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RESEARCH ARTICLE

Amyloid and SCD jointly predict cognitive decline across Chinese and German cohorts

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Clinical Trials Register NCT04696315 (Early Diagnosis of SCD Based on Radiogenomics) and German Clinical Trials Register DRKS00007966 (DZNE – Longitudinal Cognitive Impairment and Dementia Study).

Abstract

INTRODUCTION: Subjective cognitive decline (SCD) in amyloid-positive (Aβ+) individuals was proposed as a clinical indicator of Stage 2 in the Alzheimer's disease (AD) continuum, but this requires further validation across cultures, measures, and recruitment strategies.

METHODS: Eight hundred twenty-one participants from SILCODE and DELCODE cohorts, including normal controls (NC) and individuals with SCD recruited from the community or from memory clinics, underwent neuropsychological assessments over up to 6 years. Amyloid positivity was derived from positron emission tomography or plasma biomarkers. Global cognitive change was analyzed using linear mixed-effects models.

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RESULTS: In the combined and stratified cohorts, Aβ+ participants with SCD showed steeper cognitive decline or diminished practice effects compared with NC or Aβ− participants with SCD. These findings were confirmed using different operationalizations of SCD and amyloid positivity, and across different SCD recruitment settings.
DISCUSSION: Aβ+ individuals with SCD in German and Chinese populations showed greater global cognitive decline and could be targeted for interventional trials.

KEYWORDS
amyloid pathology, cognitive decline, cross-cultural study, longitudinal design, PET, plasma Aβ42/40 ratio, Stage 2 Alzheimer's disease, subjective cognitive decline

Highlights

- SCD in amyloid-positive (Aβ+) participants predicts a steeper cognitive decline.
- This finding does not rely on specific SCD or amyloid operationalization.
- This finding is not specific to SCD patients recruited from memory clinics.
- This finding is valid in both German and Chinese populations.
- Aβ+ older adults with SCD could be a target population for interventional trials.

1 | BACKGROUND

Subjective cognitive decline (SCD) refers to the perception of a decline in cognitive ability compared to previous levels of cognitive performance that persists over time, is not related to an acute event, and may be associated with concerns or worries.[1,2] SCD in older adults can occur despite normal objective cognitive performance and is considered the first symptomatic manifestation of the Alzheimer's disease (AD) continuum in those with evidence of amyloid beta (Aβ) pathology in the brain.[3–5] Considered separately, both amyloid pathology and SCD symptoms predict future cognitive decline[6,7] and may occur decades before objective cognitive impairment.[7–11] However, both are only weak predictors of short-term future cognitive decline in older adults without cognitive impairment,[12–17] and not all SCD[18–20] or amyloid-positive (Aβ+) patients[15,21,22] will develop mild cognitive impairment (MCI) or dementia in the next 2 to 6 years. In contrast, some previous studies have shown that individuals with SCD who are also Aβ+ may be at greater risk of cognitive decline compared with Aβ+ normal controls (NC) or SCD amyloid-negative (Aβ−).[5,23–27] This finding provides initial support for the use of SCD as an indicator of the second stage of the AD continuum in individuals with AD pathology, as outlined in the National Institute on Aging and Alzheimer's Association (NIA–AA) research framework.[4] However, some research gaps remain. First, there is an important source of heterogeneity in the definition of SCD, which can be categorical or dimensional across studies[28–30] and the modality used to define amyloid positivity differ.[31,32] Cerebrospinal fluid (CSF) and positron emission tomography (PET) are reliable amyloid measures that are also predictive of cognitive decline, but they are invasive or expensive.[32–35] Plasma biomarkers are less invasive and cost-effective but have not been extensively studied in SCD.[36–38] Therefore, it is unclear whether SCD with amyloid positivity indicates Stage 2 of the AD continuum, irrespective of the method used to assess SCD and amyloid positivity (eg, plasma-derived). Second, it has been suggested that different SCD recruitment settings (community vs memory clinics) should be considered when interpreting SCD study results, especially when evaluating SCD as a risk factor for MCI and dementia because memory clinic samples may be at higher risk.[19,39] To the best of our knowledge, no study has explored the impact of recruitment settings on Stage 2 of the AD continuum concept until now. Third, previous studies were mainly conducted in North American or European cohorts, and none of them looked at this according to different ethnic and cultural backgrounds, which can influence the access to memory consultation and the expression of complaints due to socioeconomic differences and the stigma of mental illness in East Asia.[40]

Thus, the main aim of this study was to investigate whether Aβ+ participants with SCD showed poorer cognitive profiles in a cross-cultural sample from China and Germany. We did this by first examining whether initial and longitudinal cognitive performance differed according to a combination of amyloid positivity and the presence of cognitive complaints with associated concerns/worries (ie, categorical SCD symptoms). Then we tested whether these findings were recovered using (1) a complementary dimensional method for assessing SCD levels (ie, the 12-item Everyday Cognition questionnaire [Ecog]), (2) different modalities for assessing amyloid positivity (PET- or plasma-derived), and through (3) different recruitment settings (community vs memory clinics) of SCD participants. We also explored the differences between countries using stratified analyses, except for the recruitment setting, because only the SILCODE cohort included both community and memory clinic participants with SCD.

