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RESEARCH ARTICLE

Characterization of white matter hyperintensities in Down syndrome

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Abstract

INTRODUCTION: In Down syndrome (DS), white matter hyperintensities (WMHs) are highly prevalent, yet their topography and association with sociodemographic data and Alzheimer's disease (AD) biomarkers remain largely unexplored.

METHODS: In 261 DS adults and 131 euploid controls, fluid-attenuated inversion recovery magnetic resonance imaging scans were segmented and WMHs were extracted in concentric white matter layers and lobar regions. We tested

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associations with AD clinical stages, sociodemographic data, cerebrospinal fluid (CSF) AD biomarkers, and gray matter (GM) volume.

RESULTS: In DS, total WMHs arose at age 43 and showed stronger associations with age than in controls. WMH volume increased along the AD continuum, particularly in periventricular regions, and frontal, parietal, and occipital lobes. Associations were found with CSF biomarkers and temporo-parietal GM volumes.

DISCUSSION: WMHs increase 10 years before AD symptom onset in DS and are closely linked with AD biomarkers and neurodegeneration. This suggests a direct connection to AD pathophysiology, independent of vascular risks.

KEYWORDS
Alzheimer's disease, Down syndrome, magnetic resonance imaging, neuroimaging, small vessel disease, white matter hyperintensities

Highlights

- White matter hyperintensities (WMHs) increased 10 years before Alzheimer's disease symptom onset in Down syndrome (DS).
- WMHs were strongly associated in DS with the neurofilament light chain biomarker.
- WMHs were more associated in DS with gray matter volume in parieto-temporal areas.

1 | BACKGROUND

Down syndrome (DS) is a genetic condition caused by an extra copy of chromosome 21 that has been associated with an ultra-high risk of developing Alzheimer's disease (AD), with virtually all individuals with DS showing full-blown AD neuropathology by the age of 40.[1,2] A key factor driving this increased risk is the triplication of the amyloid precursor protein (*APP*) gene, which is necessary and sufficient to cause AD pathology.[3] As a result of the overexpression of *APP*, amyloid beta (Aβ) plaques, a hallmark feature of AD, accumulate early and rapidly in the brain and eventually lead to cognitive impairment and dementia.[4] Thus, DS is currently considered a genetically determined form of AD.[2]

It is increasingly recognized that studying AD in individuals with DS can provide valuable insights into its pathogenesis. Alongside the predictable course of AD,[5] adults with DS present a distinct profile of vascular risk factors from aging in the general population,[6] as they are relatively protected from some conventional age-related vascular risk factors, such as hypertension.[7] Thus, this population provides a unique opportunity to further understand the emergence of cerebrovascular

diseases, specifically small vessel disease (SVD), in the context of AD without the confounds of age-related vascular risk factors.

One of the main imaging markers of SVD is white matter hyperintensities (WMHs) of presumed vascular origin.[8] WMHs are areas of increased signal on T2-weighted or fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI).[9,10] They can reflect distinct pathological processes related to SVD, including increased interstitial fluid, demyelination, gliosis, loss of fibers and oligodendrocyte precursor cells, and failure of the glymphatic system.[8,11] These lesions are frequently found in healthy older adults and their prevalence and severity increase with age.[12] The occurrence of WMHs is also increased in individuals with sporadic[10,13] and other genetic forms of AD.[14,15] In adults with DS, the prevalence and severity of WMHs are increased in both asymptomatic and symptomatic DS with respect to euploid cognitively unimpaired controls[16] and WMH volume increases along the AD continuum.[17] Altogether, this suggests that these lesions may be related to AD development. However, little is known about the spatial distribution of WMHs in DS, which could provide insight into their etiology. Moreover, to our knowledge, no study has yet

assessed the relationships between WMHs and fluid and neuroimaging biomarkers of AD in DS.

In the present study, we aimed to better characterize WMHs and their relationship to sociodemographic, clinical, genetic, and AD biomarkers in a large population-based cohort of adults with DS. We particularly focused on regional WMH burden along the AD continuum and its associations with AD biomarkers. We hypothesize that the early accumulation of AD pathologies in DS will lead to WMHs years before symptoms onset, which will eventually increase as the disease progresses.

2 | METHODS

2.1 | Study design and participants

This cross-sectional study was conducted at a single center, where adults with DS aged ≥ 18 were recruited from the population-based Down-Alzheimer Barcelona Neuroimaging Initiative (DABNI) cohort.[2] A sample of euploid cognitively unimpaired control (HC) individuals was also included from the Sant Pau Initiative on Neurodegeneration (SPIN) cohort.[18] The study was approved by the Sant Pau Ethics Committee following the standards for medical research in humans recommended by the Declaration of Helsinki. All participants or their legally authorized representatives gave written informed consent before enrollment.

The participants with DS were screened for apolipoprotein E (*APOE*) haplotype and underwent a comprehensive neurological and neuropsychological evaluation, including, among other tests, the Cambridge Cognitive Examination for Older Adults with Down Syndrome (CAMCOG-DS) Spanish version for assessing global cognition.[19,20] The CAMCOG-DS is a cognitive battery that evaluates orientation, language, memory, attention, praxis, abstract thinking, and perception.

As in previous studies,[2,21] participants were clinically classified during a consensus meeting between neurologists and neuropsychologists, masked from biomarker data, into the following groups: asymptomatic (aDS) when there was no clinical or neuropsychological suspicion of AD-related cognitive decline, prodromal AD (pDS) when there was evidence of cognitive decline due to AD, but no significant impact on baseline activities of daily living, and AD dementia (dDS) when the cognitive decline impaired daily activities. This functional status, differentiating pDS and dDS, was assessed using anamnesis, Dementia Questionnaire for Persons with Mental Retardation, and the Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with Intellectual Disabilities. Additionally, the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition, was used to stratify the level of intellectual disability (ID) into mild, moderate, or severe/profound based on the individuals' best-ever level of functioning.[22]

The HC group are volunteers, usually spouses or children of patients from the Sant Pau Memory Unit, that are informed about our studies at the outpatient clinics. They exhibited no cognitive complaints, scoring 0 on the Clinical Dementia Rating scale, and their neuropsychological

RESEARCH IN CONTEXT

1. **Systematic review**: White matter hyperintensities (WMHs) are recognized as vascular markers that contribute to cognitive decline. Previous studies have shown that WMHs are prevalent in Down syndrome (DS), a genetically determined form of Alzheimer's disease (AD) not complicated by some traditional age-related vascular risk factors. However, the evolution and topography of WMHs across age and disease severity, as well as their relationship to AD pathophysiology, have not been thoroughly studied in DS.

2. **Interpretation**: WMHs increased with age and AD clinical stage, and were correlated with cerebrospinal fluid AD biomarkers and gray matter volume in AD vulnerable areas. Our findings suggest that WMHs might be intrinsically related to AD pathophysiological processes in DS.

