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RESEARCH ARTICLE

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Impact of white matter hyperintensities on subjective cognitive decline phenotype in a diverse cohort of cognitively normal older adults

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Abstract

Objectives: Subjective cognitive decline (SCD) is a preclinical stage of AD. White matter hyperintensities (WMH), an MRI marker of cerebral small vessel disease, associate with AD biomarkers and progression. The impact of WMH on SCD phenotype is unclear.

Methods/Design: A retrospective, cross-sectional analysis was conducted on a diverse cohort with SCD evaluated at the NYU Alzheimer's Disease Research Center between January 2017 and November 2021 (n = 234). The cohort was dichotomized into none-to-mild (n = 202) and moderate-to-severe (n = 32) WMH. Differences in SCD and neurocognitive assessments were evaluated via Wilcoxon or Fisher exact tests, with p-values adjusted for demographics using multivariable logistic regression.

Results: Moderate-to-severe WMH participants reported more difficulty with decision making on the Cognitive Change Index (1.5 SD 0.7 vs. 1.2 SD 0.5, p = 0.0187) and worse short-term memory (2.2 SD 0.4 vs. 1.9 SD 0.3, p = 0.0049) and higher SCD burden (9.5 SD 1.6 vs. 8.7 SD 1.7, p = 0.0411) on the Brief Cognitive Rating Scale. Moderate-to-severe WMH participants scored lower on the Mini-Mental State Examination (28.0 SD 1.6 vs. 28.5 SD 1.9, p = 0.0491), and on delayed paragraph (7.2 SD 2.0 vs. 8.8 SD 2.9, p = 0.0222) and designs recall (4.5 SD 2.3 vs. 6.1 SD 2.5, p = 0.0373) of the Guild Memory Test.

Conclusions: In SCD, WMH impact overall symptom severity, specifically in executive and memory domains, as well as objective performance on global and domain-specific tests in verbal memory and visual working/associative memory.

KEYWORDS
Alzheimer's disease, memory, small vessel disease, subjective cognitive decline, subjective cognitive impairment, white matter disease, white matter hyperintensities

Key points

- White matter hyperintensities impact subjective cognitive decline in executive and memory domains

- White matter hyperintensities also affect objective measures of cognition in verbal memory and visual working/associative memory

1 | INTRODUCTION

White matter hyperintensities (WMH) on magnetic resonance imaging (MRI) are frequently observed in older populations, and represent changes in white matter composition from altered water content in the white matter fibers and tracts.[1] Neuropathologically, such lesions represent demyelination, axonal loss, and glial cell responses caused by cerebral small vessel disease.[2]

WMH are also associated with cognitive changes, including both global and domain-specific impairments.[1] Impaired domains include memory, processing speed, attention, executive function, and perception/construction.[3] Moreover, WMH predict future cognitive decline[4] and WMH progression tracks with decline in attention and executive function.[3] WMH are also associated with elevated cerebral amyloid[5] and they lower the threshold for the expression of Alzheimer's disease (AD) pathology, supporting an additive or synergistic role for WMH.[1,6] For instance, in patients with autosomal dominant AD mutations, WMH are a precursor to the onset of cognitive symptoms.[7]

Subjective cognitive decline (SCD), a self-experience of cognitive deterioration despite normal cognition, is a risk factor for progression to AD dementia and thus is thought to be a preclinical stage of AD.[8–11] SCD is associated with in vivo amyloid and tau biomarkers.[12,13] But the role of WMH on neuropsychiatric and psychometric measures at the SCD stage needs to be investigated as an association may exist between WMH and SCD and deterioration of cognition.[14,15] Here we investigate the impact of WMH burden on SCD phenotype in a cross-sectional analysis of a racially and ethnically diverse cohort of adults with SCD.

2 | MATERIALS AND METHODS

2.1 | Study participants

A cross-sectional analysis was performed on a de-identified dataset of consecutive patients with SCD (Global Deterioration Scale Stage 2)[8] who underwent an MRI as part of the NYU Alzheimer's Disease Research Center (ADRC) longitudinal study from January 2017 through November 2021. The NYU ADRC study is comprised of volunteers>65 years of age (>60 years if Black or Hispanic) with a wide range of cognitive phenotypes who are willing to undergo an MRI and blood draw. All participants are required to have a study partner. Both the participant and study partner are fluent in either English or Spanish. Participants are excluded based on the presence of major neurological disease other than AD and AD-related disorders, as well as severe psychiatric illness, HIV/AIDS, organ failure, organ transplant, severe autoimmune disease, active alcohol or recreational drug abuse, or significant malignancy within 5 years. Inclusion criteria for this analysis were a consensus diagnosis of SCD and completed MRI (n = 234). The ADRC study is approved by the NYU Grossman School of Medicine Institutional Review Board.

