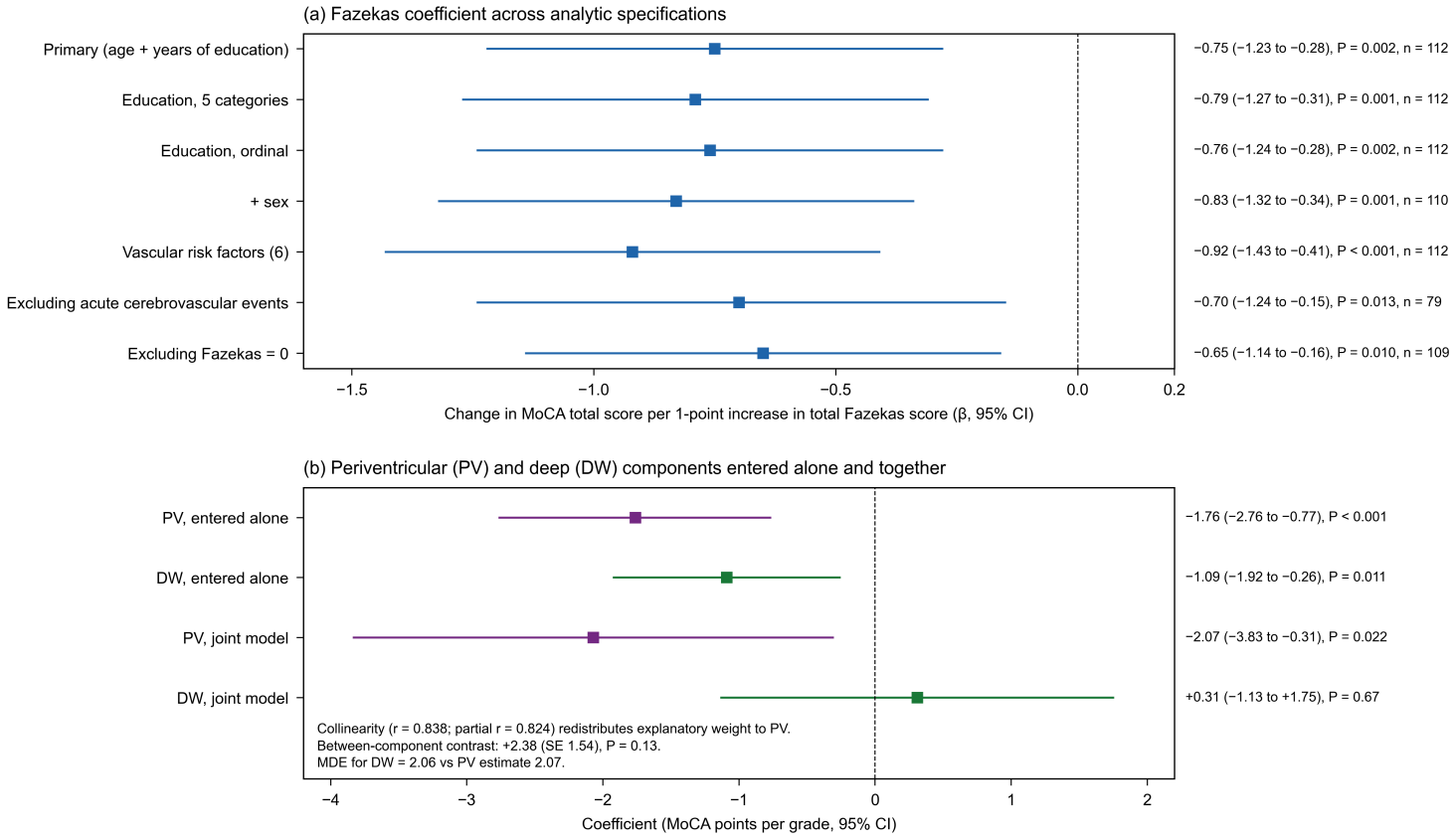


Figure 2

Association of white matter hyperintensity burden with cognition, and the periventricular-deep decomposition. (a) Point estimates and 95% confidence intervals for the coefficient of total Fazekas score across analytic specifications. All models were linear regressions of total Montreal Cognitive Assessment score with age and years of education included; the additional covariates are indicated on each row. The dashed vertical line marks no association. (b) Periventricular (PV) and deep white matter (DW) Fazekas scores entered alone and entered together. Entered alone, both components were associated with cognition; entered together, the DW coefficient reversed sign and its interval crossed zero. This pattern results from the collinearity of the two components (Pearson r = 0.838; partial r = 0.824) rather than from an absence of effect in deep white matter. The between-component contrast was not significant (difference +2.38, SE 1.54; P = 0.13), and the smallest DW effect detectable in the joint model (2.06 points per grade) was almost identical to the PV estimate (2.07). CI, confidence interval; SE, standard error.