2 | METHODS

2.1 | Study design

The Cross-Cultural Longitudinal Study on Cognitive Decline (CLoCODE) project is a collaborative study that aims to establish cross-cultural prediction models of SCD (see previously published study design[41]). CLoCODE includes data from two multicenter cohorts: the Sino Longitudinal Study on Cognitive Decline (SILCODE) from China[42] and the DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) from Germany.[43]

2.2 | Participants

This study comprised 821 participants, including 341 SILCODE participants and 480 DELCODE participants. All participants had normal cognition at baseline, as measured by comprehensive clinical neuropsychological test batteries consisting of standardized measures of memory, language, and executive function. In SILCODE, normal cognition was defined according to the Jak/Bondi criteria:[44] participants were excluded if (1) they had demographically adjusted impairments (> 1 standard deviation [SD]) on two measures within at least one cognitive domain (ie, memory, language, and executive function), if (2) they had one impaired score in each of these cognitive domains, or if (3) they had functional impairment as defined by a score of at least 9 on the Functional Activities Questionnaire (FAQ) (see Supplementary Material). DELCODE participants were excluded when test scores in the extended Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery[45] were less than −1.5 SD relative to age-, sex-, and education-adjusted normal performance on at least one subtest.

To harmonize the categorical SCD definition across cohorts and to match the inclusion criteria of the DELCODE study, all cognitively unimpaired (CU) participants were then classified into two distinct groups based on the presence or absence of concerns associated with a self-reported cognitive decline at baseline. Briefly, 272 NC ($N = 124$ in SILCODE and $N = 148$ in DELCODE) were recruited through standardized public advertisements for the absence of concerns/worries as determined by telephone screening[43] and/or response to the SCD interview.[46] A total of 549 SCD participants (presence of cognitive complaints and concerns/worries) were recruited in both cohorts through referrals from general practitioners or memory clinics (both memory clinic settings [SCDclin patients], $N = 332$ in DELCODE and $N = 78$ in SILCODE), with a subset of 139 SILCODE SCD participants recruited through standardized public advertisements (community settings [SCDcom], using SCD interview worry items). The inclusion and exclusion criteria for both cohorts were described in detail in previous publications,[42,43] and those for the collaborative study are detailed in the CLoCODE protocol[41] (Supplementary Material).

All 821 participants selected for the current study underwent an extensive battery of clinical and neuropsychological tests administered by trained physicians and neuropsychologists at least at baseline and had baseline amyloid status available based on either amyloid-PET scans or blood biomarkers (see Amyloid biomarkers section). Of these, 611 (74.42%) participants had multiple time points available and were followed up every 15 months (SILCODE) or every year (DELCODE), for up to 6 years.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature and cite publications exploring the association between subjective cognitive decline (SCD), amyloid, and cognitive decline throughout the manuscript. Cross-cultural studies are lacking, and the heterogeneity in SCD and amyloid operationalizations needs to be explored.
2. **Interpretation**: Our findings show that SCD combined with amyloid positivity is associated with steeper cognitive decline or fewer practice effects. Findings are (1) globally found across two different cohorts, (2) confirmed using dimensional SCD (Everyday Cognition [Ecog] scores), (3) replicated using amyloid status derived from plasma Aβ42/40 ratio or amyloid-PET, and (4) not specific to SCD recruited from memory clinics but also found in SCD from the community. SCD in amyloid-positive (Aβ+) individuals may help to identify individuals at risk for cognitive decline in German and Chinese populations, regardless of the method used to detect them.
3. **Future directions**: Interventional clinical trials could use Aβ+ participants with SCD as a target population.