3. **Future directions**: *Post mortem* studies could shed light on the pathological substrates of WMHs in DS and other genetically determined forms of AD.

evaluation was within the normal range for their respective normative groups regarding age and education. None of the participants in the HC group reported any neurological or psychiatric disorders, or other major medical illnesses.[18] We selected only the HC within the same age range as the DS group, from 18 to 63 years.

2.2 | Neuroimaging data

2.2.1 | MRI acquisition

T1-weighted and FLAIR images were acquired on a 3T Philips-Achieva scanner at Hospital del Mar (Barcelona, Spain) or a 3T Siemens Prisma scanner at Hospital Clinic (Barcelona, Spain). The detailed acquisition parameters of the imaging protocols are provided in Table S1 in supporting information.

The quality of each T1-weighted and FLAIR image was visually assessed. MRI scans of unsatisfactory quality in terms of low transverse resolution or low structural visibility due to movement or other sources of noise were excluded ($n = 21$ scans, 4.64%).

2.2.2 | Gray matter volume

The Computational Anatomy Toolbox (CAT12)[23] for the Statistical Parametric Mapping 12 (SPM12; Welcome Center for Human Neuroimaging) toolbox was used to preprocess the structural T1-weighted image and extract gray matter (GM) and total intracranial volumes.

2.2.3 | WMH segmentation

For the segmentation of WMHs, raw FLAIR images were first coregistered onto their corresponding T1-weighted scan using Advanced Normalization Tools (ANTs)[24] (Figure S1A in supporting information). Then, WMHs were segmented in the MRI native space using the lesion prediction algorithm (LPA)[25] implemented in the Lesion Segmentation Toolbox for SPM12. Specifically, the LPA method computed a WMH probability map for each participant based on a logistic regression algorithm to classify each voxel as either a lesion or non-lesion. The probability maps were then binarized by applying a threshold of 0.3 (Figure S1B).

2.2.4 | White matter parcellation

White matter (WM) was parcellated for each subject using an in-house pipeline inspired by the bull's-eye classification system previously developed by Sudre et al.[26] Specifically, two distinct sets of parcellations were created: concentric layers and lobar regions (for details, see supporting information). For the concentric layers, we followed the approach proposed by Jiménez-Balado et al.[27] and obtained a normalized distance map reflecting the distance of each WM voxel to the lateral and third ventricles (Figure S1C). For the lobar regions, we used the anatomical Hammers atlas to label the WM according to the lobes (frontal, parietal, temporal, occipital, and basal ganglia; Figure S1D). The normalized distance map was applied to each lobar region and subsequently divided into four concentric layers of similar volume. These layers spanned from the periventricular regions to juxtacortical areas. Regional WMH volumes were then extracted and summarized as an infographic in a bull's-eye plot (e.g., see Figure S1). Because different MRI acquisition protocols were used to acquire the data, we harmonized total and regional WMH volumes using the ComBat harmonization method[28] as implemented in the R library neuroCombat.

2.3 | Fluid biomarkers

A subset of participants underwent, within 1 year of the MRI acquisition, a lumbar puncture to acquire cerebrospinal fluid (CSF) sampling, as previously described.[21,29] Concentration levels of $A\beta_{40}$ ($n = 251$), $A\beta_{42}$ ($n = 251$), and tau phosphorylated at threonine 181 (pTau181; $n = 251$) were quantified using a commercially available immunoassay in a fully automated platform (Lumipulse; Fujirebio-Europe), following a previously published protocol.[18] CSF glial fibrillary acidic protein (GFAP; $n = 183$) concentrations were measured using the SR-X single molecule array. CSF neurofilament light chain (NfL; $n = 267$) and YKL-40 (also known as chitinase 3-like 1; $n = 236$) levels were measured with enzyme-linked immunosorbent assay (ELISA; NF-Light Assay; UmanDiagnostics) according to the manufacturer's recommendations. CSF $A\beta_{42}/A\beta_{40}$ ratio and p-tau181 were used to stratify individuals with DS according to the presence of amyloid (A+) and tau (T+) pathologies using previously established cutoff values (i.e., CSF $A\beta_{42}/A\beta_{40} < 0.062$; CSF p-tau181 > 63 pg/mL[30]).

2.4 | Statistical analyses

All statistical analyses were performed with R software, version 4.3.1. Differences in baseline sociodemographic characteristics between DS and HC participants were assessed using the compareGroups library.[31] This package tests the normality of continuous variables and subsequently performs parametric or non-parametric statistical tests accordingly. Chi-squared tests were used for categorical variables, such as sex and *APOE ε4* status, while Mann–Whitney tests were applied for continuous variables, including age, and CSF biomarkers, because they did not follow normality. To reduce skewness, total and regional volumes of WMHs, as well as concentrations of CSF biomarkers, were log-transformed.

To examine the association between WMH volume and age, we performed locally estimated scatterplot smoothing (LOESS) curves with a tricubic weight function and a span parameter of 0.75, providing an informative representation of the data. To assess the effect of factors such as sex, *APOE ε4* status, ID, and AD clinical status on the distribution of WMH volume, we performed either a Mann–Whitney or Kruskal–Wallis test followed by the Dunn test as post hoc analysis. To investigate the relationship between total and regional WMH volume and CSF biomarkers, we performed Spearman correlation tests.

We used univariate linear regression models to assess the predictive capacity of individual CSF biomarkers on total WMH volume in the whole DS cohort, but also in aDS and symptomatic DS (sDS; comprising pDS and dDS) separately. Subsequently, we conducted a multivariate analysis incorporating all the CSF biomarkers to assess their relative contribution to the prediction of WMH volume. Additionally, we repeated both univariate and multivariate models including age as a predictor to evaluate its effect in relation to the CSF biomarkers. The standardized regression coefficients were used to compare the strength of the association between the predictors and total WMH volume. The threshold for significance was set at $p = 0.05$ and Bonferroni corrections were applied in regional volume analyses to account for multiple comparisons.

Finally, we used voxelwise linear models to compare the association of GM volume and WMHs in the DS cohort. Analyses were performed in a mask that excluded non-GM voxels, and the statistical models were corrected for total intracranial volume and the MRI acquisition protocol. Voxelwise results are presented at a corrected threshold $p < 0.05$ (family-wise error [pFWE], cluster size k > 100 mm^3).

