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RESEARCH ARTICLE

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Brain structure, amyloid, and behavioral features for predicting clinical progression in subjective cognitive decline

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Abstract

As a potential preclinical stage of Alzheimer's dementia, subjective cognitive decline (SCD) reveals a higher risk of future cognitive decline and conversion to dementia. However, it has not been clear whether SCD status increases the clinical progression of older adults in the context of amyloid deposition, cerebrovascular disease (CeVD), and psychiatric symptoms. We identified 99 normal controls (NC), 15 SCD individuals who developed mild cognitive impairment in the next 2 years (P-SCD), and 54 SCD individuals who did not (S-SCD) from ADNI database with both baseline and 2-year follow-up data. Total white matter hyperintensity (WMH), WMH in deep (DWMH) and periventricular (PWMH) regions, and voxel-wise grey matter volumes were compared among groups. Furthermore, using structural equation modelling method, we constructed path models to explore SCD-related brain changes longitudinally and to determine whether baseline SCD status, age, and depressive symptoms affect participants' clinical outcomes. Both SCD groups showed higher baseline amyloid PET SUVR, baseline PWMH volumes, and larger increase of PWMH volumes over time than NC. In contrast, only P-SCD had higher baseline DWMH volumes and larger increase of DWMH volumes over time than NC. No longitudinal differences in grey

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; ANOVA, analysis of variance; ANCOVA, analysis of covariance; CCI, Cognitive Change Index; CDR, clinical dementia rating; CDR-SB, clinical dementia rating sum of boxes; CeVD, Cerebrovascular disease; CFI, comparative fit index; CI, confidence interval; df, degree of freedom; DWMH, deep white matter hyperintensities; ECog, everyday cognition; FAQ, functional questionnaire; FLAIR, fluid attenuated inversion recovery; GDS, Geriatric Depression Scale; GMV, grey matter volume; LST, Lesion Segmentation Toolbox; MCI, mild cognitive impairment; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; MPRAGE, Magnetization Prepared-RApid Gradient Echo; NC, normal control; NPI, Neuropsychiatric inventory; PET, positron emission tomography; P-SCD, progressive subjective cognitive decline; PWMH, periventricular white matter hyperintensities; RMSEA, root-mean-square error of approximation; SCD, subjective cognitive decline; SE, bootstrap standard error; SEM, structural equation modelling; SRMR, standardized root-mean-square residual; S-SCD, stable subjective cognitive decline; SUVR, standardized uptake value ratio; TE, echo time; TI, inversion time; TR, repetition time; VBM, Voxel-based morphometry; WMH, white matter hyperintensities; WMS-LM, Wechsler Memory Scale logical memory.

Siwei Liu and Xiao Luo contributed equally to this study.

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matter volume and amyloid was observed among NC, S-SCD, and P-SCD. Our path models demonstrated that SCD status contributed to future WMH progression. Further, baseline SCD status increases the risk of future cognitive decline, mediated by PWMH; baseline depressive symptoms directly contribute to clinical outcomes. In conclusion, both S-SCD and P-SCD exhibited more severe CeVD than NC. The CeVD burden increase was more pronounced in P-SCD. In contrast with the direct association of depressive symptoms with dementia severity progression, the effects of SCD status on future cognitive decline may manifest via CeVD pathologies. Our work highlights the importance of multi-modal longitudinal designs in understanding the SCD trajectory heterogeneity, paving the way for stratification and early intervention in the preclinical stage.

Practitioner Points

- Both S-SCD and P-SCD exhibited more severe CeVD at baseline and a larger increase of CeVD burden compared to NC, while the burden was more pronounced in P-SCD.
- Baseline SCD status increases the risk of future PWMH and DWMH volume accumulation, mediated by baseline PWMH and DWMH volumes, respectively.
- Baseline SCD status increases the risk of future cognitive decline, mediated by baseline PWMH, while baseline depression status directly contributes to clinical outcome.

KEYWORDS
Alzheimer's disease, amyloid deposition, depression, subjective cognitive decline, white matter hyperintensities

1 | INTRODUCTION

Subjective cognitive decline (SCD) refers to individuals who perceive memory decline but perform typically on objective neuropsychological assessments. Despite normal cognitive performance, evidence suggests that SCD individuals are at risk for cognitive decline and dementia (Jessen et al., 2014, 2020, 2023; Rabin et al., 2017). In a study involving 2978 individuals with SCD, a dementia incidence of 17.7% was identified. Within 4 years, 14% progressed to dementia, and 27% developed mild cognitive impairment (MCI) (Mitchell et al., 2014; Slot et al., 2019). Within 15 years, nearly 60% of SCD individuals progress to MCI or Alzheimer's disease (AD) (Reisberg & Gauthier, 2008; Rostamzadeh et al., 2022), suggesting that SCD may be stage 2 of the AD continuum (Jessen et al., 2023). However, the fact that the conversion rate is far less than 100% indicates uncertainty in the clinical trajectory of SCD and considerable heterogeneity within the SCD population. In addition, nearly 40% of older adults with SCD complain of conditions other than AD, such as depressive symptoms, which also increases the risk of future cognitive decline and dementia onset (Liew, 2019; Perrotin et al., 2017; Zlatar et al., 2018). Therefore, understanding the risk factors related to diverse SCD clinical progression is of great clinical value.

The underlying mechanism of SCD is still unclear. Post-mortem brain autopsy studies reported increased amyloid deposition in SCD individuals, which may trigger neurodegenerative processes leading to dementia severity progression (Kryscio et al., 2014; Samieri et al., 2014). SCD could be a potential behavioral marker bridging amyloid pathology and AD clinical manifestation. Recent neuroimaging studies have associated SCD with grey matter atrophy in temporal–parietal regions and medial temporal structures (e.g., hippocampus) (Arrondo et al., 2022; Morrison et al., 2022; Peter et al., 2014), as well as abnormalities in white matter microstructure and network property such as efficiency and clustering coefficient (Li et al., 2016; Sun et al., 2016; Tijms et al., 2018). Brain regions vulnerable to AD pathologies have also shown functional and metabolic deficits among SCD (Chen et al., 2020; Tondo et al., 2022). However, most studies are cross-sectional, and little is known about the longitudinal neurodegeneration trajectory underlying the diverse SCD clinical outcomes.

Cerebrovascular disease (CeVD) is a major contributor to cognitive decline among older adults (Pasi & Cordonnier, 2020; Prins & Scheltens, 2015). Both cross-sectional and longitudinal studies have demonstrated that white matter hyperintensities (WMH), a crucial MRI marker for CeVD, could predict cognitive decline in non-

demented older adults (Hilal et al., 2021; Luo et al., 2017; Roseborough et al., 2023). Evidence from the patient populations also suggests that existing WMH severity was related the rate of WMH future progression (Schmidt et al., 2003) and the rate of WMH progression may be closely associated with cognitive decline (Brown et al., 2021). Moreover, SCD was related to WMH. Within the community, SCD individuals exhibited elevated white matter abnormalities. Among patients with cardiovascular disease, WMH was related to more severe SCD (Diaz-Galvan et al., 2021; Haley et al., 2009). The links between SCD and WMH and between WMH and cognitive decline suggest that WMH may be a potential marker for predicting cognitive decline and clinical progression in SCD (Brown et al., 2021). Nevertheless, longitudinal evidence still lacks to demonstrate the link between SCD and cognitive impairment via the CeVD burden. Furthermore, WMH consists of periventricular WMH (PWMH) and deep WMH (DWMH). Although the two are correlated, PWMH might have a stronger link to vascular risk factors than DWMH (DeCarli et al., 2005; Griffanti et al., 2018). Therefore, it is crucial to consider the spatial distribution of WMH when studying the relationship between WMH and SCD.