2.3 | Cognitive and behavioral assessments

2.3.1 | Subjective cognition

Complementary to the categorical definition of the SCD population (described earlier in the *Participants* section; ie, presence/absence of cognitive complaints with associated concerns/worries), both cohorts assessed SCD levels (ie, dimensional SCD) using the 12-item short form of the Ecog. This questionnaire required participants to rate their ability to perform everyday tasks now compared to 10 years ago on a 4-point scale (from "no change" [1] to "consistently much worse" [4]).[47] Each question could also be answered with "I do not know," which is treated as a missing value in this questionnaire. The total Ecog score was therefore calculated as the sum of all available items divided by the number of completed items, ranging from 1 to 4, with higher scores indicating higher self-reported SCD levels.

2.3.2 | Objective cognition

In both studies, cognitive composite scores assessing global cognitive performance were calculated based on *z*-scores derived from the mean and SD at baseline for all CU participants within each cohort.

In SILCODE, the composite score was calculated as the mean performance on the Auditory Verbal Learning Test–Huashan version 20-min long delayed recall (AVLT-Retrieve, scale range: 0 to 12[48]) and recognition (AVLT-Recognition, scale range: 0 to 24[48]), the completion time of the Shape Trails Test A and B (STT-A, scale range: 0 to 180s; STT-B, scale range: 0 to 300s[49]), Verbal Fluency Test (VFT[50]), 30-item Boston Naming Test (BNT, scale range: 0 to 30[51]), Memory and Executive Screening (MES, scale range: 0 to 100[52]), and the Montreal Cognitive Assessment-Basic version (MoCA, scale range: 0 to 30[53]).

In DELCODE, the composite score used is the Preclinical Alzheimer's Cognitive Composite (PACC5), which was developed to sensitively track cognitive decline in the early phase of AD.[54] It was calculated as the mean performance of the total and free recall of the Free Cued and Selective Reminding Test (FCSRT, scale range: 0 to 96[55]), the Symbol Digit Modalities Test (SDMT, scale range: 0 to 90[56]), the logical memory delayed recall (scale range: 0 to 25[57]), a test of semantic fluency (sum of the animals and groceries named in 1 min, scale range: 0 to 60[58]), and the Mini-Mental State Examination (MMSE, scale range: 0 to 30[59]). The details were provided in a previous study.[5]

2.4 | Amyloid biomarkers

Amyloid beta (Aβ) deposition was assessed for all participants in our study using either amyloid-PET or the plasma Aβ42/40 ratio at baseline, depending on data availability (described in what follows). In the presence of amyloid-PET scans, these data were preferred over plasma levels to determine amyloid positivity in the case of conflicting results. This was done to reliably assess amyloid pathology in the most comprehensive set of participants available.

All participants were divided into the following four groups: NC amyloid-negative or positive (NC_Aβ− and NC_Aβ+) and SCD amyloid-negative or positive (SCD_Aβ− and SCD_Aβ+). Briefly, there were 179 (21.8%) NC_Aβ−, 334 (40.68%) SCD_Aβ−, 93 (11.32%) NC_Aβ+, and 215 (26.18%) SCD_Aβ+ in the two combined cohorts (Table 1, with cohort details in Table S1).

2.4.1 | Amyloid-PET

In our study, 82 (24.05%, NC and SCD) SILCODE participants underwent an ^{18}F-florbetapir PET (FBP-PET) scan on a 3.0 T time-of-flight (TOF) scanner (Signa, GE Healthcare, Milwaukee, Wisconsin, USA) at XuanWu Hospital,[42] and 84 (24.63%, NC and SCD) participants underwent an ^{18}F-D3FSP-PET scan (a deuterated ^{18}F-florbetapir PET) on a 3.0 T TOF scanner (GE Discovery 710, Milwaukee, Wisconsin, USA) at Hainan General Hospital. For the amyloid-PET imaging, participants were injected intravenously with either FBP[42] or D3-FSP[60] at 370 MBq (10 mCi ± 10%), rested for 45 min, and prepared for the scanning. PET imaging was performed 50 min after injection, and the PET acquisition time was 20 min. The FSP and FBP standardized uptake value ratio (SUVR) of the AD summary cortical regions (posterior cingulate cortex, precuneus, frontal lobe, parietal lobe, and lateral temporal lobe) was obtained by dividing the radiotracer uptake value of typical AD brain regions by that of the entire cerebellum. The cutoff of FBP SUVR in the AD summary cortical region was defined as ≥1.11.[61] For FSP, we used Gaussian mixed-model analysis to estimate two Gaussian distributions of low Aβ and high Aβ for FSP SUVR to define an unsupervised threshold ≥1.03, which corresponds to a 90% probability of belonging to the high-Aβ distribution (not yet published).