3 | RESULTS

3.1 | Population

The study included 261 adults with DS from the DABNI cohort and 131 HC from the SPIN study (see Table 1 for demographic data). Individuals

TABLE 1 Study participants.

|	HC N = 131	DS N = 261	p-value
Age, y, median [IQR]	53.65 [48.70;57.81]	46.96 [37.77;51.81]	<0.001
Sex, no. (%)			<0.001
Female	93 (70.99%)	108 (41.38%)	
APOE ε4 status, no. (%)			0.15
ε4+	36 (27.69%)	51 (20.56%)	
Intellectual disability, no. (%)			
Mild		76 (29.46%)	
Moderate		148 (57.36%)	
Severe/profound		34 (13.18%)	
AD diagnostic group, no. (%)			
aDS		158 (60.54%)	
pDS		41 (15.71%)	
dDS		62 (23.75%)	
Vascular risk factors, no (%)			
Hypertension (N = 323)	14 (21.88%)	4 (1.54%)	<0.001
Dyslipidemia (N = 323)	17 (26.56%)	47 (18.15%)	0.18
Diabetes mellitus (N = 322)	2 (3.12%)	12 (4.65%)	0.74
CAMCOG-DS, median [IQR]		69.00 [51.00;82.00]	
CSF biomarkers, pg/mL, median [IQR]			
$A\beta_{42}/A\beta_{40}$ (N = 251)	0.11 [0.10;0.11]	0.06 [0.04;0.08]	<0.001
pTau181 (N = 251)	32.30 [24.90;41.40]	55.05 [24.52;133.55]	<0.001
NfL (N = 267)	349.80 [298.92;418.61]	542.30 [304.32;871.20]	<0.001
GFAP (N = 183)	3.35 [3.14;3.50]	3.61 [3.40;3.78]	<0.001
YKL-40 (N = 236)	2.20 [2.11;2.29]	2.26 [2.03;2.37]	0.50

Notes: Data are n (%) or median (IQR).

Abbreviations: $A\beta_{42}/A\beta_{40}$, concentration ratio between amyloid beta peptide 1-42 and amyloid beta peptide 1-40 (pg/mL); AD, Alzheimer's disease; aDS, asymptomatic Down syndrome; APOE, apolipoprotein E; CAMCOG-DS, Cambridge Cognitive Examination for Older Adults with Down Syndrome; CSF, cerebrospinal fluid; dDS, Down syndrome with Alzheimer's disease dementia; DS, Down syndrome; GFAP, glial fibrillary acidic protein concentration (pg/mL); HC, euploid cognitively unimpaired controls; IQR, interquartile range; NfL, neurofilament light chain concentration (pg/mL); pDS, prodromal Down syndrome; pTau181, tau phosphorylated at threonine 181 concentration (pg/mL); YKL-40, chitinase 3-like 1.

in the DS group spanned the whole AD continuum; 158 were aDS, 41 pDS, and 62 dDS. Regarding the level of ID, 76 DS subjects had mild ID, 149 moderate ID, and 34 severe/profound ID. The HC group was significantly older than the DS group (W = 24666, p < 0.05). There was also a significant difference in the sex distribution, with fewer male participants in the HC group (29.01%) than in the DS group (58.62%, p < 0.001). No significant between-group differences were found for APOE ε4 status. Only 1.5% of individuals with DS presented hypertension, a significantly lower proportion compared to the HC group (21.9%, p < 0.001). Additionally, 18% had dyslipidemia and 4.7% had diabetes mellitus, versus 27% (p = 0.18) and 3.12% (p = 0.74), respectively. As expected, individuals with DS demonstrated lower values in CSF for the $A\beta_{42}/A\beta_{40}$ ratio and higher concentrations of pTau181, NfL, and GFAP than HC (all p < 0.001). CSF YKL-40 levels were not significantly different across groups (p = 0.50).

3.2 │ Associations between WMH volume and sociodemographic, clinical, and genetic data

Total WMH volume was positively associated with age in both HC (rho = 0.36, p < 0.001) and adults with DS (rho = 0.67, p < 0.001). Looking at the LOESS curves (Figure 1A), we found an earlier increase in total WMH volume in DS with age. Specifically, the regression lines between DS and HC started diverging at age 40, and the confidence interval (CI) ceased to overlap at the age of 43.8. Regional associations revealed that, in HC, a significant relationship with age was mainly observed in the first layer (Figure 1B and Table S2 in supporting information for more details). In contrast, regional associations with age were more widespread and stronger in DS, including all lobes. The first and second layers (i.e., the region closest to the ventricles) showed the highest correlation strength and earliest changes
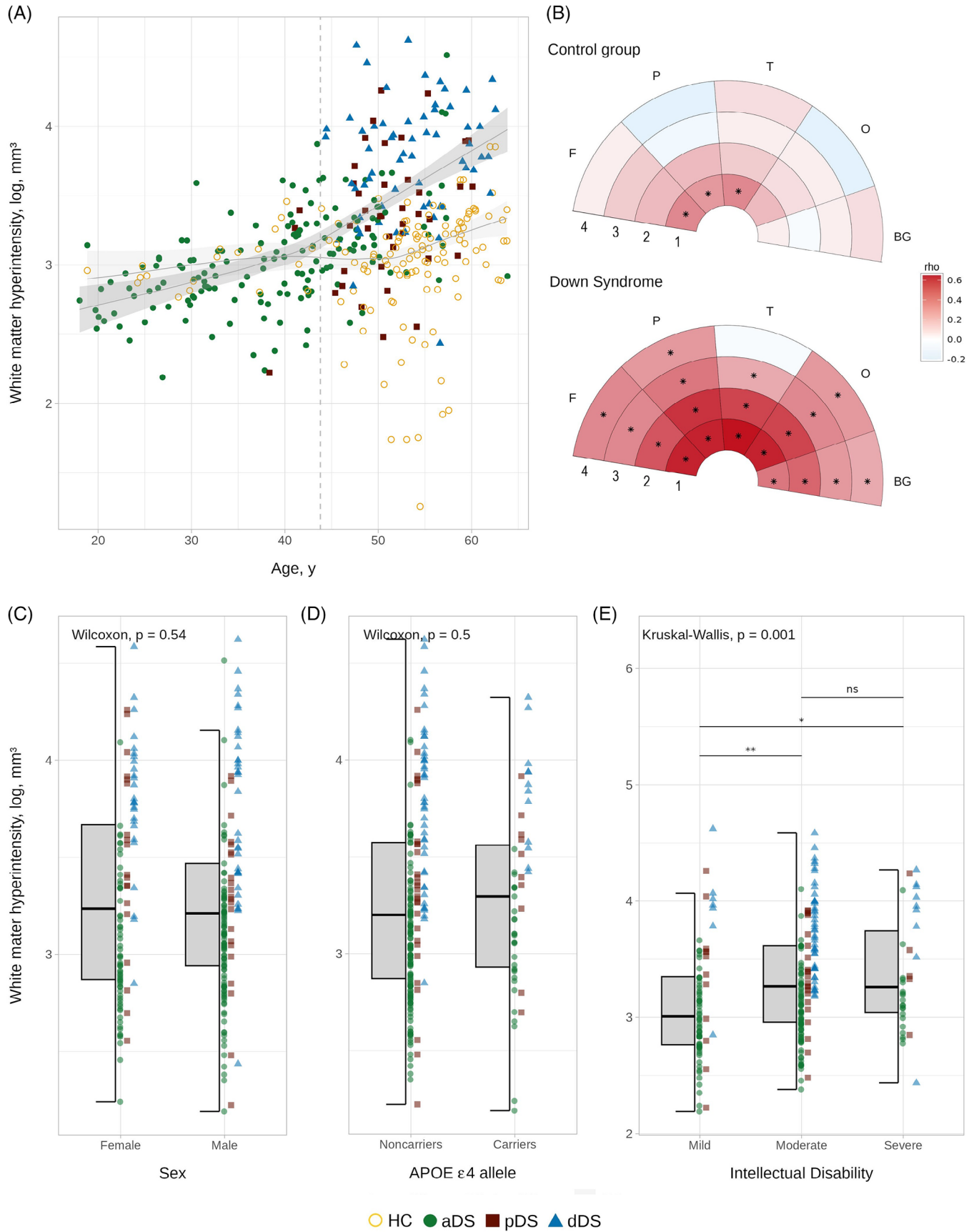
(Figures 1B, S2 in supporting information, and Table S2 for more details).