Moreover, amyloid deposition and CeVD pathology can interact with each other. Amyloid deposition can damage arterial walls, undermine cerebral autoregulation, and reduce vessel lumen, contributing to CeVD development (Keable et al., 2016). On the other hand, CeVD contributes to neurodegeneration by reducing brain perfusion and damaging the blood–brain barrier (Roseborough et al., 2017; Wardlaw et al., 2019). However, the combined effects of these pathologies on disease progression remain largely unknown. It is critical to study multi-modal features longitudinally and determine their combined effects on cognitive decline and dementia severity progression.

In this study, we aimed to address gaps by studying a longitudinal SCD cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Participants underwent baseline amyloid positron emission tomography (PET) scan and longitudinal assessments of behavioral characteristics, WMH burden, and neurodegeneration at baseline and 2-year follow-up. SCD individuals were categorized into stable SCD (S-SCD) and progressive SCD (P-SCD) groups based on whether they remained SCD or progressed to MCI or dementia during follow-up. The study aimed to answer three questions: (1) How did S-SCD and P-SCD differ in neurodegeneration and CeVD at baseline and over 2 years? This is to understand how the heterogeneity in SCD trajectories relates to AD and CeVD. We hypothesized that P-SCD would have a higher brain atrophy rate and faster WMH progression than S-SCD and normal controls (NC). (2) How was the presentation of baseline SCD related to the brain markers of AD and CeVD at baseline and over 2 years? This is to understand the relationship between SCD and brain markers of AD and CeVD in the context of normal aging and depressive symptoms, controlling for genetic risk, and other demographic information. We expected the presentation of SCD associated with amyloid deposition and WMH. (3) To understand the longitudinal clinical implications, we asked whether the brain markers of AD and CeVD at baseline explained the prediction of baseline SCD on future cognitive decline and dementia progression, in the context of other baseline factors. In addition to subjective decline in cognition commonly linked with normal aging and depressive symptoms (Jessen et al., 2014), we expected the association between the baseline subjective decline and the future objective decline in cognition, mediated by the MRI markers.

2 | MATERIALS AND METHODS

2.1 | Participants

Data used in the preparation of this article were obtained from the ADNI database (https://adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. The local Institutional Review Boards at each participating institution approved participant recruitment and data collection for the ADNI project. Informed written consent was obtained from all participants at each participating site.

We identified 183 participants from the ADNI GO and ADNI 2, comprising 112 NC and 71 SCD participants. The inclusion criteria were as follows: (1) At baseline (referring to their initial time point within the selected project), all participants exhibited no objective memory impairment, measured by the Wechsler Memory Scale logical memory (WMS-LM) (Wechsler, 1987), and had a clinical dementia rating (CDR) (Morris, 1993) score of zero. (2) All NC participants had a Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score of at least 24 and a Geriatric Depression Scale (GDS) (Kurlowicz & Greenberg, 2007) score of lower than 6. (3) Each participant underwent amyloid PET scanning at baseline and two-time longitudinal assessment of neuropsychological battery and MRI scanning (i.e., baseline and 2-year later). Exclusion criteria included: (1) significant neurological (e.g., Parkinson's disease, multiple sclerosis) or psychiatric disorders (e.g., anxiety disorder); (2) a history of apparent head trauma; (3) taking medication known to influence brain function; (4) alcohol or drug abuse; and (5) left-handedness. We excluded one participant with significant occipital lobe calcification and nine dues to excessive head motion during T1 or FLAIR imaging. Two NC individuals with a baseline CDR-SB score of 0.5 were also excluded. The final sample included 168 participants (99 NC and 69 SCD).

We defined SCD as: (1) a Cognitive Change Index score ≥16 in the first 12 items indicating memory changes (Risacher et al., 2015; Saykin et al., 2006); (2) participants expressing concern about memory/cognitive abilities; and (3) clinical diagnosis of subjective memory complaints by ADNI site clinicians. In contrast, NC fulfilled none of these three criteria. Moreover, while our analyses were primarily based on the three criteria above, we are aware that the current SCD definitions vary across scales (Morrison et al., 2022; Ohlhauser, Parker, Smart, Gawryluk, & Alzheimer's Disease Neuroimaging

Initiative, 2019; van Harten et al., 2018). Therefore, to evaluate the sensitivity of our findings to different SCD definitions, we also repeated the analyses based on the criteria proposed by Morrison et al. (2022), resulting in a subsample of 125 participants in total (63 NC, 48 S-SCD, and 14 P-SCD; see Tables S1 and S2, Supporting Information for details).

2.2 | Stable SCD versus progressive SCD

At the 2-year follow-up visit, we defined disease progression based on global CDR scores (change from 0 to 0.5 or 1) and medical records. Specifically, we categorized SCD fulfilling the MCI/dementia diagnostic criteria as P-SCD ($N = 15$) and those SCD without objective cognitive decline as S-SCD ($N = 54$). Notably, no SCD individuals progressed to dementia, and no NC developed MCI or dementia during the 2-year follow-up period. We also searched the ADNI database for later follow-up visits of the P-SCD participants. None of them reverted to a CDR global score of 0 in subsequent follow-ups.

2.3 | Clinical and neuropsychological assessments

All participants underwent a comprehensive neuropsychological assessment, which included several tests to evaluate cognitive function. The MMSE (Folstein et al., 1975) was administered to assess cognitive decline, while the CDR scale (both global and sum of box scores) (Morris, 1993) was used to determine dementia severity. The WMS-LM, consisting of both immediate and delayed recall tests, was used to evaluate memory function (Wechsler, 1987). The instrumental activities of daily living were also obtained using the Functional Activities Questionnaire (FAQ), rated by a knowledgeable informant, evaluating the abilities to perform daily-life activities (Pfeffer et al., 1982). Depression and general psychopathology in dementia were examined by the 15-item GDS (Kurlowicz & Greenberg, 2007) and Neuropsychiatric Inventory (NPI, 12 items version), respectively (Cummings et al., 1994). Furthermore, we obtained medical history records to extract information about other non-AD etiologies, including treatment of diabetes or hypertension, sleep problems, and smoking history.

2.4 | MR image and florbetapir PET acquisition

Each participant had high-resolution structural MRI using a T1-weighted sequence and T2-weighted FLAIR acquired using a 3 T scanner (Philip Medical Systems, Siemens, or GE Healthcare) at baseline and again 2 years later. The T1-weighted sequence was acquired with sagittal slices and voxel size of $1.1 \times 1.1 \times 1.2\ mm^3$. The T2 FLAIR scans were obtained with axial slices and voxel size of $0.86 \times 0.86 \times 5\ mm^3$. Detailed MRI scanner protocols are available online at http://adni.loni.usc.edu/methods/documents/. The processed data of florbetapir PET (UCBERKELEYAV45) was obtained from the ADNI database. The detailed processing procedure was described previously (Landau et al., 2013). We used the summary florbetapir cortical standardized uptake value ratio (SUVR) normalized by the whole cerebellum. Some participant had amyloid PET data for a 2-year follow-up, including 93 NC (93.94%), 48 S-SCD (88.89%), and all P-SCD individuals (see Table S3).

2.5 | WMH segmentation and quantification

We quantitatively assessed WMH burden by normalizing 3D T1-weighted and T2 FLAIR images to MNI space and creating WMH lesion segmentation maps using the Lesion Segmentation Toolbox (LST) (Schmidt et al., 2012). Specifically, lesions were segmented by the lesion growth algorithm implemented in the LST toolbox version 2.0.15 (www.statistical-modelling.de/lst.html) for SPM 12 (www.fil.ion.ucl.ac.uk/spm/software/spm12/). The resulting WMH lesion maps were visually checked and manually corrected by two experienced radiologists who were blinded to clinical information. Lesion maps were divided into periventricular (PWMH) and deep (DWMH) using ITK-SNAP software (Yushkevich et al., 2016). We defined PWMH as WMHs contiguous with the margins of each lateral ventricle and within a distance of 10 mm from the ventricle edge on each axial slice (Seo et al., 2012). WMHs exceeding the 10 mm cutoff were categorized as DWMH. Subsequently, we calculated the volumes (ml) of both PWMH and DWMH for each participant. Due to the positively skewed distribution of WMH, a log-transform using the base 10 was applied.