In DELCODE, only SCD patients received amyloid-PET scans. Sixty (12.50%) participants with SCD underwent an ^{18}F-florbetaben (FBB; Neuraceq) PET scan at the nuclear medicine departments of the participating sites during baseline. A 20-min scan was acquired approximately 90 min after an intravenous injection of 260 to 300 MBq.[43] The detailed acquisition procedure is available in previous publications.[43,62] Briefly, amyloid positivity was determined by visually reading the FBB-PET scans.[62]

2.4.2 | Plasma Aβ measurements

Procedures for plasma acquisition, processing, and analysis in SILCODE[42] and DELCODE[43] were described previously and followed standardized assessment protocols. Briefly, Meso Scale Diagnostics (MSD) kits (V-PLEX Aβ Peptide Panel 1 [4G8] Kit, K15199E, Mesoscale Diagnostics, Rockville, Maryland, USA) and Single-Molecule Array (SIMOA, Neurology 4-PLEX E, Quanterix, USA) technology were used in SILCODE to quantify plasma Aβ concentrations and stratify the population according to the Aβ42/40 ratio threshold for amyloid positivity (≤0.0145 for MSD[63] and ≤0.0663 for SIMOA). Only MSD (V-Plex Aβ Panel 1 [6E10] multiplex assay kit) was used in DELCODE with a cutoff of ≤0.106.[64] Thresholds for each assay were defined with receiver operating characteristic curve (ROC) analysis using amyloid-PET (SILCODE) or CSF Aβ42/40 (DELCODE) pathology as the reference standard. In both studies, the area under the ROC curve (AUC) for all plasma assays was >0.8 (SILCODE unpublished data) and, thus, similar to the accuracy of plasma Aβ reported in other studies.[31] In our study, 163 SILCODE participants (73 NC, 90 SCD) and 474 DELCODE participants (148 NC, 326 SCD) used the MSD method, whereas 174 SILCODE participants used the SIMOA method (50 NC, 124 SCD).

2.5 | Statistical analysis

The main statistical analyses were executed in the combined CLoCODE sample regrouping SILCODE and DELCODE participants according to the combination of categorical SCD with amyloid positivity (ie, four groups: NC_Aβ−, SCD_Aβ−, NC_Aβ+, SCD_Aβ+). Statistical analyses were performed with statistical significance set at $p < 0.05$, using R software (version 4.3.0, https://www.r-project.org/).

The mean and SD, or sample size with percentage, were used to describe the baseline demographic and cognitive features of the sample according to the four groups. Group differences were determined

TABLE 1 Demographic information at baseline in combined CLoCODE sample ($N = 821$).

	NC_Aβ−	SCD_Aβ−	NC_Aβ+	SCD_Aβ+	*p*-value	Post hoc analysis
N	179	334	93	215		
SILCODE, *n* (%)	67 (37.4%)	127 (38.0%)	57 (61.3%)	90 (41.9%)	**<0.001**[b]	NC_Aβ+ < NC_Aβ−, SCD_Aβ−, SCD_Aβ+
Age, mean (SD)	68.51 (5.61)	68.18 (6.04)	68.58 (5.81)	70.41 (6.88)	**<0.001**[a]	NC_Aβ−, SCD_Aβ−, NC_Aβ+ < SCD_Aβ+
Sex, female, *n* (%)	108 (60.3%)	192 (57.5%)	52 (55.9%)	105 (48.8%)	0.11[b]	
Education, mean (SD)	14.01 (2.94)	14.59 (3.07)	13.40 (3.31)	14.00 (3.11)	**0.005**[a]	NC_Aβ+ < SCD_Aβ−
MMSE, mean (SD)	29.15 (1.16)	29.02 (1.36)	29.09 (1.40)	28.85 (1.28)	**0.007**[a]	SCD_Aβ+ < NC_Aβ−, SCD_Aβ−, NC_Aβ+
Ecog, mean (SD)	1.18 (0.20)	1.51 (0.43)	1.22 (0.32)	1.51 (0.46)	**<0.001**[a]	NC_Aβ−, NC_Aβ+ < SCD_Aβ−, SCD_Aβ+
APOE ε4 carriers, *n* (%)	20 (11.5%)	72 (21.8%)	22 (24.4%)	90 (42.7%)	**<0.001**[b]	NC_Aβ- < SCD_Aβ−, NC_Aβ+ < SCD_Aβ+
Aβ_method, PET, *n* (%)	43 (24.0%)	133 (39.8%)	6 (6.5%)	44 (20.5%)	**<0.001**[b]	NC_Aβ+ < SCD_Aβ+, NC_Aβ- < SCD_Aβ−
FU years, mean (SD)[c]	3.88 (1.44)	3.23 (1.40)	4.00 (1.34)	3.27 (1.46)	**<0.001**[a]	SCD_Aβ−, SCD_Aβ+ < NC_Aβ−, NC_Aβ+

Note: Percentages in table represent proportions within each group. Across the whole sample, there was 21.80% of NC_Aβ−, 40.68% of SCD_Aβ−, 11.32% of NC_Aβ+, 26.18% of SCD_Aβ+.