In DS, sex and *APOE* ε4 status did not significantly influence total WMH volume (Figure 1C,D) or the association between total WMH volume and age (Figure S3 in supporting information). However, we found a significant difference according to the degree of ID, with the moderate and severe ID levels showing greater WMH volume than the mild level (Figure 1E). Given that this result was unexpected, we assessed whether it may be explained by differences in clinical status across the ID groups. Results showed a higher proportion of moderate ID in dDS (77.97%) than aDS (50.64%; X^2 [4, $N = 259$] = 14.462, $p < 0.05$). Moreover, the effect of ID on WMH volume was no longer significant when groups were stratified by AD clinical diagnosis ($p > 0.05$; Figure S4 in supporting information) and associations with age appeared similar across ID groups (Figure S3).

3.3 | Spatial distribution of WMHs in DS

To assess the spatial distribution of WMHs in DS, we computed a frequency map of WMHs for all adults with DS. Results showed that WMHs had a symmetrical distribution, and were most frequently located in periventricular and deep regions (Figure 2). Specifically, WMHs were predominantly found in the corona radiata (mainly the posterior part), the posterior thalamic radiation, and the corpus callosum, especially in the splenium.

3.4 | Effect of AD clinical status on WMH volume

Total WMH volume progressively increased with AD clinical status in DS: dDS and pDS groups demonstrated significantly greater WMH volumes than aDS and HC, and dDS greater volumes compared to pDS. No significant differences were observed between HC and aDS (Figure 3A). Regarding regional WMH volumes, aDS showed significantly greater volumes in the temporal lobe with respect to the HC, while HC showed greater WMH in the occipital lobe and basal ganglia (Figure 3C). pDS presented significantly more WMH volume than aDS in the first and second WM layers, and in all lobes (Figure 3B,C). In the other regions (i.e., layers 3–4, and basal ganglia), there was a visible trend toward higher volumes in pDS compared to aDS, although statistical significance was not reached (Figure 3B-D). dDS consis-

tently had greater WMH volumes compared to pDS in all regions of interest, except in the fourth WM layer (Figure 3B-D). Analyses considering both the concentric layers and lobar regions showed similar results, where the first WM layer and the occipital lobes showed the greatest WMH load in all the diagnostic groups. The dDS groups demonstrated both higher and more widespread WMH load compared to other disease stages (Figure 3E).

3.5 | Associations between WMH volume and CSF biomarkers

In DS, total WMH volume was negatively related to CSF $A\beta_{42}/A\beta_{40}$ ratio (rho = −0.58, $p < 0.001$) and positively associated with CSF pTau181 (rho = 0.63, $p < 0.001$), CSF NfL (rho = 0.72, $p < 0.001$), CSF GFAP (rho = 0.61, $p < 0.001$), and CSF YKL-40 (rho = 0.63, $p < 0.001$) concentrations (Figure 4A). Additionally, A+ and T+ individuals with DS presented greater WMH volume compared to negative participants ($p < 0.001$; Figure 4A). When assessed regionally, the strongest associations between CSF biomarkers of AD and WMHs were found in the frontal, parietal, and occipital lobes and in the first and second layers (Figure 4B). The univariate models revealed that all five CSF biomarkers were significant predictor variables in the whole DS cohort ($A\beta_{42}/A\beta_{40}$: $p < 0.001$, estimate: −0.59, 95% CI: [−0.70, −0.47]; pTau181: $p < 0.001$, estimate: 0.60 [0.48, 0.71]; NfL: $p < 0.001$, estimate: 0.68 [0.57, 0.79]; GFAP: $p < 0.001$, estimate: 0.57 [0.42, 0.69]; YKL-40: $p < 0.001$, estimate: 0.58 [0.47, 0.70]). Considering the groups separately, we found significant relationships between the five biomarkers and WMHs in aDS ($A\beta_{42}/A\beta_{40}$: $p < 0.001$, estimate: −0.40, [−0.60, −0.21]; pTau181: $p < 0.001$, estimate: 0.37 [0.18, 0.56]; NfL: $p < 0.001$, estimate: 0.44, [0.27, 0.62]; GFAP: $p < 0.001$, estimate: 0.32 [0.12, 0.52]; YKL-40: $p < 0.001$, estimate: 0.46 [0.29, 0.63]). In sDS, only the association with NfL concentrations reached significance ($A\beta_{42}/A\beta_{40}$: $p = 0.81$, estimate: 0.03 [−0.21, 0.27]; pTau181: $p = 0.06$, estimate: 0.21 [−0.01, 0.44]; NfL: $p < 0.001$, estimate: 0.44 [0.22, 0.66]; GFAP: $p = 0.08$, estimate: 0.21 [−0.03, 0.45]; YKL-40: $p = 0.20$, estimate: 0.16 [−0.09, 0.40]). When performing a multivariate analysis incorporating all five CSF AD biomarkers, only NfL significantly predicted total WMH volume in the whole DS cohort ($p < 0.001$, estimate: 0.37 [0.13, 0.61]) and in sDS ($p < 0.001$, estimate: 0.54 [0.18, 0.90]) group (Figure 4C). When age was included as a covariate, several results lost significance, especially in the aDS group, but the associations with NfL remained sig-