2.6 | Voxel based morphometry

Individual voxel-wise grey matter volume probability maps at all time points were obtained from T1-weighted images using voxel-based morphometry (VBM). VBM was performed using the computational anatomy toolbox v12.7 (CAT12; Structural Brain Mapping Group; http://www.neuro.uni-jena.de/cat/) for Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). For this study, we used the longitudinal VBM pipeline optimized for capturing larger changes over time (such as ageing), as well as a customized study-specific DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) template, which was created from the affine-registered (to the tissue probability maps) grey matter and white matter tissue segments of all participants in the study. Briefly, realignment of T1-weighted images for all time points using inverse-consistent rigid-body registrations and intra-participant bias field correction were first performed to create a high-quality mean image across all time points for each participant. The resultant mean images were then segmented using the standard CAT12 processing pipeline to obtain participant-specific tissue probability maps, which were used to refine the time point-specific processing to create the final tissue segments (grey matter, white matter and cerebrospinal fluid). Deformations for

DARTEL registration of the tissue segments to the customized DARTEL template in MNI space were subsequently estimated, with additional deformations added between individual images across time points to account for age-related changes over time. Finally, the mean deformation across all time points was calculated and applied to individual grey and white matter segments. All resultant normalized images were modulated with the Jacobian determinant (linear and nonlinear components) from the spatial normalization to enable comparison of absolute amount of tissue, and smoothed using an 8 mm full-width at half-maximum (FWHM) kernel to improve signal-to-noise ratio.

3 | STATISTICAL ANALYSES

3.1 | Group comparisons

Differences in demographic information and neuropsychological measures were assessed among NC, S-SCD and P-SCD groups (Table 1). We employed sample-size weighted ANOVA to analyze normally distributed continuous data (age, education years, and WMS-LM), Kruskal–Wallis test for continuous data that did not follow a normal distribution (MMSE, CDR-SB, FAQ, GDS, NPI, CSF markers, and baseline amyloid SUVR), and sample-size weighted chi-square test for categorical data (sex, APOE4, hypertension, diabetes, smoker, and sleep disorder status). Significant differences among the three groups were followed up by pair-wise post hoc comparisons.

To test any group difference in the longitudinal changes of amyloid SUVR, we performed linear mixed modelling (LMM) with amyloid SUVR as dependent variable, group, months since baseline, the interaction between group and months, age, sex and education as fixed effects, and subject intercepts as random effect.

To examine differences in WMH burden, we conducted separate analyses for baseline WMH volumes and progression of WMH over time. The progression of WMH was determined by subtracting the follow-up WMH volumes by the baseline volumes. ANCOVA was conducted to examine group differences in both PWMH and DWMH at baseline and in progression, controlling for age, sex, and education for baseline comparisons and controlling for age, sex, education, and scan interval months for longitudinal comparisons. Subsequently, significant group differences were further examined through post hoc two-sample *t* tests.

To examine baseline differences in GMV among S-SCD, P-SCD, and NC groups, we conducted voxel-wise ANCOVA while controlling for age, sex, education, and total intracranial volume (TIV). To explore group differences in longitudinal changes in GMV, a 2-by-3 flexible factorial design was employed, incorporating two time points per participant and three groups, while controlling for age, sex, education, baseline TIV, interval months between baseline and follow-up visit. The threshold of voxel-wise $p < 0.001$ and cluster-wise family-wise error (FWE) $p < 0.05$ corrected was applied to identify the significant clusters.

3.2 | Path model construction

Two models were constructed to answer research question (2) and (3), respectively. To understand the association between SCD and AD/CeVD-related brain markers, we considered the presentation of SCD (SCD vs. NC group) as a predictor, along with demographics (age, sex, and education), genetic risk (carrying APOE ε4 allele), and baseline depressive symptoms (GDS scores) (Figures 2 and 3, black boxes). For brain outcomes, we only included brain changes that showed significant group differences over time in the unimodal analysis. Two-year change rates of CeVD (PWMH and DWMH volume), calculated as the difference between baseline and the follow-up (follow-up minus baseline) divided by the number of interval days, were considered as the outcomes (Figure 2, dark blue boxes). The baseline CeVD markers (baseline PWMH and DWMH volumes) and amyloid pathology marker (amyloid PET SUVR) were considered as mediators to simultaneously evaluate their associations with baseline predictors on one side and with longitudinal brain changes on the other side (Figure 2, light blue boxes).

To examine the clinical implications, we built a second model with the same predictors and mediators as in the first model. The outcomes (Figure 3, red boxes) were cognitive decline rates (MMSE score decrease from the first to the second time point) and dementia progression rates (CDR-SB score increase from the first to the second time point), calculated as the difference between baseline and the follow-up (follow-up minus baseline) divided by the number of interval days.

We estimated the path model using SEM methods with Lavaan (version 0.6–1.1185) in R (version 3.4.3). For each path, standard error was obtained using bootstrapping method. Test estimate was calculated to determine whether path coefficient or covariance was statistically significant. We also assessed the model with four model fit measures: chi-square test, root-mean-square error of approximation (RMSEA), standardized root-mean-square residual (SRMR), and comparative fit index (CFI). We defined a satisfactory fitting using the following criteria: (1) The models should not be significantly different from the just-identified model based on the chi-square tests ($p > 0.05$); (2) RMSEA should not be larger than 0.08 with the upper boundary of the confidence interval (CI) less than 0.1; (3) SRMR should be less than 0.1; (4) CFI should be larger than 0.9 (Hu & Bentler, 1999; Steiger, 2007).

The path models were constructed in three steps. First, we established a full model where all paths and covariates were estimated. In other words, a full model assumes everything is related to everything else, and therefore estimates all relationships. Note that the full model was just-identifiable with zero degree of freedom, and thus cannot be formally assessed by chi-square test. However, our hypotheses do not necessarily demand all relationships in the full model to be statistically significant. For example, we expected that APOE ε4 carrier showed higher amyloid deposition, but we did not expect the APOE ε4 allele to be related to age or sex.

Therefore, in the second step, guided by our hypotheses and the test estimates of the full model, we pruned down the full model, aiming to create one that would be simpler (with more degrees of freedom)

TABLE 1 Participant demographics, behavioral, pathological, and neuroimaging features.