Abbreviations: *APOE*, apolipoprotein E; Aβ, amyloid beta; CLoCODE, cross-cultural longitudinal study on cognitive decline; Ecog, Everyday Cognition questionnaire; FU, follow-up time for those who had at least two visits. MMSE, Mini-Mental State Examination; NC, normal control; PET, positron emission tomography; SCD, subjective cognitive decline; SD, standard deviation; SILCODE, Sino Longitudinal Study on Cognitive Decline.

[a]Kruskal–Wallis test between groups, post hoc Dunn's tests.

[b]$\chi 2$ between groups.

[c]Follow-up time corresponded to 74.42% of participants who had at least two time points available.

using chi-squared tests for categorical variables and Kruskal–Wallis test with post hoc Dunn's test for continuous variables (assumptions for parametric testing not met; ie, normality and/or homogeneity of variance).

To address our first aim, we performed linear mixed-effects models (using lmer models in R) with longitudinal data to determine whether baseline cognitive performance and cognitive decline over time differed among the four groups in the combined sample (Model 1). To determine whether the findings differed between cohorts, and thus between different ethnic and cultural backgrounds, a three-way interaction term between time, groups, and cohorts was included in the models (Model 2). To confirm that differences in outcome measures did not affect the statistical results, Model 1 was repeated separately in the stratified analyses for each cohort, and a complementary fixed-effects meta-analysis based on the extracted summary statistics (metafor package via the "rma" function) was conducted to determine whether the findings highlighted in the combined sample were recovered.

Our second objective was to test whether these findings were recovered when dimensional SCD (Ecog score) was used instead of categorical SCD. We examined the three-way interaction between time, baseline Ecog score, and amyloid positivity in lmer models (Model 3), as well as the four-way interaction by adding an interaction with cohorts (Model 4). As described previously, Model 3 was repeated in the analyses stratified by cohort. In these four models (Models 1 to 4), amyloid positivity was first defined based on PET data and, if not available, based on the plasma Aβ42/40 ratio.

Second, to test the impact of different modalities used to assess amyloid status, we first performed the same previous four models using amyloid positivity determined by either plasma Aβ42/40 ratio or amyloid-PET only (instead of combined) in smaller samples. The last analyses restricted to amyloid-PET data were specific to SILCODE, the only cohort where the reference group (NC_Aβ−) has data available.

Third, to determine the impact of the recruitment setting (community vs memory clinic) on participants with SCD, we categorized SILCODE participants into six groups according to their recruitment settings combined with their baseline amyloid status determined by PET and plasma (ie, NC_Aβ−, NC_Aβ+, SCDcom_Aβ−, SCDcom_Aβ+, SCDclin_Aβ−, SCDclin_Aβ+). We then explored the two-way interaction between time and groups in a lmer model (Model 5) conducted in this restricted SILCODE sample (not replicated in DELCODE, where there were only SCDclin participants).

All mixed models included random intercepts and random slopes for time in years after baseline and were adjusted for age, sex, and years of education and for their interaction with time in the lmer models. In addition, combined sample analyses were adjusted for cohorts (summarized in Supplementary Material). When the interaction was significant, post hoc comparisons (for baseline performances and slopes) between groups and/or cohorts were conducted with a false discovery rate (FDR) correction for multiple comparison,[65,66] using the "hypothesis_test" function from the ggeffects package.[67] Please note that the main aim of the current study was to determine how amyloid pathology per se interacted with a clinical feature (here SCD) on present and future objective cognitive performance in CU older adults from two countries with different ethnic and cultural backgrounds. To achieve this objective, it is not necessary to include all potential drivers in the modeling. Therefore, we decided not to include apolipoprotein E allele ε4 (*APOE ε4*), which is known to be a driver of amyloid pathology,[68,69] as an additional covariate in our models.