FIGURE 1 Associations between white matter hyperintensity volume and demographic, clinical, and genetic factors. (A) Association between total WMH volume and age. The points represent individual participants, and the color indicates their clinical diagnosis. Shaded areas represent 95% CI: dark gray represents the age-related change in DS and light gray in the HC group for visual reference. The dashed line indicates when the CI stops overlapping between DS and HC groups (43.8 years). (B) Spearman correlation coefficients between age and regional WMH volumes. The color scale represents the strength (rho) of Spearman correlation for significant results ($p < 0.05$). The star (*) indicates results surviving to the Bonferroni correction ($\alpha = 0.05$, $p < 0.0025$). (C), (D) and (E) Boxplots showing the effect of sex, *APOE* haplotype, and intellectual disability, respectively, on the distribution of the total WMH volume in DS. Abbreviations: 1, first layer; 2, second layer; 3, third layer; 4, fourth layer; aDS, asymptomatic Down syndrome; *APOE*, apolipoprotein E; BG, basal ganglia; CI, confidence interval; DS, Down syndrome; F, frontal; HC, euploid cognitively unimpaired controls; dDS, Down syndrome with Alzheimer's disease dementia; O, occipital; P, parietal; pDS, prodromal Down syndrome; rho, strength of the correlation; T, temporal; WMH, white matter hyperintensity.
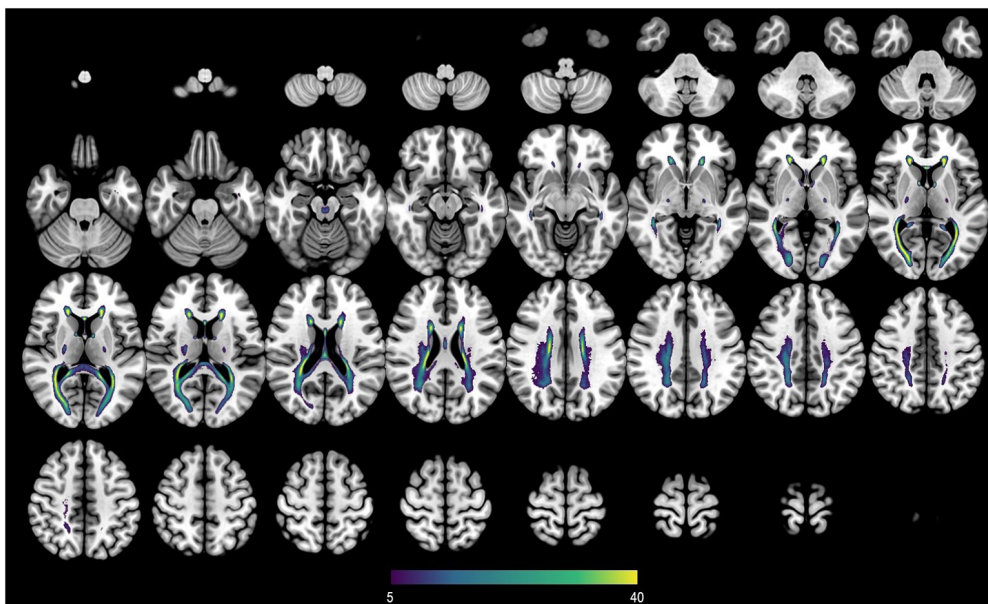
FIGURE 2 Lesion prevalence map of white matter hyperintensities in Down syndrome. Lesion frequency map of white matter hyperintensities is shown in the Montreal Neurological Institute 152 T1 template. The color of each voxel indicates the percentage of subjects that had white matter hyperintensities in this voxel, ranging from at least 5% (purple) to 40% or more (yellow).

nificant or showed a trend toward significance in the whole DS and sDS cohorts (Figure 5S in supporting information).

3.6 | Associations between WMH volume and GM volume

Finally, we also investigated voxelwise associations between total WMH volume and GM volumes within the DS population. These analyses revealed significant associations across the entire cortex for the whole cohort (Figure 5A). Specifically, the pattern predominated in the medial and lateral temporo-parietal regions, medial prefrontal and orbitofrontal cortex, anterior insula, hippocampi, and thalamus. The stratification of DS by clinical status revealed a very similar pattern in both aDS and sDS, although slightly less widespread and significant than in the whole population (Figure 5B,C).

4 | DISCUSSION

Our results highlighted an increase in the presence and severity of WMHs with age in DS, as well as with the incidence of both AD symptoms and AD pathology. We further demonstrated that lesions are mostly located in periventricular regions, especially in the frontal, parietal, and occipital lobes. WMHs expand into more cortical layers throughout the AD continuum in DS, suggesting a distinct underlaying pathophysiology compared to the general population. Together, these findings underscore that WMHs represent a core neuroimaging feature in DS, and provide novel insight into the interplay between these lesions and AD processes.

Consistent with previous studies,[17] we observed that WMH volume gradually increased with age in both DS and euploid populations. This age-related increase is stronger in DS individuals. This finding expands previous evidence from our group obtained in a smaller sample of DS and using the Fazekas visual scale.[16] We further demonstrated that WMHs emerge at a younger age in DS than HC, with CI no longer overlapping at the age of 43, around 10 years before symptom onset.[5] Interestingly, a recent study on *PSEN1* mutation carriers also reported a sharp increase in WMHs at 43 years,[15] and WMHs were found to increase approximately 6.6 years before estimated symptom onset in mutation carriers of AD-causing genes.[14] The presence of WMHs at an early age across distinct genetically determined AD forms suggests that AD-related mechanisms contribute, at least partially, to these lesions. Indeed, in population-based studies, WMHs typically increased at a later age,[10,32] starting from 55 years.[33]

We mapped WMH topography and found different associations in both populations. Associations with age predominated in the frontal lobe in HC, as previously described in elderly populations.[34] By contrast, associations in DS involved all brain lobes, particularly the fronto–parieto–occipital regions. This aligns with previous evidence showing a widespread age-related pattern of WMHs in DS, driven by frontal, parietal, and occipital lobes,[17] as well as the typical parieto–occipital AD pattern.[12] Further, correlation coefficients were strongest in the periventricular region, showing earlier age-related changes than total WMH volume, and progressively decreased in deep and juxtacortical areas. These results add to a body of work identifying different WMH topography in AD compared to age-related WMHs.[12]