2.2 | Clinical measures

Cognitive evaluations were performed as part of the ADRC and included a range of cognitive tests and questionnaires, conducted in accordance with the National Alzheimer's Coordinating Center's Uniform Data Set 3.0 (NACC UDS), and other surveys. For each subject the visit was done in person, and the study partner was interviewed in person or over the phone. Clinicians interviewed--in English or Spanish--the participants about medical history, medications, SCD, function, and neuropsychiatric symptoms. They also interviewed study partners about cognition, function, and neuropsychiatric symptoms. Paper-based psychometric testing was administered in English or Spanish by a tester who had undergone the requisite training. Performance was determined by normative data adjusted for age, education, and sex. Deficits were defined as Z-scores < -1.5, and the absence of such deficits was used to adjudicate participants as cognitively normal. SCD was identified and its severity and quality characterized using the Global Deterioration Scale, Cognitive Change Index (CCI), and Brief Cognitive Rating Scale (BCRS). Neuropsychiatric symptoms were evaluated using the Geriatric Depression Scale (GDS), Neuropsychiatric Inventory Questionnaire (NPI-Q), and Epworth sleepiness scale (ESS). Psychometric testing was based on the NACC UDS battery. This included the Montreal Cognitive Assessment (MoCA), Craft Story, Benton Copy, Digits Forward and Backward, Multilingual Naming Test (MINT), Verbal fluency (F, L words), Animals, Vegetables, Trails A and B. Additional psychometric tests included the Mini-Mental State Examination (MMSE), Rey Auditory Verbal Learning Test (RAVLT), Digit Symbol Substitution Test (DSST) and perceptual speed of the Wechsler Adult Intelligence Scale, and the Guild Memory Test,[16] comprised of subscales to measure immediate and delayed recall of paragraphs, immediate and delayed recall of paired associates and digit span, and recall of geometric designs.

2.3 | MRI

All participants underwent 3 T MRI with fluid attenuated inversion recovery (FLAIR) sequence as a requirement of the study. WMH on FLAIR were visually rated by ADRC clinicians blinded to participant status using the Cardiovascular Health Study (CHS) scale, with a range from 0 (no WMH) to 9 (severe WMH).[17] Subjects were then

divided into none-to-mild (CHS 0–4; $n = 202$) and moderate-to-severe (CHS 5–9; $n = 32$) WMH groups (Figure 1).[17,18] The scale is based on a visual comparison of MRIs from subjects to standardized MRIs—it is not a quantitative measurement of WMH burden but rather a qualitative measurement based on visual inspection of subcortical WMH and ventricular size.[19]

2.4 | Statistical analysis

Statistical analysis was performed using the statistical package R, version 4.2. Group comparisons (none-to-mild WMH vs. moderate-to-severe WMH) were achieved using Wilcoxon Rank-Sum tests for all measures except for elements of the NPI-Q, which were compared using the Fisher exact test. For comparisons with p-values less than 0.2, multivariable logistic regression was applied and p-values were adjusted for demographic variables (age, sex, education, and race/ethnicity). Statistical significance was defined via p-value <0.05.

3 | RESULTS

There were 234 subjects in the NYU ADRC who were included in this analysis based on having an MRI of the brain and a consensus diagnosis of normal cognition with SCD. The overall composition of the included cohort was 73.9% female, 9.4% Black, and 12.8% Hispanic. Those with moderate-to-severe WMH were older than those with none-to-mild WMH, but the two groups were otherwise similar with respect to demographics (Table 1). However, there was no significant association between race and ethnicity and WMH severity ($p = 0.3523$). Vascular comorbidities are reported in Table 2. The moderate-to-severe WMH participants were more than twice as

FIGURE 1 An Example of None-to-Mild versus Moderate-to-Severe WMH on MRI based on the CHS scale.