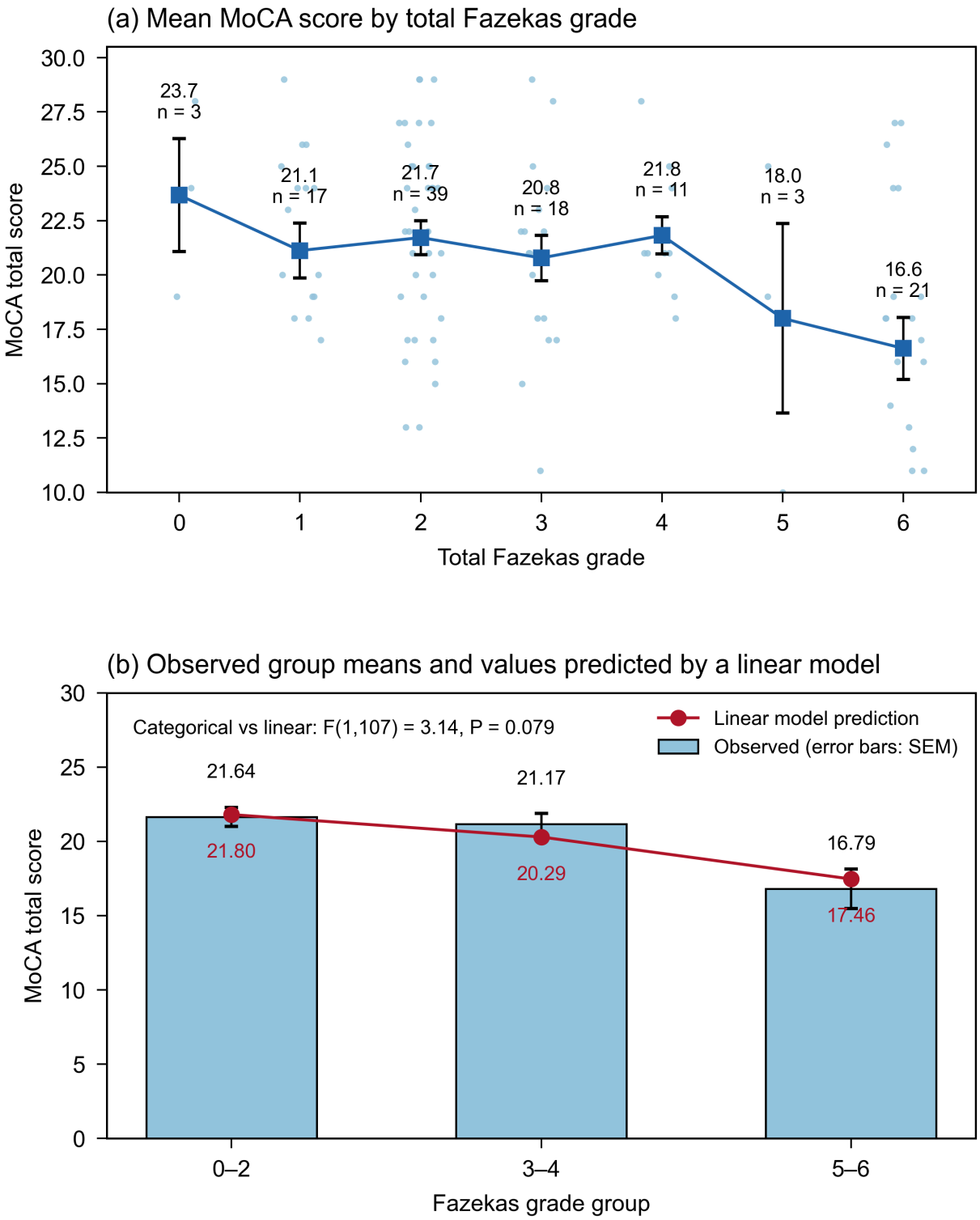


Figure 3

Montreal Cognitive Assessment score across Fazekas grades. (a) Mean score at each total Fazekas grade (0-6), with individual patients shown as jittered points and error bars indicating the standard error of the mean. (b) Observed group means (light bars) and values predicted by a model containing Fazekas score as a single continuous term (red line and markers); error bars indicate the standard error. Observed and predicted means differed by less than 0.9 points in all three groups, and a categorical

model did not fit better than the linear model (F(1,107) = 3.14; P = 0.079). MoCA, Montreal Cognitive Assessment.