Other sociodemographic and genetic factors may also contribute to WMHs. In line with previous studies,[16,17] we did not evidence an effect of sex or *APOE* haplotype on total WMH volume in DS. The specific
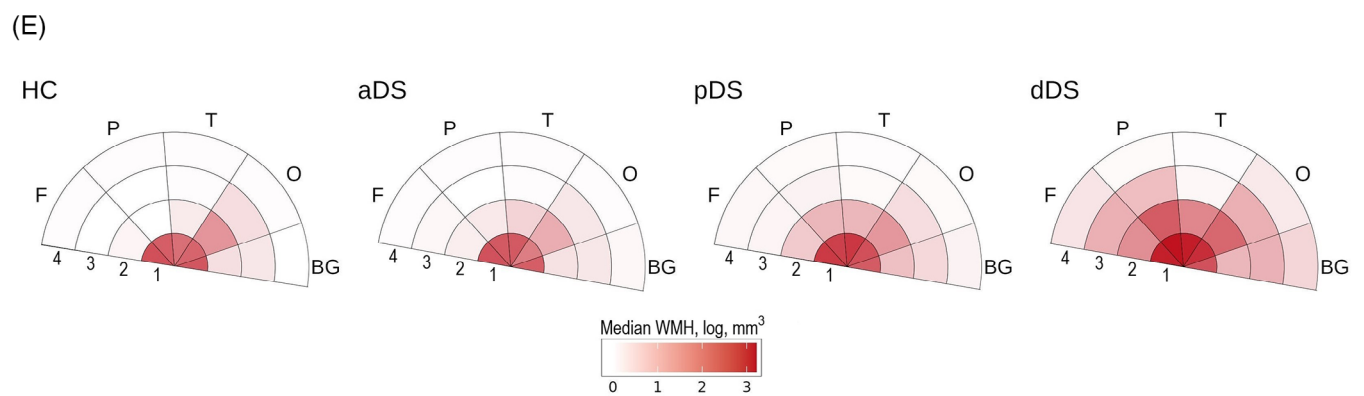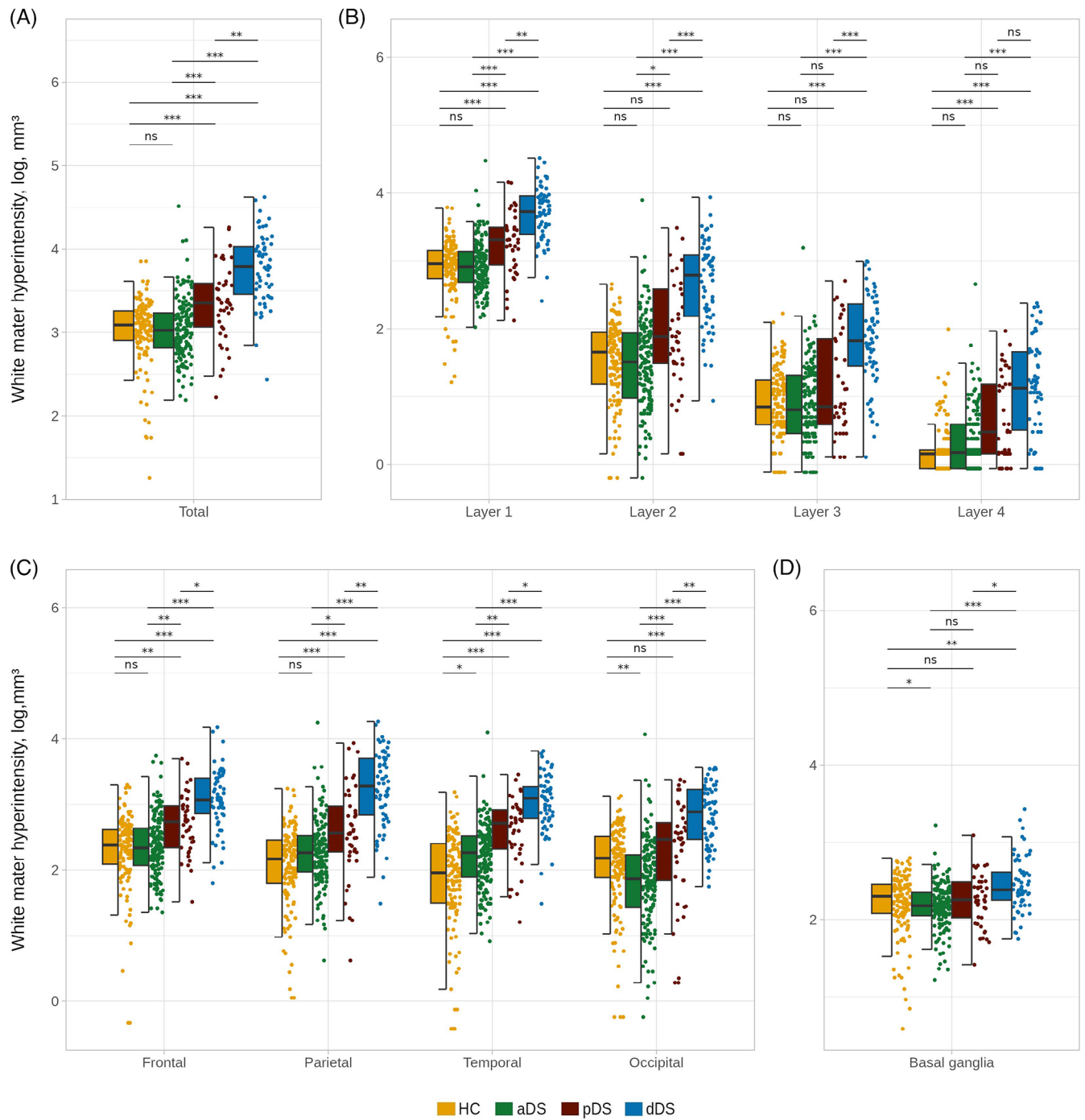
sex effect on AD in DS is still debated, with a recent study showing no impact on AD biomarkers.[35] Concerning the *APOE ε4* allele, it was found to influence AD processes in DS,[36] but this effect might be too subtle to be identified in WMHs. The link between *APOE ε4* and WMHs is also inconsistent in the general population and sporadic AD, with some studies suggesting a gene–dose effect on WMHs[37,38] and others reporting opposite or no effect.[39–42]

Surprisingly, greater ID was associated with higher WMH volumes. However, sensitivity analyses suggested that this effect might result from the different proportion of symptomatic cases across the different ID groups, that is, a higher proportion of moderate level in dDS. Two recent studies examining the effect of ID on AD trajectory in DS revealed no differences in AD biomarkers, cognitive impairments,[43] or decline.[44] Together these results suggest that ID has a limited impact on AD and vascular changes in DS. However, further research is warranted to confirm this result and assess if differences in lifestyle factors across ID can lead to differences in WMHs.

WMH volumes increased linearly with AD stage (aDS < pDS < dDS), consistent with previous studies in DS,[16,17] and investigations in early-[45] and late-onset sporadic AD[10,46] and autosomal dominant AD (ADAD),[14,47] all of which showed a gradual increase in WMH burden with disease severity. Topographically, WMHs increased locally and expanded to new layers as the disease progressed. Mainly circumscribed to the periventricular region at the asymptomatic stage, the lesions extended into deep and juxtacortical areas, including the frontal, parietal, and occipital lobes at the prodromal stage, and further increased in the same regions at the dementia stage. Similar topographical progression has been previously described in sporadic AD,[48] where periventricular WMHs were common at the mild cognitive impairment (MCI) stage, and in the AD group expanded outward, particularly to affect the corpus callosum. The frequency map further showed that posterior corona radiata, posterior thalamic radiation, and splenium of the corpus callosum were the most affected areas in DS. These structures were previously found vulnerable to AD processes,[49] and associated with Aβ pathology.[50]

Compared to HC, the aDS group presented increased WMH volume only in the temporal lobe. Previous studies in preclinical AD revealed larger WMH total volume in Aβ-positive compared to Aβ-negative individuals.[51] In ADAD, asymptomatic carriers present with increased WMHs in parieto-occipital regions.[14] Taken together, these results suggest that WMHs emerge at an early preclinical stage of AD. The different topographic patterns may reflect specificities of each presentation or differences in the preclinical or control groups. For instance, our aDS cohort included adults ranging from 19 to 63 years, with 32.9% at > 20 years from the estimated age of symptom onset (i.e., 53.8 years[5]).