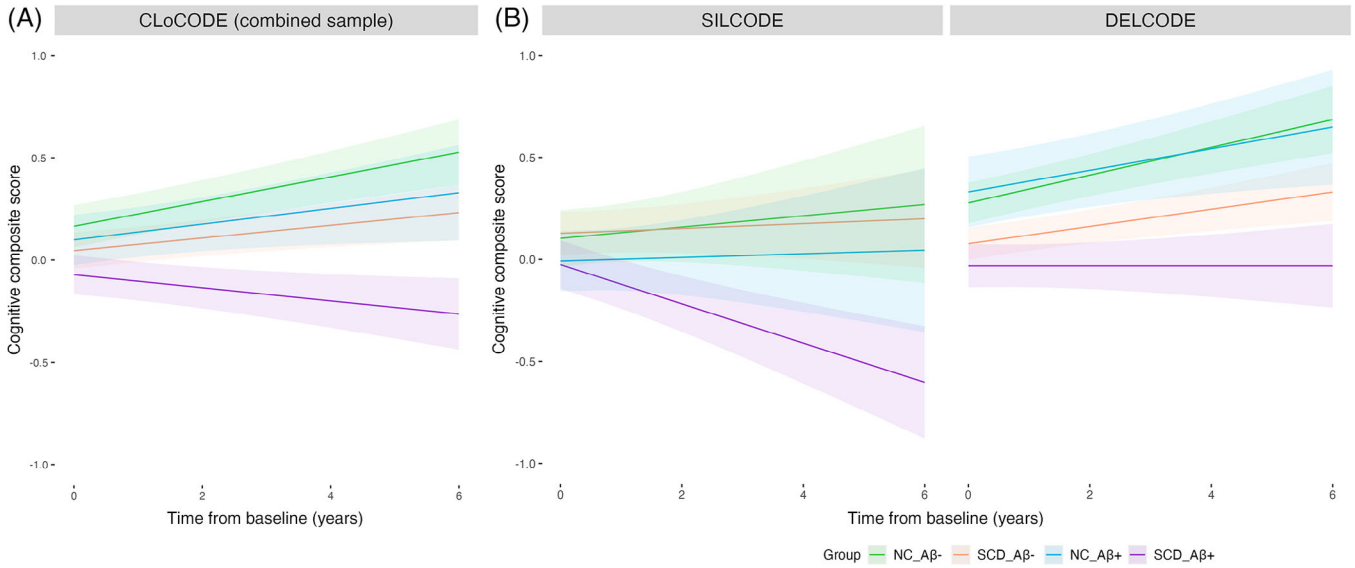

FIGURE 1 Longitudinal cognitive performance according to baseline categorical SCD definition combined with baseline amyloid status. Plots are derived from linear mixed-effects models looking at (A) the two-way interaction between time and group (Model 1) and (B) the three-way interaction between time, group, and cohort (Model 2), with cognitive measures (*z*-composite score in SILCODE or PACC5 score in DELCODE) as outcome. Aβ, amyloid beta; CLoCODE, Cross–Cultural Longitudinal Study on Cognitive Decline; DELCODE, DZNE-Longitudinal Cognitive Impairment and Dementia Study; Est, estimate; PACC5, Preclinical Alzheimer's Cognitive Composite; SE, standard error; SILCODE, Sino Longitudinal Study on Cognitive Decline.

3 | RESULTS

3.1 | Demographics

The data from 821 participants were analyzed, and the baseline participants' characteristics are detailed in Table 1. They were followed over a mean period of time of 3.45 ± 1.45 years (for participants having at least two time points available). At baseline, there were no differences in sex distribution ($p = 0.11$) between the four groups. SCD_Aβ+ was older than the three other groups (SCD_Aβ–, $p < 0.001$; NC_Aβ–, $p = 0.01$; NC_Aβ+, $p = 0.04$), and NC_Aβ+ had a lower level of education than SCD_Aβ– ($p = 0.003$). SCD_Aβ+ had lower MMSE score than the three other groups (SCD_Aβ–, $p = 0.03$; NC_Aβ–, $p = 0.01$; NC_Aβ+, $p = 0.02$). Regarding the proportion of *APOE ε4* carriers, it was higher in the SCD_Aβ+ group compared to the SCD_Aβ– and NC_Aβ+ groups, all three compared to the NC_Aβ– group (all $p < 0.007$, except for NC_Aβ– < NC_Aβ+, $p = 0.01$). Detailed information stratified by cohort is presented in Figure S1 and Table S1.

3.2 | Baseline and longitudinal cognition across groups

Detailed information on the linear mixed-effects model results is provided in Tables S2 and S3, and the derived plots are presented in Figure 1. The raw data of the cognitive trajectories by groups are visualized in Figure S2 through spaghetti plots.