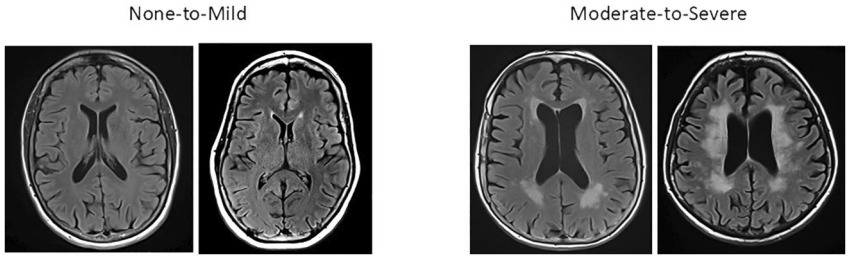

TABLE 1 Baseline demographics.

Characteristic Mean (SD) or *n*, (%)	None-to-mild WMH $n = 202$	Moderate-to-severe WMH $n = 32$	p-value
Age in years	72.6 (7.9)	79.6 (7.9)	**<0.001**
Female	145 (71.8)	28 (87.5)	0.096
Education	16.7 (2.5)	17.6 (2.3)	0.075
Hispanic (%)	28 (14.0)	2 (6.2)	0.353
Race (%)			0.291
White	176 (88.4)	27 (84.4)	
Black	17 (8.5)	5 (15.6)	
Other	6 (3.0)	0 (0.0)	

Note: Adjusted p-values meeting criterion for statistical significance ($p < 0.05$) are bolded.

TABLE 2 Vascular comorbidities.

Condition *n* (%)	None-to-mild WMH $n = 202$	Moderate-to-severe WMH $n = 32$	p-value	adjusted p-value
Hypertension	73 (36.1)	21 (65.6)	0.003	0.0688
Diabetes Mellitus	7 (3.5)	4 (12.5)	0.073	**0.0466**
Hyperlipidemia	86 (42.6)	17 (53.1)	0.355	n/a
Myocardial infarction	5 (2.5)	0 (0.0)	0.809	n/a
Congestive heart failure	2 (1.0)	0 (0.0)	1	n/a
Obstructive sleep apnea	29 (15.4)	4 (13.8)	1	n/a

Note: Adjusted p-values meeting criterion for statistical significance ($p < 0.05$) are bolded.

likely to have diabetes (adjusted $p = 0.0466$). This group also had a higher prevalence for hypertension, but this was no longer statistically significant after adjusting for demographic factors.

Measures of SCD are presented in Table 3. Total CCI scores were not significantly different between the two WMH cohorts but analyzing the subgroup scores (amnestic and executive function) raised the possibility of a greater level of subjective executive impairment amongst those with moderate-to-severe WMH. Indeed, the moderate-to-severe WMH group had increased scores in all questions in the executive subgroup, reaching statistical significance in decision making (1.5 SD 0.7 vs. 1.2 SD 0.5; adjusted $p = 0.0187$). BCRS total scores, which reflect concentration, recent memory, past memory, orientation, and function, were higher in the moderate-to-severe WMH group compared to the none-to-mild WMH group, indicating increased overall SCD magnitude (9.5 SD 1.6 vs. 8.7 SD 1.7, adjusted $p = 0.0411$). Examining individual BCRS items, the moderate-to-severe WMH group responded with higher scores across all items, reaching statistical significance specifically in the recent memory domain (2.2 SD 0.4 vs. 1.9 SD 0.3, adjusted $p = 0.0049$).

Study partner report of neuropsychiatric symptoms (NPI-Q) and participant report of depression (GDS) and sleepiness (ESS) are shown in Table 4. The most common symptoms endorsed in the NPI-Q were anxiety, depression, and nighttime behaviors, and many symptoms were higher in frequency in the none-to-mild WMH group. Of note, there was a nearly 2-fold increased prevalence of anxiety and exclusive reporting of nighttime behaviors in the none-to-mild WMH group. However, group differences across NPI-Q as well as GDS and ESS did not reach statistical significance.