	NC	S-SCD	P-SCD	F/χ^2	*p*-value
Number	99	54	15		
Age, years	75.10 ± 5.65	73.59 ± 5.22	74.82 ± 5.63	4.432	0.013[a,b]
Education, years	16.85 ± 2.30	16.48 ± 2.70	16.07 ± 2.49	0.874	0.419
Sex (F, M)	46, 53	33, 21	8, 7	3.018	0.221
APOE E4, *n* (%)	25 (25.3)	19 (35.2)	4 (26.7)	1.718	0.423
Hypertension, *n* (%)	45 (45.5)	21 (38.9)	7 (46.7)	0.682	0.711
Diabetes, *n* (%)	7 (7.1)	4 (7.4)	2 (13.3)	0.728	0.695
Smoking, *n* (%)	21 (21.2)	14 (25.9)	4 (26.7)	0.546	0.761
Sleeping disorder, *n* (%)	9 (9.1)	10 (18.5)	1 (0.07)	3.392	0.183
MMSE (max = 30)	29.16 ± 1.15	28.94 ± 1.34	29.27 ± 0.88	0.736	0.480
MMSE_2y	28.94 ± 1.34	28.81 ± 1.40	28.07 ± 1.83	3.067	**0.049**[c]
FAQ (max = 50)	0.24 ± 0.85	0.56 ± 1.28	0.40 ± 0.74	5.393	0.067[a]
FAQ_2y	0.18 ± 0.75	0.35 ± 0.85	1.20 ± 2.21	12.255	**0.002**[a,c]
CDR, sum of boxes	0 ± 0	0.07 ± 0.17	0.17 ± 0.24	25.732	**<0.001**[a,c,d]
CDR, sum of boxes_2y	0.03 ± 0.12	0.07 ± 0.17	1.03 ± 0.40	94.684	**<0.001**[a,b,c]
GDS	0.60 ± 1.11	1.06 ± 1.00	1.67 ± 1.54	21.691	**0.001**[a,c,d]
GDS_2y	0.82 ± 1.13	1.33 ± 1.58	2.00 ± 1.46	13.308	**0.001**[a,c,d]
NPI, frequency × severity (max = 144)	0.59 ± 1.76	1.21 ± 2.47	1.71 ± 1.73	6.715	**0.035**[a,c]
NPI_2y	1.13 ± 3.89	1.02 ± 2.04	3.29 ± 4.21	18.472	**<0.001**[a,c,d]
LM-immediate (max = 25)	14.81 ± 2.72	13.77 ± 3.67	13.93 ± 3.71	1.522	0.222
LM-immediate_2y	15.44 ± 2.67	14.33 ± 3.76	11.36 ± 4.60	19.880	**<0.001**[a,b,c]
LM-delayed (max = 25)	14.44 ± 2.87	13.10 ± 3.39	11.57 ± 2.79	11.810	**<0.001**[a,b,c,d]
LM-delayed_2y	14.65 ± 3.11	13.10 ± 3.96	10.21 ± 4.12	22.560	**<0.001**[a,b,c,d]
CSF, pg/ml					
$A\beta_{1\text{-}42}$	1583.34 ± 610.16	1340.08 ± 561.28	1099.10 ± 654.14	4.190	**0.024**[c,d]
T-Tau	232.12 ± 80.40	239.81 ± 95.07	222.58 ± 114.71	0.203	0.817
$P\text{-}Tau_{181}$	20.85 ± 7.65	22.17 ± 10.03	20.71 ± 12.33	0.275	0.760
Composite SUVR	0.90 ± 0.10	1.01 ± 0.17	1.05 ± 0.17	21.034	**<0.001**[a,c,d]
WMH burden (log-trans)					
total WMH	−0.15 ± 0.77	0.24 ± 0.81	0.56 ± 0.55	13.940	**<0.001**[a,b,c,d]
PWMH	−0.64 ± 0.76	0.06 ± 0.65	0.20 ± 0.44	29.050	**<0.001**[a,c,d]
DWMH	−0.30 ± 0.79	−0.08 ± 0.86	0.27 ± 0.62	8.153	**<0.001**[a,b,c]
proWMH	−0.27 ± 0.64	0.02 ± 0.44	0.22 ± 0.41	12.230	**<0.001**[a,c,d]
proPWMH	−0.76 ± 0.83	−0.29 ± 0.43	−0.07 ± 0.29	12.360	**<0.001**[a,c,d]
proDWMH	−0.36 ± 0.59	−0.29 ± 0.69	0.15 ± 0.27	13.430	**<0.001**[a,b,c]

Note: Values are expressed as mean ± standard deviation. Bold *p*-values signify significant group differences (ANOVA, $p < 0.05$); pair-wise *t* tests with Bonferroni correction ($p < 0.05$) followed.

Abbreviations: CDR, clinical dementia rating; FAQ, functional questionnaire; GDS, geriatric depression scale; LM, logical memory; MMSE, mini-mental state examination; NC, normal controls; NPI, neuropsychiatric inventory; pro, progression; SUVR, standardized uptake value ratio; S-SCD and P-SCD denote stable and progressive subjective cognitive decline, respectively; WMH, white matter hyperintensities (log-transformed); proWMH, log-transformed (WMH at follow-up-baseline WMH); proPWMH and proDWMH follow the same logic.

[a]The Kruskal–Wallis test adopted for continuous data that did not follow a normal distribution.

[b]The group difference between P-SCD and S-SCD. _2y denotes values at the 2-year follow-up.

[c]The group difference between P-SCD and NC.

[d]The group difference between S-SCD and NC.

but not significantly worse than the full model (based on model fits). We fixed all path coefficients and covariates that were not significant in the full model to zero and estimate the pruned model again.

Lastly, we concluded the model construction where the final model showed satisfactory model fits. We also tested the mediation effects of each mediator on different predictors in the final model.

3.3 | Sensitivity analysis

To test the sensitivity of our results to different definitions of SCD, we repeated all the group comparisons and path model constructions using the same statistical methods but with the alternative definition of SCD to define the three groups (see Data S1).

4 | RESULTS

4.1 | Worse clinical and neuropsychological performance was observed in the P-SCD group

Despite of all participants with CDR global score of zero, both SCD groups had higher baseline CDR-SB scores than NC. At Year 2, P-SCD