Relationships between WMHs and CSF AD biomarkers revealed robust associations in DS with both Aβ and pTau181 concentrations. In the literature, the link between WMHs and AD pathology is inconsistent. Several studies in the euploid population reported no association between WMHs and Aβ-[52] and tau positron emission tomography (PET)[53] load. In DS, WMHs were also not significantly associated with Aβ PET.[17] However, some evidence supported a relationship with Aβ PET in non-demented individuals[12,53] and tau PET in preclinical ADAD.[45] Moreover, Aβ in CSF, but not tau, was found related to WMHs in ADAD,[14,54,55] MCI, and sporadic AD.[14,54–57] These discrepant results might be explained by the modality to measure AD pathology, or the composition of the cohort studied. Indeed, when we stratified our analyses by disease stage, we found significant associations at the asymptomatic but not symptomatic stages, aligning with findings in the AD continuum.[57]

Associations between WMHs and neurodegenerative markers were also strong. Consistent with previous observations in cognitively normal,[54] MCI,[54,58,59] sporadic AD,[59,60] and ADAD,[61] we found that NfL levels in CSF were associated with WMHs. Indeed, NfL showed i) the strongest association with total WMH volume, ii) was significantly related to WMH volume at different disease stages, and iii) was the only CSF biomarker to remain significantly associated with WMHs in the multivariate analyses. This strong link between WMHs and NfL is not surprising because WM mainly consists of myelinated axons and NfL, an axonal cytoskeleton protein particularly expressed in long myelinated axons, is released upon axonal damage.[62]

To further understand WMHs and neurodegeneration, we explored the association with GM volume. There were significant associations that encompassed the entire cortex, but were more pronounced in lateral and medial temporo-parietal regions. This pattern overlaps with the typical AD regions showing tau accumulation[63] and atrophy.[64] Similar associations between WMH burden and lower GM volume[9] and cortical thickness[65] were previously reported in sporadic AD.

The link between WMHs and both AD pathology and neurodegeneration can be explained by different non-exclusive hypotheses.[12,66] First, it is possible that WMHs, in the AD context, are caused by Wallerian degeneration secondary to neurofibrillary tangles.[67–69] Indeed, disruption of microtubules containing tau could lead to axonal degeneration, resulting in WM damage observed as WMHs on MRI.[70] Second, WMHs might be induced by subtle hypoperfusion or other cerebrovascular diseases, which in turn contribute to tau pathology[71] and/or the disruption of WM tracts affecting the cortical regions.[11] For instance, cerebral amyloid angiopathy is frequently found in AD[72] and DS,[16] and likely causes some posterior WM damage.[53,73] Another hypothesis is that neuroinflammation, which is a key pathogenic factor of both AD and vascular pathologies, might also participate in the gen-

FIGURE 3 Between-group differences for total and regional white matter hyperintensity volumes. (A), (B), (C) and (D) The boxplots illustrate WMH volumes across the brain regions. Significant results at $p < 0.05$ using the Bonferroni correction. (E) Median of WMH volume per region represented in bull's-eye plot. Colors represent the burden of WMH volume in log mm^3, darker colors indicate higher WMH load. Abbreviations: ns, no significance; $^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; 1, first layer; 2, second layer; 3, third layer; 4, fourth layer; aDS, asymptomatic Down syndrome; BG, basal ganglia; dDS, Down syndrome with Alzheimer's disease dementia; DS, Down syndrome; F, frontal; HC, euploid cognitively unimpaired controls; O, occipital; P, parietal; pDS, prodromal Down syndrome; T, temporal; WMH, white matter hyperintensity.
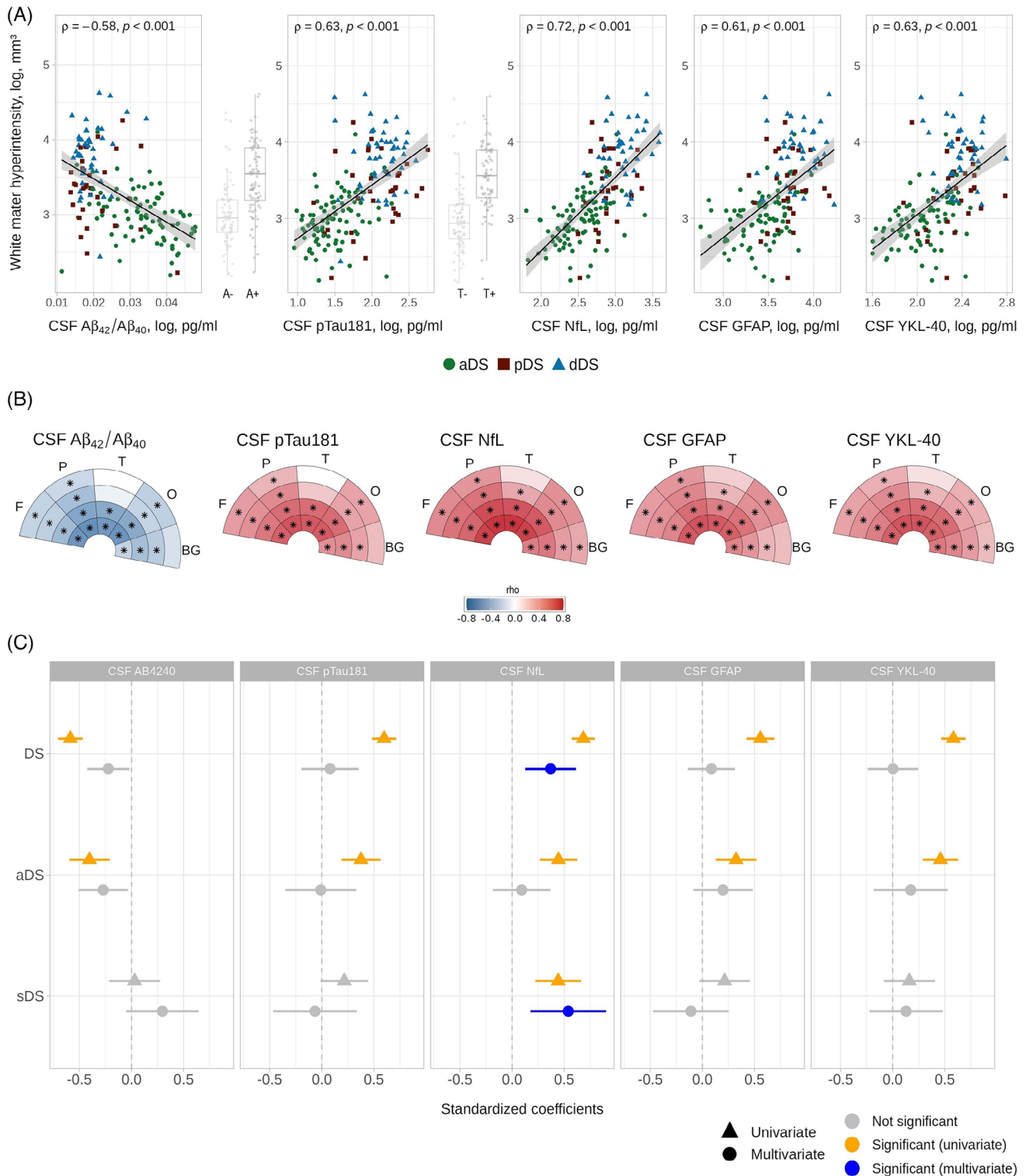
FIGURE 4 Associations between white matter hyperintensities and cerebrospinal fluid biomarkers in DS. (A) Correlation between total WMH volume and each corresponding CSF biomarker. Boxplots illustrate WMH volumes across the amyloid and tau status. The points represent individual participants, and the color indicates the clinical diagnosis. Shaded areas represent 95% CI. (B) Spearman correlation coefficients between each corresponding CSF biomarker and regional WMH volume in DS. The color scale represents the strength (rho) of Spearman correlation for significant results ($p < 0.05$). The star (*) indicates results surviving the Bonferroni correction ($\alpha = 0.05$, $p < 0.0025$). (C) Standardized coefficient of univariate and multivariate linear regression models for the WMH volume. The triangles and circles represent the univariate and multivariate models, respectively. The lines represent the 95% CI. Gray color indicates non-significant values, while orange color indicates significant values ($p < 0.01$) and blue color after applying Bonferroni correction ($\alpha = 0.05$, $p < 0.01$). Abbreviations: 1, first layer; 2, second layer; 3, third layer; 4, fourth layer; A$^-$, amyloid negative; A$^+$, amyloid positive; Aβ_{42}/Aβ_{40}, concentration ratio between amyloid beta peptide 1-42 and amyloid beta peptide 1-40 (pg/mL); aDS, asymptomatic Down syndrome; BG, basal ganglia; CI, confidence interval; CSF, cerebrospinal fluid;