On psychometric tests (Table 5), moderate-to-severe WMH participants demonstrated reduced performance on global measures of cognition as assessed by the MMSE and MoCA, however after adjustment for demographic variables this relationship remained true only for the MMSE (28.0 SD 1.6 vs. 28.5 SD 1.9, adjusted $p = 0.0491$). Domain-specific differences were apparent on the Rey Auditory Verbal Learning Test (first recall of list A and B), DSST and perceptual speed of the Wechsler Adult Intelligence Scale, and three components of the Guild Memory Test: immediate and delayed paragraph recall and designs recall. After correcting for demographics, the moderate-to-severe WMH participants remained with statistically significant lower scores on the Guild delayed paragraph recall (7.2 SD 2.0 vs. 8.8 SD 2.9, adjusted $p = 0.0222$) and designs recall (4.5 SD 2.3 vs. 6.1 SD 2.5, adjusted $p = 0.0373$).

As a supplementary analysis we also examined the association between BCRS and the RAVLT in order to elucidate the possible association between SCD and immediate recall or memory. We did this analysis because there is certain data to suggest that impairment in episodic memory, the capacity to acquire and recall information, may lead to a lack of awareness, or anosognosia, of one's cognitive decline.[20] This might call into question whether SCD is truly subjective or indicates anosognosia among participants with objective deficits that may not reach the clinical threshold of MCI. For each RAVLT item we fit a linear model to predict BCRS score and adjusted for age, gender, race/ethnicity, and education. We found that for the total BCRS score, RAVLT is a significant predictor of BCRS scores ($p < 0.05$). This indicates an association between assessment of SCD and objective impairment in immediate recall and memory.

TABLE 3 Measures of subjective cognitive decline.

Subjective cognitive test mean (SD)	None-to-mild WMH	Moderate-to-severe WMH	*p*-value	Adjusted *p*-value
CCI items 1–20	33.3 (10.1)	34.6 (12.5)	0.528	n/a
CCI amnestic items 1–12	22.2 (7.6)	22.7 (8.2)	0.758	n/a
CCI executive function items 13–17	6.9 (2.6)	7.9 (3.3)	0.067	0.144
CCI 13: Making decisions about every day matters	1.2 (0.5)	1.5 (0.7)	0.009	**0.0187**
CCI 14: Reasoning through a complicated problem	1.5 (0.8)	1.6 (0.8)	0.738	n/a
CCI 15: Focusing on goals and carrying out a plan	1.5 (0.8)	1.6 (0.7)	0.085	0.656
CCI 16: Shifting easily from one activity to the next	1.4 (0.8)	1.6 (0.8)	0.054	0.179
CCI 17: Organizing my daily activities	1.3 (0.6)	1.5 (0.8)	0.08	0.200
BCRS items 1–5	8.7 (1.7)	9.5 (1.6)	0.041	**0.0411**
BCRS 1: Concentration	1.9 (0.7)	2.0 (0.8)	0.526	n/a
BCRS 2: Recent memory	1.9 (0.3)	2.2 (0.4)	<0.001	**0.0049**
BCRS 3: Past memory	1.7 (0.6)	1.8 (0.7)	0.455	n/a
BCRS 4: Orientation	1.4 (0.5)	1.5 (0.6)	0.229	n/a
BCRS 5: Function	1.8 (0.5)	2.0 (0.6)	0.095	0.203

Note: Adjusted *p*-values meeting criterion for statistical significance ($p < 0.05$) are bolded.

Abbreviations: BCRS, Brief Cognitive Rating Scale; CCI, Cognitive Change Index.

TABLE 4 Neuropsychiatric symptoms.

Scale mean (SD)	None-to-mild WMH	Moderate-to-severe WMH	*p*-value	Adjusted *p*-value
NPI-Q	0.8 (1.3)	0.4 (0.9)	0.07	0.199
Delusions	0 (0.0)	0 (0.0)	1	n/a
Hallucinations	0 (0.0)	0 (0.0)	1	n/a
Agitation/aggression	3 (1.5)	1 (3.1)	0.448	n/a
Depression/dysphoria	39 (19.3)	5 (15.6)	0.808	n/a
Anxiety	51 (25.2)	4 (12.9)	0.174	0.353
Elation/euphoria	1 (0.5)	0 (0.0)	1	n/a
Apathy/indifference	4 (2.0)	0 (0.0)	1	n/a
Motor disturbance	3 (1.5)	0 (0.0)	1	n/a
Nighttime behaviors	17 (8.4)	0 (0.0)	0.39	n/a
GDS	1.6 (1.9)	1.6 (2.1)	0.854	n/a
ESS	4.7 (3.5)	4.8 (3.4)	0.719	n/a

Abbreviations: ESS, Epworth Sleepiness Scale; GDS, Geriatric Depression Scale; NPI-Q, Neuropsychiatric Inventory Questionnaire.