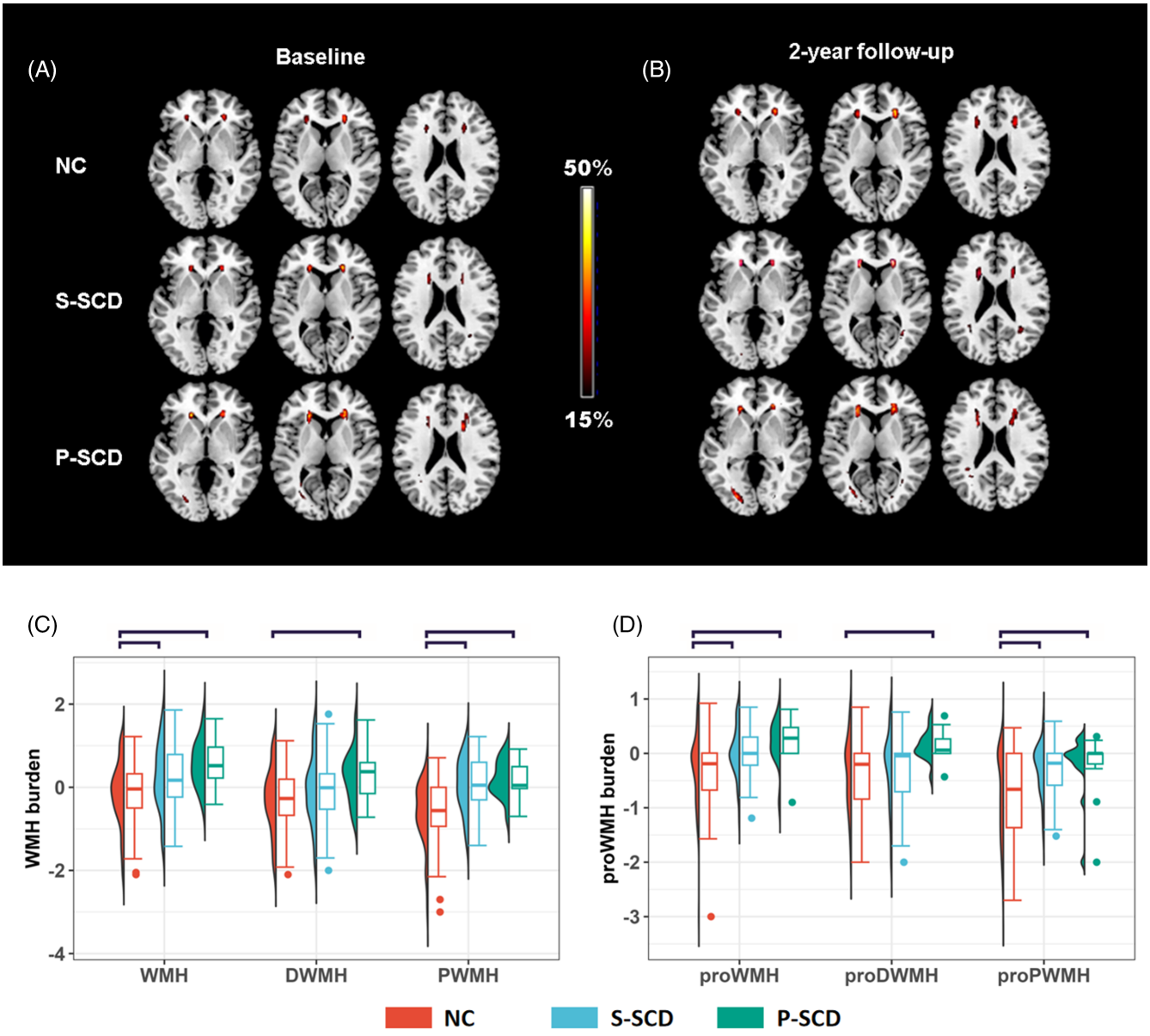

FIGURE 1 Differences in WMH burden among three groups at baseline and 2-year follow-up. (A, B) Only areas with WMH appearing in at least 15% of the participants within each group are shown (yellow represents higher prevalence). (C, D) In the box-and-whisker plots with data distribution, both SCD groups had higher baseline and greater 2-year increases in total WMH volumes compared to the NC group. Both SCD groups also exhibited higher baseline burden and greater increases in PWMH volume compared to NC, with no differences between P-SCD and S-SCD. For DWMH, only the P-SCD group had a greater baseline burden and greater increase in DWMH volume than NC. The boxes show the range between the upper and lower quantile of the data. The bar inside the box shows the median. The whiskers indicate the variability outside of the upper and lower quantiles. Outliers are plotted as dots. Due to the positively skewed distribution of WMH, a base 10 log-transform was applied. The red, blue, and green bars represent NC, S-SCD, and P-SCD, respectively, and square brackets demote significant group differences. DWMH, deep WMH; NC, normal controls; P-SCD, progressive subjective cognitive decline; PWMH, periventricular WMH; S-SCD, stable subjective cognitive decline; WMH, white matter hyperintensities; proWMH/proPWMH/proDWMH, total WMH/PWMH/DWMH volume increase in 2 years (follow-up minus baseline).

had higher CDR-SB scores compared to S-SCD and NC, while S-SCD showed no significant difference from NC. Despite the majority of participants falling within the normal range of the GDS scores, S-SCD and P-SCD had higher GDS scores than NC at both baseline and Year 2 (see Table 1). Such group differences remained when using the alternative SCD definition to define the groups (see Table S1). Further, we found no significant differences in scan intervals (in months) among the three groups (see Data S1).

4.2 | SCD group exhibits higher and faster progression of WMH volume, especially in P-SCD

Both SCD groups had higher baseline and greater 2-year increases in total WMH volumes compared to the NC (Figure 1 and Tables S7 and S8). No differences were observed in total WMH volume between P-SCD and S-SCD at baseline and longitudinally. Both SCD groups also exhibited higher baseline burden and greater increases in PWMH volume compared to NC, with no differences between P-SCD and S-SCD. In contrast, for DWMH, only the P-SCD group had a greater baseline burden and greater increase in DWMH volume than NC.

4.3 | SCD does not differ from NC in longitudinal changes in GMV and amyloid deposition

No GMV differences among NC, S-SCD, and P-SCD were observed at baseline using the original SCD definition. Based on the alternative stricter SCD definition, P-SCD showed lower GMV in the right insula than NC and lower GMV in right supramaginal gyrus than S-SCD (details in Table S4), suggesting baseline grey matter profiles being sensitive to different definitions of SCD. In contrast, there was no longitudinal GMV change difference among the groups over 2 years regardless the SCD definition used, indicating that GMV changes did not accompany CDR progression in P-SCD.

Both S-SCD ($p < 0.001$) and P-SCD ($p < 0.001$) showed higher amyloid SUVR than NC at baseline. Amyloid SUVR also became higher over time ($p = 0.043$) across all groups. However, the three groups did not differ in longitudinal changes in amyloid ($p > 0.178$) for both SCD definitions (see Data S1).

4.4 | Multiple factors predicted the future CeVD progression

Based on the findings above, only CeVD markers (i.e., WMH volumes) showed differential longitudinal changes across the three groups, therefore were used as outcomes in the path model. In quest of the SCD-brain relationship, we identified a path model (Figure 2) with good model fits (see Table 2 for model fit measures, path coefficients, and indirect effects). Figure 2 shows the significant regression paths, where the orange arrows highlight the significant mediations in the model.

From the perspective of baseline SCD status, we found that baseline status of SCD was associated with a higher burden of baseline PWMH and DWMH volumes, as well as elevated baseline amyloid deposition. Baseline PWMH mediated the association between baseline SCD status and PWMH volume increase rate, in addition to the direct association between baseline SCD status and higher future PWMH volume increase rate. It indicates that baseline SCD status was related to future PWMH volume increase both directly and indirectly via higher baseline PWMH volume. On the contrary, baseline DWMH volume showed a full mediation effect on the association between baseline SCD status and DWMH volume increase rate. Moreover, despite significantly related to baseline PWMH volume and SCD status, baseline amyloid deposition was not related to future change rates of PWMH or DWMH volume.

From the perspective of normal aging, we found that older baseline age was also associated with a higher burden of baseline PWMH and DWMH, as well as elevated baseline amyloid deposition. Similar to baseline SCD status, baseline PWMH mediated the association between older age and PWMH increase rate, while baseline DWMH mediated the association between older age and DWMH increase rate. Unlike baseline SCD status, both mediation effects were full mediations. Note that the age and SCD effects were evaluated simultaneously in the model. The path model supports the additive effects of SCD and age on the WMH burdens, which are common mediators of the association with longitudinal changes of WMH burden.

From the perspective of baseline depressive symptoms, higher baseline GDS scores were related to the SCD status. However, our model did not support the association between baseline GDS scores and CeVD/AD brain markers.

We evaluated the sensitivity of our SCD-brain model to different SCD definitions. Based on the same sample ($N = 168$) and model structure, we changed the definition of SCD (1 for those fulfilling the alternative SCD definition and 0 for the rest) and repeated the three model construction steps. We identified the same path model (Figure 2) with good model fits (see Table S5 for model fit measures, path coefficients, and indirect effects), supporting the robustness of our model to different SCD definitions.

4.5 | Multiple factors predicted the future cognitive decline and dementia severity progression

Baseline PWMH further demonstrated the central role in the model examining how baseline factors were linked to cognition decline and disease progression. We identified a path model (Figure 3) with good model fits (see Table 3 for model fit measures, path coefficients, and indirect effects). Figure 3 shows the significant regression paths, where the orange arrows highlight the significant mediations in the model.

From the perspective of baseline SCD status, we found that baseline SCD status was associated with higher baseline PWMH and DWMH volumes, and higher amyloid deposition. Furthermore,

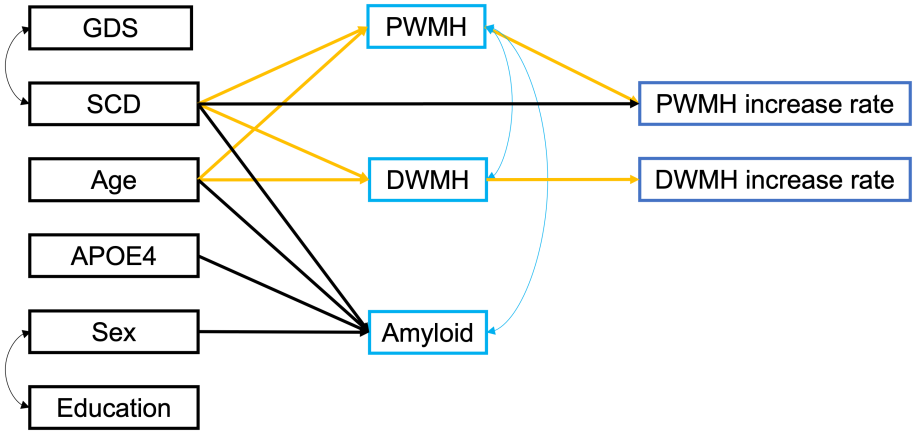

FIGURE 2 Schematic diagrams of the SCD-brain path model. This diagram shows the path model with predictors (black boxes), mediators (light blue boxes), and brain outcomes (dark blue boxes) that are linked by significant regression paths (unidirectional straight arrows) or covariance (bidirectional curved arrows). We only drew arrows where the regression coefficient or the covariance was freely estimated. All the freely estimated relationships shown by the arrows were also significant (details in Table 2). For any pair of variables that is not linked by any arrow, the coefficient has been fixed to zero by the model design during model pruning step 2. The significant mediations in the path model are highlighted in orange. Baseline PWMH volume showed partial mediation effect on the association between baseline SCD status and PWMH increase rate. Baseline PWMH volume showed full mediation effect on the association between older age and PWMH increase rate. Baseline DWMH volume showed full mediation effects for both baseline SCD and age. No mediation effect of baseline amyloid deposition was found despite of the higher baseline amyloid deposition in S-SCD and P-SCD than NC. Amyloid, amyloid positron emission tomography standardized uptake value ratio; GDS, Geriatric Depression Scale; PWMH/DWMH, periventricular/deep white matter hyperintensities; PWMH/DWMH increase rate, calculated as the difference between baseline and the follow-up (follow-up minus baseline) divided by the number of interval days; SCD, subjective cognitive decline.