Significant differences in baseline cognition were found between four groups in the CLoCODE combined sample (Model 1), where post hoc comparison showed that the SCD_Aβ+ group performed worse than the three other groups, and SCD_Aβ– performed worse than the NC_Aβ– group after FDR correction (all $p \leq 0.001$, Figure 1A and Table S2A). Stratified analyses replicated this main effect of the groups in DELCODE ($p < 0.001$), where post hoc comparisons showed that cognitive performances were significantly lower in SCD_Aβ+ compared to SCD_Aβ– compared to both NC groups (all $p < 0.002$, except SCD_Aβ+ vs SCD_Aβ–, $p = 0.01$; Table S2C). This did not replicate the main effect of the SILCODE groups ($p = 0.38$, Table S2B). This difference led to a significant interaction between groups and cohorts in Model 2 ($p = 0.006$; Figure 1B and Table S3).

Regarding longitudinal cognitive change, Model 1 revealed an overall significant increase in cognitive performance over time (estimate [Est] = 0.38, SE = 0.08, $p < 0.001$) for the CLoCODE combined sample, with significant differences between the four groups ($p < 0.001$). Overall, all groups showed increasing cognitive performance over time except the SCD_Aβ+ group, which showed a slight decline (Est = –0.03, SE = 0.02, $p = 0.03$). The post hoc comparison showed that the SCD_Aβ+ group had a significantly steeper cognitive decline than the three other groups (all $p \leq 0.001$; Figure 1A and Table S2A). Stratified analyses showed the same main effect of the groups in both cohorts (DELCODE, $p < 0.001$; SILCODE, $p = 0.002$). Post hoc comparisons showed significant differences between the SCD_Aβ+ group and the three others in both cohorts after FDR correction (all $p < 0.009$, except with NC_Aβ+, $p = 0.03$ in DELCODE, and $p = 0.06$ in SILCODE; Table S2B-C), although the slopes within each subgroup were not always significantly different from zero. Model 2 confirmed the absence of significant differences across cohorts by revealing no significant interactions between time, groups, and cohorts ($p = 0.27$; Figure 1B and Table S3).