4 | DISCUSSION

This cross-sectional study of 234 diverse, cognitively normal adults with SCD demonstrates that moderate-to-severe WMH impacts the subjective and objective neurocognitive phenotype at this preclinical stage of AD. WMH burden was associated with worsened self-reported measures of cognitive decline, decision making and recent memory, in addition to worsened objective measures of global and domain specific impairment in verbal memory and visual working/associative memory.

WMHs are known to be associated with age and vascular risk factors, consistent with what was observed in this study.[21] Interestingly, hypertension was nearly twice as prevalent in those with moderate-to-severe WMH (as compared to none-to-mild WMH), but after adjusting for demographics this was no longer statistically significant. This likely reflects limited power given the relatively small number of patients with moderate-to-severe WMH. Alternatively, the moderate-to-severe WMH rating is heavily influenced by location and morphology of WMH, which is not necessarily taken into full account by the CHS scale. For instance, deep WMH volume is less related to hypertension than circumferential periventricular lesions.[22] The location and morphology influences cognitive outcomes, too.[18] Frontal WMH tend to affect executive function while parieto-temporal WMH affect memory.[23] WMH heterogeneity, which is associated with different vascular etiologies, may not be captured in this rating scale either.[24] Thus, the CHS does not give a comprehensive assessment of WMH which may confound results both when taking into account vascular risk factors and cognitive outcomes.

Prior studies have reported an inconsistent relationship between WMH and memory complaints in cognitively normal adults.[14,25–27] This may stem from methodological variability in assaying SCD. Here we found that the BCRS score differentiates WMH severity but the CCI total score does not. Notably, the CCI assesses perceived cognitive decline over the last 5 years while the BCRS does not require a temporal component. We cannot rule out that the CCI failed to achieve statistical significance potentially due to the small number of moderate-to-severe WMH and existence of missing data. Across both scales, questions related to decision-making and recent memory did show statistically significant differences. Of note, the BCRS was also found to be useful in tracking decline from the SCD stage over a 2-year interval.[11] Moreover, when a supplementary analysis was performed, the BCRS did have a significant association with the RAVLT, indicating that SCD may be more than just subjective and that there are objective deficits for these patients that do not reach the clinical threshold of MCI. However, here, too, the power was low.

Interestingly, our study noted no relationship between particular neuropsychiatric symptoms, such as apathy, and extensive WMH in persons with SCD. This finding is in contrast with a recent large meta-analysis showing that WMH severity correlates with apathy in patients with WMH, a common feature of vascular dementia.[28,29] However, the meta-analysis included a broad population of individuals with WMH, not just those with SCD. Here, <2% reported apathy, as it is a more relevant feature in subjects with significant cognitive impairment. Our analysis of neuropsychiatric symptoms was primarily limited to informant-based report. However, self-report at early stages may elicit a better correlation to WMHs. Finally, neuropsychiatric symptoms may be better detectable in objective cognitive impairment and are associated with subsequent cognitive deterioration via an interaction between more prominent AD pathology and cerebral small vessel disease.[30]

With regard to impact on objective cognition, in studies with smaller and less diverse cohorts, the impact of WMH at the SCD stage has been inconsistent, with one study showing association with executive dysfunction,[31] and another showing an influence on episodic memory.[32] Our prior work showed that NACC UDS psychometric tests did not differentiate cerebral small vessel disease and AD (or

TABLE 5 Psychometric performance.