dDS, Down syndrome with Alzheimer's disease dementia; DS, Down syndrome; F, frontal; GFAP, glial fibrillary acidic protein concentration (pg/mL); NfL, neurofilament light chain concentration (pg/mL); O, occipital; P, parietal; pDS, prodromal Down syndrome; pTau181, tau phosphorylated at threonine 181 concentration (pg/mL); sDS, symptomatic Down syndrome; T, temporal; T⁻, tau negative; T⁺, tau positive; WMH, white matter hyperintensity.
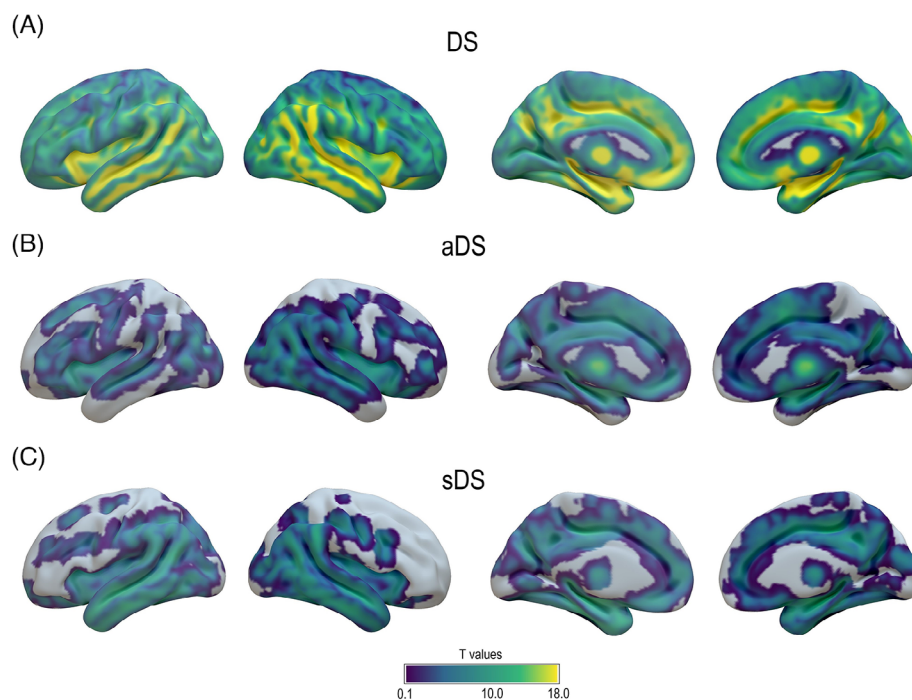
FIGURE 5 Voxelwise associations between white matter hyperintensities and gray matter volume. Results of voxelwise regression model showing gray matter volume negatively associated with WMH in (A) whole DS cohort and (B) aDS and (C) sDS subgroups. The significance of the results (T values) is shown using a threshold pFWE < 0.05. Abbreviations: aDS, asymptomatic Down syndrome; DS, Down syndrome; sDS, symptomatic Down syndrome; FWE, family-wise error.

esis of part of WMHs,[74,75] as suggested by the association with GFAP and YKL-40. Finally, we cannot exclude that the associations between these different biomarkers are partially driven by disease progression.

The current study has some limitations. First, the WMH segmentation algorithm and templates to parcellate the WM were not specifically designed for the DS population. Although a thorough visual quality control demonstrated that the segmentation and WM parcellation were correctly performed, with no visible impact of DS brain anatomy, we cannot discard a reduced sensitivity to detect some lesions. Second, the cross-sectional design of this study does not allow for the assessment of causality, such as the relationships among WMHs, AD pathology, and neurodegeneration. Future longitudinal studies will undoubtedly provide new insight into the etiology of WMHs in DS.

In summary, this study offers a comprehensive understanding of the development and distribution of WMHs in DS. Our findings revealed that WMHs are associated with AD clinical stages, manifesting even at the asymptomatic phase. The parcellation of the WM revealed the predominance of WMHs in periventricular regions of frontal, parietal, and occipital lobes, and their expansion into cortical layers with AD progression. These results demonstrate that WMHs are a core imaging feature in DS and shed light on their relationship with AD pathological processes.

CONFLICT OF INTEREST STATEMENT

DATA AVAILABILITY STATEMENT

The authors may share de-identified data that underlie the results reported in this article. Data will be available upon receipt of a request detailing the study hypothesis and statistical analysis plan. All requests should be sent to the corresponding authors. The steering committee of this study will discuss all requests and decide, based on the novelty and scientific rigor of the proposal, whether data sharing is appropriate. All applicants will be asked to sign a data access agreement.

CONSENT STATEMENT

All participants and/or their legally authorized representatives gave written informed consent.

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SUPPORTING INFORMATION

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