baseline PWMH volume fully mediated the effects of SCD status on future cognitive decline. Neither baseline DWMH volume nor amyloid deposition was linked to cognitive decline or disease progression.

From the perspective of normal aging, we found that older baseline age was also associated with a higher burden of baseline PWMH and DWMH, as well as elevated baseline amyloid deposition. Similar to baseline SCD status, baseline PWMH volume fully mediated the effects of older age on future cognitive decline. Note that the age and SCD effects were evaluated simultaneously in the model. The path model supports the additive effects of SCD and age on baseline PWMH volume, which is a common full mediator of the association with future cognitive decline.

From the perspective of baseline depressive symptoms, disease progression in 2 years was directly associated with higher baseline GDS scores. Higher GDS scores were also related to SCD status at baseline. However, GDS sores were not associated with any of the brain mediators in the model.

We evaluated the sensitivity of our SCD-cognition model to different SCD definition. Based on the same sample ($N = 168$) and model structure, we changed the definition of SCD (1 for those fulfilling the alternative SCD definition and 0 for the rest) and repeated the three model construction steps. We identified the same path model (Figure 3) with good model fits (see Table S6 for model fit measures, path coefficients, and indirect effects), supporting the robustness of our model to different SCD definitions.

5 | DISCUSSION

Using longitudinal multi-modal neuroimaging and neuropsychological data, we have answered the three research questions: (1) Both SCD groups show a higher burden of CeVD compared to NC. However, only the P-SCD exhibits significantly higher baseline DWMH volume and a larger longitudinal DWMH volume increase compared to NC. On the other hand, no significant group differences in gray matter volume changes over 2 years, indicating that CDR progression in P-SCD was not accompanied by more pronounced neurodegeneration in P-SCD than S-SCD or NC. (2) Our path model showed that SCD status was positively associated with baseline WMH burden and further WMH progression. (3) Moreover, baseline SCD status increases the risk of future cognitive decline, which was mediated by PWMH volume, while baseline depressive symptoms influenced dementia severity progression. Our findings highlight the potential clinical benefits of preventing WMH formation and addressing alleviating depressive symptoms in managing AD-related clinical outcomes.

5.1 | Greater baseline DWMH burden and faster DWMH progression in P-SCD

Edema, gliosis, demyelination, and axon loss contribute to the WMH burden in the non-demented brain of older adults (Gouw et al., 2011; Rosenberg, 2009). The association with the lesion location further

TABLE 2 Regression coefficients, mediation coefficients, and model fits of the path model predicting the brain markers of AD and CeVD over 2 years.

	PWMH			DWMH			Amyloid		
	Beta	**SE**	***p***	**Beta**	**SE**	***p***	**Beta**	**SE**	***p***
SCD	0.463	0.134	<0.001	0.172	0.144	0.015	0.269	0.145	0.001
Age	0.227	0.066	0.001	0.405	0.068	<0.001	0.153	0.061	0.024
APOE4	—	—	—	—	—	—	0.357	0.185	<0.001
Sex	—	—	—	—	—	—	−0.146	0.139	0.022
	PWMH increase rate			**DWMH increase rate**					
	Beta	**SE**	***p***	**Beta**	**SE**	***p***	**Model fits**		
SCD	0.199	0.156	0.009	—	—	—	Chi-square (df = 40) = 41.079, $p = 0.423$		
PWMH	0.289	0.090	0.001	—	—	—	CFI = 0.996		
DWMH	—	—	—	0.612	0.066	<0.001	RMSEA (CI) = 0.013 (0.000, 0.055)		
							SMRM = 0.055		

Indirect effects

Predictor	**Mediator**	**Outcome**	**Beta**	**SE**	***p***
Age	PWMH	PWMH increase rate	0.065	0.029	0.022
SCD	PWMH	PWMH increase rate	0.134	0.091	0.003
Age	DWMH	DWMH increase rate	0.248	0.049	<0.001
SCD	DWMH	DWMH increase rate	0.105	0.088	0.015

Note: The table shows the path coefficients of column variables regressed on row variables, the model fit measures, and the indirect effects. Path coefficients that were fixed to zero were either marked as—or not shown. PWMH/DWMH increase rate, calculated as the difference between baseline and the follow-up (follow-up minus baseline) divided by the number of interval days.

Abbreviations: CFI, comparative fit index; CI, confidence interval; df, degree of freedom; GDS, Geriatric Depression Scale; PWMH/DWMH, periventricular/deep white matter hyperintensities; RMSEA, root-mean-square error of approximation; SCD, subjective cognitive decline; beta, standardized regression coefficient; SE, bootstrap standard error; SRMR, standardized root-mean-square residual.

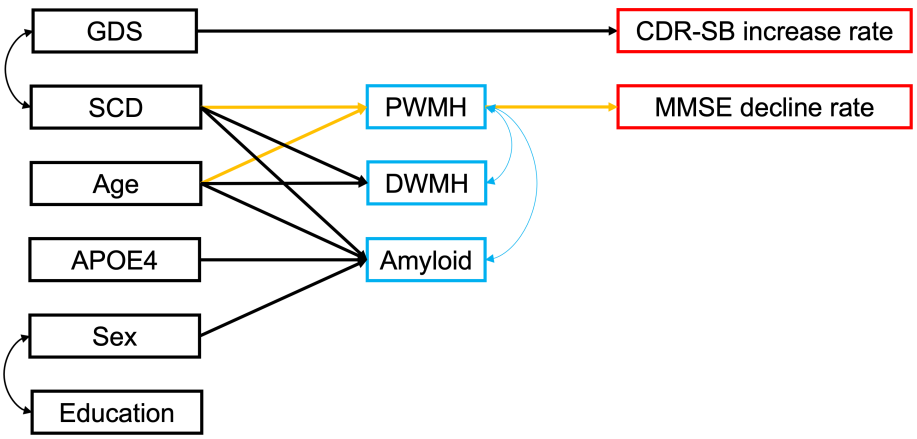

FIGURE 3 Schematic diagrams of the SCD-Cognition path model. This diagram of the path model includes predictors (black boxes), mediators (light blue boxes) and outcomes (red boxes) linked by regression paths (unidirectional straight arrows) or covariance (bidirectional curved arrows). We only drew arrows where the regression coefficient or the covariance was freely estimated. All the freely estimated relationships shown by the arrows were also significant (details in Table 3). For any pair of variables that is not linked by any arrow, the coefficient has been fixed to zero by the model design during model pruning step 2. Significant mediations were notated as orange arrows. Baseline PWMH volume showed full mediation effects for both baseline SCD status and age. No mediation effect of baseline amyloid deposition or DWMH volume was found despite of the cross-sectional group differences. Amyloid, amyloid positron emission tomography standardized uptake value ratio; CDR-SB, clinical dementia rating sum of boxes; GDS, Geriatric Depression Scale; MMSE, mini-mental state examination; PWMH/DWMH, periventricular/deep white matter hyperintensities; SCD, subjective cognitive decline. The increase rate of CDR-SB or the decline rate of MMSE was calculated as the difference between baseline and the follow-up (follow-up minus baseline) divided by the number of interval days.