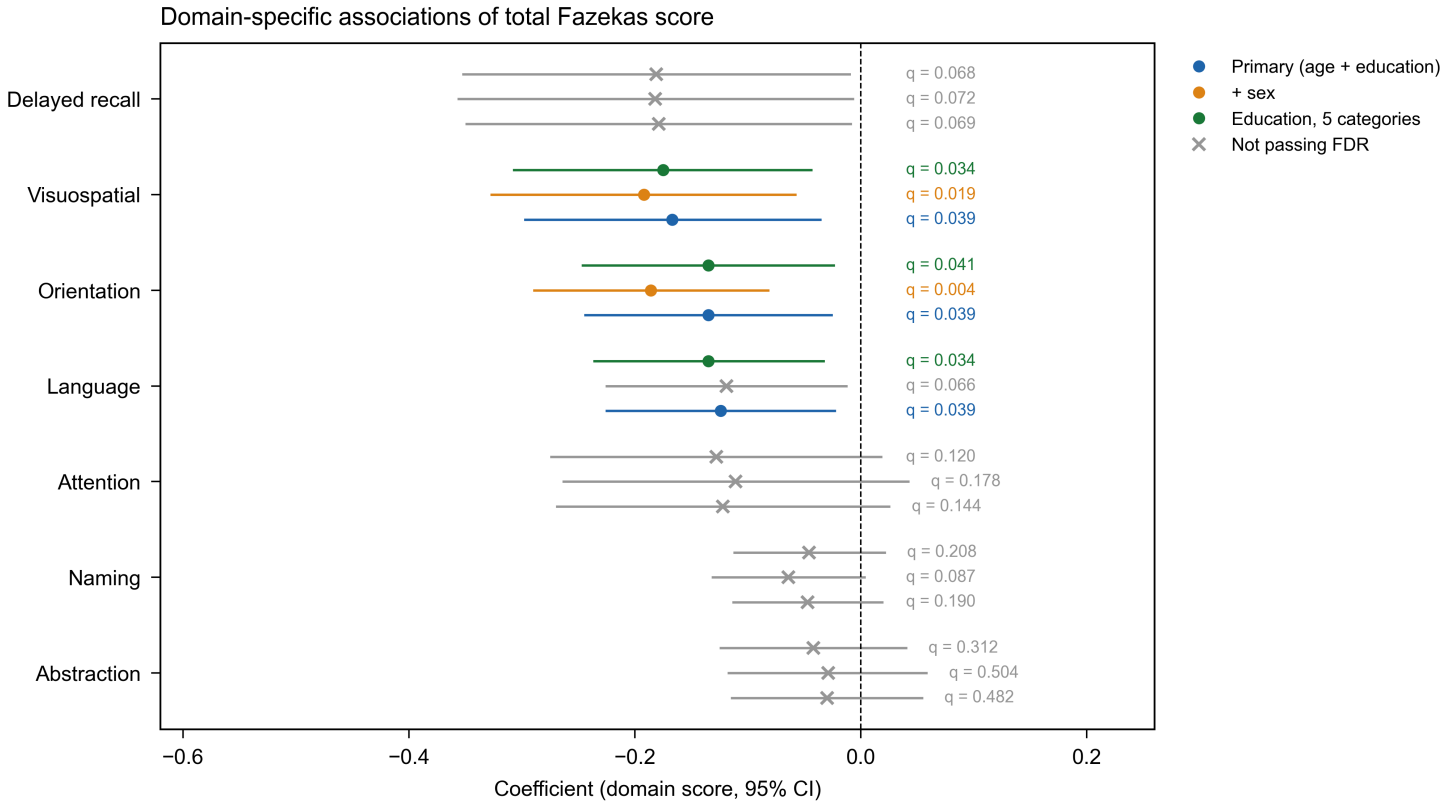


Figure 4

Domain-specific associations of total Fazekas score under three covariate specifications. Domains are ordered by the absolute value of the coefficient in the primary specification. For each domain, three estimates are shown: blue, primary model adjusted for age and years of education; orange, additionally adjusted for sex; green, education entered as a five-level categorical variable. Horizontal lines are 95% confidence intervals; the value at the right of each row is the Benjamini-Hochberg adjusted q value computed within that specification across the seven domains. Filled markers indicate q < 0.05; crosses indicate that the threshold was not met. The visuospatial and orientation domains met the threshold in all three specifications, whereas language met it in two of three (q = 0.066 with sex adjustment) and was therefore not considered robust. MoCA, Montreal Cognitive Assessment.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterialEN.xlsx