Psychometric test	None-to-mild WMH	Moderate-to-severe WMH	*p*-value	adjusted *p*-value
MMSE	28.5 (1.9)	28.0 (1.6)	0.03	**0.0491**
MoCA[a]	27.3 (2.3)	26.4 (2.1)	0.011	0.0716
RAVLT—List a 1st trial recall	6.7 (2.1)	5.9 (1.9)	0.043	0.134
RAVLT—List B 1st trial recall	5.8 (1.9)	4.8 (2.0)	0.007	0.0768
Craft story—immediate, verbatim[a]	24.1 (6.0)	23.1 (5.1)	0.368	n/a
Craft story—delayed, verbatim[a]	21.7 (5.9)	21.6 (6.3)	0.956	n/a
Benton copy immediate[a]	15.2 (1.3)	15.2 (0.9)	0.523	n/a
Benton copy delayed[a]	10.8 (2.7)	10.2 (2.8)	0.308	n/a
Digits forward—longest span[a]	6.9 (1.3)	6.6 (1.1)	0.204	n/a
Digits backward—longest span[a]	5.4 (1.3)	5.1 (1.0)	0.238	n/a
MINT[a]	30.1 (2.4)	30.4 (2.0)	0.576	n/a
Verbal fluency—F words[a]	16.8 (4.9)	16.2 (4.1)	0.607	n/a
Verbal fluency—L words[a]	15.3 (4.7)	15.7 (4.3)	0.697	n/a
Animals[a]	21.9 (5.4)	20.8 (4.4)	0.232	n/a
Vegetables[a]	15.3 (4.3)	15.3 (3.7)	0.802	n/a
Trails A[a]	31.6 (13.3)	33.0 (10.0)	0.149	0.553
Trails B[a]	79.2 (42.9)	83.9 (34.5)	0.203	n/a
Guild paragraph immediate recall	6.4 (2.2)	5.6 (1.7)	0.042	0.107
Guild paragraph delayed recall	8.8 (2.9)	7.2 (2.0)	0.006	**0.0222**
Guild designs recall	6.1 (2.5)	4.5 (2.3)	0.005	**0.0373**
Guild paired associates- immediate	4.9 (2.6)	4.1 (2.4)	0.193	0.459
Guild paired associates- delayed	6.1 (2.9)	6.0 (2.5)	0.914	n/a
Perceptual speed - correct responses	71.3 (12.2)	65.1 (11.4)	0.006	0.194
DSST	51.8 (11.3)	44.1 (8.5)	0.005	0.105

Note: Adjusted *p*-values meeting criterion for statistical significance ($p < 0.05$) are bolded.

Abbreviations: DSST, Digit Symbol Substitution Test; MINT, Multilingual Naming Test; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test.

[a]NACC UDS 3.0 psychometric battery.

their combination) at the stage of MCI.[33] Similarly, here we find that UDS tests largely did not differentiate WMH burden in persons with SCD. However, we reveal a relationship between extensive WMH and lower performance on a verbal memory task (Guild story) and a task involving visual working and associative memory (Guild designs) as well as the MMSE. The Guild Design performance is particularly relevant as we have recently shown that the right temporal lobe, which plays a role in visual working and associative memory,[34–38] is vulnerable to the combination of AD and small vessel disease.[39] Moreover, while faster progression has been linked to extensive WMH in the SCD stage,[40] it has also been associated with preferential right temporal neurodegeneration and tauopathy.[41,42]

This study has multiple strengths. Our cohort is larger and more racially and ethnically diverse than most other WMH studies at the SCD stage. Moreover, the cohort was characterized via multiple measures of SCD and extensive neuropsychiatric and psychometric measures. There are limitations to our methodology, including the cross-sectional nature of the analysis and potential limitations of application to the general population given that this is a research cohort with generally high educational and socioeconomic status. The current study does not include a group of cognitively normal adults without SCD for comparison. Moreover, WMH were graded using visual ratings rather than using more quantitative measurements. Furthermore, it did not account for WMH morphology and location, which has been shown to correlate with certain vascular risk factors and cognitive outcomes.[24] Nor did it account for the degree of WMH using a quantitative scale, which in future studies may allow for more exact measurement of degree of WMH than the CHS. Additionally, we were not able to use WMH grading as a continuous variable because the NACC data groups the 0–4 population into one cohort. This means

our study would be underpowered when using WMH as a continuous variable. If we were able to use WMH as a continuous variable it would have made our conclusions stronger and demonstrated how significant slightly increasing WMH burden affects SCD and other objective cognitive measures. This is something that ought to be done for future studies. In sum, our results suggest that WMHs play a critical role in shaping the phenotype of SCD, a preclinical stage of AD. Nevertheless, we need to be careful when assuming that these patients with SCD and WMH are in a preclinical stage of AD. In truth, patients with moderate-severe WMH might be preclinical vascular dementia and AD rather than just AD given the association of significant WMH with vascular dementia.[43] Additionally, our results suggest a role for particular SCD assay components and psychometric tests that may highlight the presence of significant WMHs and, in turn, serve as potential markers of clinical progression. This promotes further work to examine the impact of WMHs, a potentially modifiable lesion, on SCD outcomes, AD biomarkers, and specific brain networks.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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