TABLE 3 Regression coefficients, mediation coefficients, and model fits of the path model predicting future cognitive decline and dementia progression.

	PWMH			DWMH			Amyloid		
	Beta	**SE**	***p***	**Beta**	**SE**	***p***	**Beta**	**SE**	***p***
SCD	0.463	0.135	<0.001	0.172	0.148	0.017	0.269	0.143	<0.001
Age	0.227	0.066	0.001	0.405	0.068	<0.001	0.153	0.062	0.013
APOE4	—	—	—	—	—	—	0.357	0.179	<0.001
Sex	—	—	—	—	—	—	−0.146	0.135	0.031
	MMSE change rate			**CDR-SB change rate**					
	Beta	**SE**	***p*-value**	**Beta**	**SE**	***p*-value**	**Model fits**		
GDS	—	—	—	0.276	0.107	0.010	Chi-square (df = 41) = 48.273, $p = 0.203$		
PWMH	−0.270	0.074	<0.001	—	—	—	CFI = 0.962		
							RMSEA (CI) = 0.032 (0.000, 0.065)		
							SMRM = 0.067		

Indirect effects					
Predictor	**Mediator**	**Outcome**	**Beta**	**SE**	***p*-value**
Age	PWMH	MMSE change rate	−0.061	0.022	0.006
SCD	PWMH	MMSE change rate	−0.125	0.082	0.002

Note: The table shows the path coefficients of column variables regressed on row variables, the model fit measures, and the indirect effects. Path coefficients that were fixed to zero were either marked as—or not shown. The increase rate of CDR-SB or the decline rate of MMSE was calculated as the difference between baseline and the follow-up (follow-up minus baseline) divided by the number of interval days.
Abbreviations: CI, confidence interval; beta, standardized regression coefficient; CDR-SB, clinical dementia rating sum of boxes; CFI, comparative fit index; df, degree of freedom; GDS, Geriatric Depression Scale; MMSE, mini-mental state examination; PWMH/DWMH, periventricular/deep white matter hyperintensities; RMSEA, root-mean-square error of approximation; SCD, subjective cognitive decline; SE, bootstrap standard error; SRMR, standardized root-mean-square residual.

adds complexity to the heterogeneous causes of the abnormal MR signal. While PWMH and DWMH share common pathological features such as demyelination and gliosis, DWMH reflects more severe ischemic tissue damage than PWMH (Griffanti et al., 2018; Kim et al., 2008). PWMH, on the other hand, typically has higher water content due to edema compared to DWMH (Iordanishvili et al., 2019). Moreover, while PWMH was more often linked to cognitive impairment (Garnier-Crussard et al., 2022; Tabei et al., 2017; Wang et al., 2018), DWMH correlated more closely with WMH severity graded according to the Fazekas rating scale compared to PWMH (Iordanishvili et al., 2019), indicating that WMH severity increases as the lesion penetrates deeper into white matter regions. In our study, we observed a greater baseline DWMH burden in P-SCD and higher baseline total WMH volumes in SCD compared to NC, indicating higher WMH severity in SCD, particularly in P-SCD. Such WMH burden in P-SCD was present before any participant developed objective cognitive impairment. Longitudinally, P-SCD also showed faster DWMH accumulation over 2 years. Our path analysis showed that the WMH burden predicts an increase in WMH in the same region. Consequently, a higher baseline DWMH burden and, subsequently, a faster accumulation of DWMH in P-SCD suggest an increase rate of change in CeVD pathology, leading to heightened WMH severity in P-SCD.

Despite our findings, some studies reported no disparity in WMH burden between SCD and NC (Shu et al., 2018; Tabei et al., 2017; Wang et al., 2018). A potential reason for these discrepancies is the recruitment of younger SCD participants in those studies compared to our average age of 72.29 ± 5.62 years. Another possible explanation is the method used to evaluate WMH burden. Studies with negative findings used the Fazekas semi-quantitative scale to evaluate WMH burden, whereas we used an automatic WMH segmentation method to quantify the WMH volumes. Although the automatically segmented WMH volumes increased with higher Fazekas semi-quantitative scale grading (Iordanishvili et al., 2019), voxel-wise segmentation is more sensitive in detecting small changes in WMH progression than the four-level grading method. Furthermore, the MRI field strength in these earlier studies was lower at 1.5 T, which could affect the signal-to-noise ratio of the images used to grade WMH (Zwanenburg et al., 2010). Lastly, we observed higher longitudinal DWMH progression in P-SCD, which is consistent with cross-sectional findings.

5.2 | SCD does not differ from NC in longitudinal changes in GMV

Atrophy in specific brain regions serves as a common imaging marker for clinical progression in those at high risk for AD. Notably, previous literature often highlights atrophy in medial temporal regions, such as the hippocampus, in SCD compared to NC (Arrondo et al., 2022; Morrison et al., 2022). Nevertheless, among the 15 VBM studies reviewed by Arrondo and colleagues (Arrondo et al., 2022; Morrison

et al., 2022), eight found significant difference between SCD and healthy controls, five of which showed reduction in hippocampus, but seven others did not. Both baseline and longitudinal GMV analyses in our study also revealed no group differences in GMV among NC, S-SCD, and P-SCD. Inconsistencies may arise due to high heterogeneity among SCD patients. For example, our sensitivity analysis showed that cross-sectional GMV group differences could be affected by SCD definitions. Despite baseline grey matter profiles being sensitive to SCD definition, the lack of longitudinal GMV change group difference indicated that CDR progression in P-SCD might not be accompanied by GMV changes. An alternative but not exclusive possibility was the relatively small size of our P-SCD group that lacks sufficient power to detect the subtle preclinical GMV changes in SCD. Future research should validate these results in a larger sample.

5.3 | CeVD mediates the relationship of SCD status with future brain and cognitive decline

To better understand the impact of the baseline SCD status on future brain changes and clinical outcomes, we constructed two path models using baseline data that predicted future brain changes and cognitive decline/disease progression, respectively. Baseline SCD status was found to predict future increases in PWMH and DWMH volume. The association with future PWMH burden increase was partially driven by the elevated baseline PWMH volumes, while the association with future DWMH burden increase was fully mediated by the baseline DWMH volume. Furthermore, baseline SCD status was related to future cognitive decline, fully mediated by baseline PWMH volume. These results highlighted the importance of baseline CeVD markers, especially PWMH volume, in predicting future brain change and cognitive decline. Note that the age and SCD effects were evaluated simultaneously in the model. The path models support the additive effects of SCD and age on the WMH burdens. In other words, baseline CeVD markers might be bridging the association of both SCD and normal ageing with future CeVD progression and cognitive decline.

In the introduction, we discussed the possible underlying mechanisms of SCD, including AD and CeVD pathologies. The path models we identified were consistent with the literature, showing that SCD status was positively associated with baseline WMH volumes (CeVD markers) and amyloid deposition (AD pathology markers). However, only baseline PWMH was associated with future cognitive decline and served as a mediator between baseline SCD status and future cognitive decline rate. In contrast, baseline summary amyloid PET SUVR was associated with most baseline predictors, including APOE ε4 allele and demographic information, but did not have a direct link with future cognition beyond covarying with PWMH. Disease progression was not related to baseline amyloid PET SUVR.

The observed mediation effects of PWMH align with prior research linking WMH to cognitive decline and dementia severity progression in older adults (de Groot et al., 2001; Mungas et al., 2001; Tabei et al., 2017; Wang et al., 2018). For instance, De Groot and colleagues interviewed a population-based sample of 1049 participants with a mean age of 72.1 years on subjective cognitive failure in the past month and whether reported failures progressed over the last 5 years. The researchers found that a greater WMH burden was associated with more subjective cognitive failure, and participants who reported cognitive failure progression over time had more severe white matter lesions than those who did not (de Groot et al., 2001). In addition, our previous cross-sectional study using a local multi-modal imaging and neuropsychological dataset also found an association between WMH and cognitive function through white matter microstructure of projection and commissure fibers in non-demented older adults (Hilal et al., 2021). Consistent with these findings, the current study, using the longitudinal ADNI database comprising both multimodal imaging and neuropsychological data, further demonstrated the association of PWMH with future cognitive decline.

It is noteworthy that in our study, amyloid pathology did not have a direct impact on the future clinical outcome or cognitive decline, despite its associations with baseline SCD status, APOE ε4 allele carrying, and age. Potentially, tau pathology, not included in the current model, might be needed to bridge the gap between amyloid pathology and the eventual clinical progression. Current models of AD pathogenesis have proposed that amyloid acts as an initiator of other downstream processes, in particular tau aggregation, which drive neurodegeneration (Musiek et al., 2015). In support of this, tau has been demonstrated to be more closely related to cognitive decline than amyloid burden (Brier et al., 2016; Hanseeuw et al., 2019; Ossenkoppele et al., 2022; Strikwerda-Brown et al., 2022). Amyloid and tau-PET positive cognitively unimpaired individuals have been reported to show greater risk for progression to mild cognitive impairment than amyloid-PET positive and tau-PET negative individuals (Ossenkoppele et al., 2022; Strikwerda-Brown et al., 2022). In another longitudinal study (Hanseeuw et al., 2019), the link between baseline amyloid burden and the future cognition was found to be mediated by the initial amyloid accumulation and the subsequent tau accumulation. Therefore, our current model and previous studies suggest that SCD might indicate an important early stage of amyloid pathology in clinically healthy old adults, though β-amyloid accumulation alone may not be sufficient to result in clinical progression.

Another possible pathway of the amyloid effect on cognitive decline is through CeVD pathology. Amyloid deposition can damage arterial walls, disrupt cerebral autoregulation, and reduce the lumen of blood vessels (Kalaria, 1997; Keable et al., 2016). Conversely, CeVD can contribute to neurodegeneration by reducing brain perfusion and damaging the blood–brain barrier (Ostergaard et al., 2016; Roseborough et al., 2017; Vipin et al., 2018; Wardlaw et al., 2019). Previous studies have found a topographic overlap between β-amyloid accumulation and PWMH (Graff-Radford et al., 2019). In addition, SCD individuals with positive amyloid status had higher burdens of PWMH and DWMH than NC individuals with negative amyloid status (Palhaugen et al., 2021). Consistent with previous findings, both amyloid PET SUVR and WMH burdens were higher in SCD individuals than NC individuals in this study. Moreover, the amyloid–CeVD relationship was demonstrated in our models as a significant covariance between baseline amyloid PET SUVR and PWMH volumes.

Interestingly, there have been debates on whether amyloid and cerebral vascular factors contribute independently to cognitive change (Keuss et al., 2022; Rabin et al., 2018). Despite of the significant covariation, our current path models only tested the additive effects of amyloid PET SUVR and WMH volumes on future outcomes. The path models did not evaluate, for example, the moderation effect of amyloid deposition on the association between CeVD markers and cognitive decline, which is beyond the scope of the current study. Future studies could further explore the topic and accumulate more evidence for the discussion.

Furthermore, despite that we found higher baseline DWMH not in S-SCD but in P-SCD compared to NC, it might seem to be surprising that baseline DWMH was not associated with cognitive decline or clinical progression in the path model. However, the SCD-cognition path model aimed to answer our research question 3, which concerns how information available at baseline may be related to future cognition changes. At baseline, we can gather demographic information from an individual with SCD, estimate the genetic risk, evaluate the depressive symptoms, and check the brain markers related to AD and CeVD. However, we do not know whether the individual belongs to S-SCD or P-SCD. Therefore, we combined both S-SCD and P-SCD into one variable SCD as a predictor. We showed that, with information possibly available at baseline, depressive symptoms would likely be related to clinical progression in 2 years, while PWMH volumes would likely explain the cognitive decline in 2 years. These results would be informative for clinical decisions at baseline. However, to build a model specifically explaining the clinical progression in the P-SCD group, a larger sample of P-SCD would be desired in future studies.

5.4 | Depressive symptoms directly related to disease progression in cognitively normal individuals

The literature suggests that approximately 40% of older adults with SCD complain of conditions other than AD, including depressive symptoms (Liew, 2019; Perrotin et al., 2017; Reisberg & Gauthier, 2008), which also increases the risk of future cognitive decline and dementia onset (da Silva et al., 2013; Diniz et al., 2013; Steffens & Potter, 2008). Our results agreed with the literature that baseline SCD status and GDS scores covaried. Furthermore, our path model suggests that depressive symptoms represent an independent pathway for predicting dementia severity progression. Many studies have linked major depression disorder to grey matter atrophy and white matter impairment within areas implicated in emotional regulation, such as the frontal cortex, amygdala, and medial temporal lobe (Regenold et al., 2007; Tham et al., 2011). Elevated corticosteroids in depression have also been shown to lead to decreased neurogenesis, contributing to cognitive impairment and increasing the risk for dementia (Baune et al., 2010; Zhao et al., 2008). Our results indicate that severe depressive symptoms (sub-clinical depression) were directly associated with higher dementia risk (i.e., CDR-SB increase). However, depressive symptom effects on clinical progression did not manifest via CeVD or amyloid pathology. Jessen and colleagues have proposed that SCD studies should exclude participants with depression because depression may induce hypersensitivity to perceive cognitive failure and reduce the predictive value of memory complaints (Jessen et al., 2014; Peckham et al., 2010). Future studies should dissociate psychiatric conditions from dementia pathologies and study their possible interactions to understand longitudinal changes of SCD (Peckham et al., 2010). We further argue that depressive symptoms are predictive of disease progression in addition to CeVD pathologies among individuals initially without objective memory impairment. Timely mitigating depression symptoms in NC and SCD may reduce the disease progression risk.

5.5 | Limitations and future directions

Our study presents several limitations. Firstly, we focused solely on depressive symptoms as a risk factor for psychiatric disorders in the context of SCD. Future research could broaden the scope to include other psychiatric symptoms (e.g., anxiety and apathy) to examine their associations with SCD trajectory (Liew, 2020). Secondly, while our study is the first to explore disease conversion in SCD using multimodal imaging and behavioral metrics, the findings are derived from a 2-year follow-up period. Longer-term, multi-time point studies would be necessary for a comprehensive understanding of SCD's trajectory. Thirdly, the limited number of P-SCD cases may restrict statistical power and generalizability. Future research should involve larger samples and extended follow-up periods. Additionally, there are still ongoing rebate about SCD definitions involving subjective complaints, Cognitive Change Index and Everyday Cognition scores, or a combination (Morrison et al., 2022). Our key results remained with minor differences when using the two different SCD definitions. Careful consideration of these variations is essential for future investigation of the mechanisms underlying SCD progression (Morrison et al., 2022; Ohlhauser et al., 2019; van Harten et al., 2018).

6 | CONCLUSION

In summary, our study used longitudinal neuroimaging and neuropsychological data to examine brain changes in P-SCD and S-SCD. Significant differences, especially in CeVD were observed between the two groups. Our path model suggests that baseline SCD status influences long-term cognitive decline through PWMH mediation, and depressive symptoms independently contribute to AD-related clinical progression. These findings suggest that preventing WMH formation and alleviating depressive symptoms could be effective interventions for mitigating cognitive decline and dementia severity progression.

AUTHOR CONTRIBUTIONS

XL, YJ, and MZ conceived and designed the study. SL and XL contributed to the statistical analysis and the writing of the original draft of the manuscript. YJ, JSXC, and SHY contributed to the

processing of the imaging data. HJZ provided critical feedback of the manuscript and contributed to project administration and supervision. All authors contributed to the editing of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. This study used the longitudinal data obtained from the ADNI database (https://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. For up-to-date information, see https://www.adni-info.org.

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SUPPORTING INFORMATION

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

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