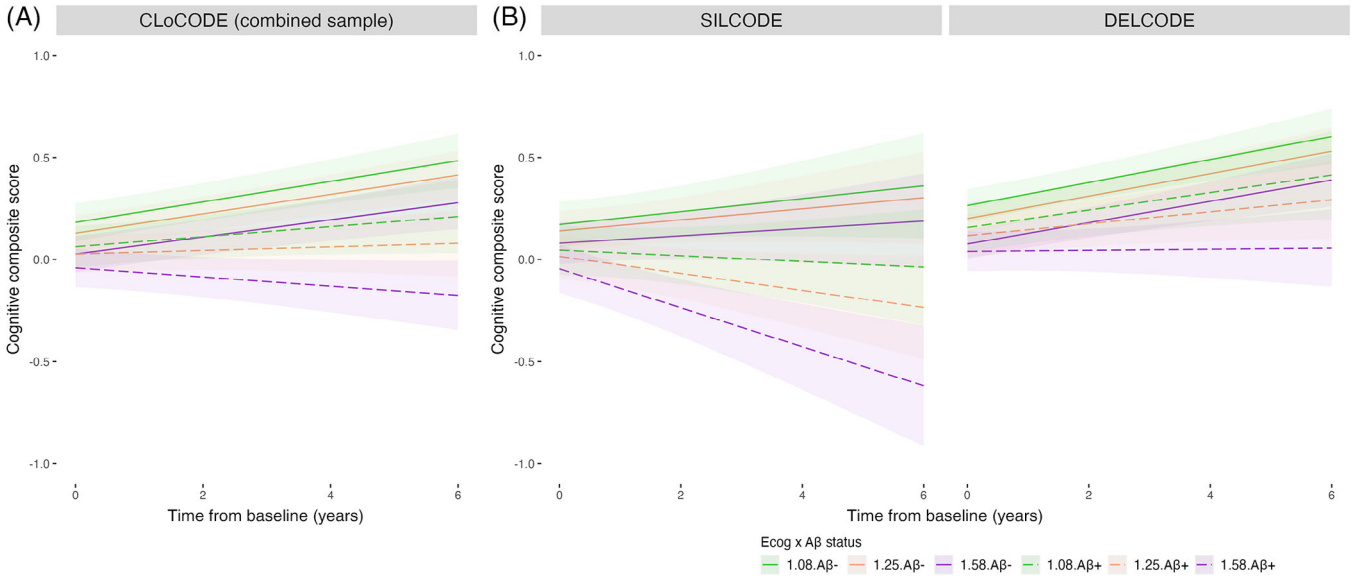

FIGURE 2 Longitudinal cognitive performance according to baseline Ecog levels and amyloid status. Plots are derived from linear mixed-effects models looking at (A) the three-way interaction among time, Ecog, and amyloid status (Model 3) and (B) the four-way interaction among time, Ecog, amyloid status, and cohort (Model 4), with cognitive measure (*z*-composite score in SILCODE or PACC5 score in DELCODE) as outcome. For visualization purposes, Ecog levels are divided here into quartiles with lower, median, and upper modelized as separate lines (the lower quartile is 1.08, the median is 1.25, the upper quartile is 1.58). A*β*, amyloid beta; CLoCODE, Cross–Cultural Longitudinal Study on Cognitive Decline; DELCODE, DZNE-Longitudinal Cognitive Impairment and Dementia Study; Ecog, self-reported 12-item short form of Everyday Cognition questionnaire; Est, estimate; PACC5, Preclinical Alzheimer's Cognitive Composite; SE, standard error; SILCODE, Sino Longitudinal Study on Cognitive Decline.

It should be noted that similar results were found when summary statistics from both cohorts were used to determine pooled estimates and confidence intervals for slopes and group comparisons in fixed-effects meta-analyses (Table S4A).

3.3 | Replication with a dimensional SCD measure (Ecog)

Detailed information on the linear mixed-effects model results is provided in Tables S5 and S6, and the derived plots are presented in Figure 2.

Significant differences in baseline cognition were found according to baseline Ecog scores in the CLoCODE combined sample, where higher Ecog scores were negatively associated with objective cognitive performance (Est = −0.31, SE = 0.06, $p < 0.001$), and no significant differences were found according to baseline amyloid status (Est = −0.23, SE = 0.14, $p = 0.09$) or their interaction (Est = 0.10, SE = 0.09, $p = 0.27$; Model 3; Figure 2A and Table S5A). Stratified analyses replicated this main Ecog effect in DELCODE (Est = −0.36, SE = 0.07, $p < 0.001$, Table S5C), but not in SILCODE (Est = −0.12, SE = 0.15, $p = 0.43$, Table S5B), although no significant interaction with cohorts was found in Model 4 (Ecog × A*β* status × cohort, $p = 0.45$; Figure 2B and Table S6).

Regarding longitudinal cognitive decline, Model 3 revealed no significant interaction between time and Ecog (Est = −0.02, SE = 0.02, $p = 0.36$), or time and amyloid status (Est = 0.06, SE = 0.04, $p = 0.18$) separately, but a significant three-way interaction between them (Time × Ecog × A*β* status, Est = −0.08, SE = 0.03, $p = 0.01$), where A*β*+ participants with higher Ecog scores showed a steeper cognitive decline over time (Figure 2A and Table S5A, recovered by fixed-effect meta-analyses in Table S7A). Stratified analyses revealed the same significant associations in DELCODE (Est = −0.07, SE = 0.03, $p = 0.03$; Table S5C) and a trend in SILCODE (Est = −0.13, SE = 0.07, $p = 0.06$; Table S5B), without any significant interaction with cohorts in Model 4 (Time × Ecog × A*β* status × Cohort, $p = 0.36$; Figure 2B and Table S6).

3.4 | Analyses using different amyloid modalities

Linear mixed-effects models were replicated in additional analyses based on a smallest sample using amyloid status based either on the plasma A*β*42/40 ratio (Models 1 to 4) or on the amyloid-PET (Models 1 and 3, restricted to SILCODE participants), instead of both combined. Detailed information on the models' results is provided in Tables S8 to S11.

3.4.1 | Plasma amyloid

Regarding categorical SCD, findings were recovered in the combined CLoCODE sample with significant differences at baseline ($p < 0.001$) and over time ($p < 0.001$) between groups, where the SCD_A*β*+ group had lower baseline cognitive performances and a steeper cognitive decline than the three other groups (all $p < 0.003$), and the SCD_A*β*–

TABLE 2 SCD source comparison in SILCODE ($N = 146$).

	NC_Aβ−	SCDcom_Aβ−	SCDclin_Aβ−	NC_Aβ+	SCDcom_Aβ+	SCDclin_Aβ+	*p*-value
N	25	23	39	18	19	22	
Age, mean (SD)	66.04 (4.49)	64.57 (4.93)	66.36 (4.70)	65.56 (5.98)	63.26 (6.09)	67.55 (5.50)	0.31[a]
Sex, female, *n* (%)	17 (68.0%)	13 (56.5%)	21 (53.8%)	12 (66.7%)	14 (73.7%)	17 (77.3%)	0.42[b]
Education, mean (SD)	12.84 (2.98)	13.24 (3.77)	13.51 (2.85)	13.00 (3.22)	12.90 (2.83)	13.00 (3.06)	0.07[a]
MMSE, mean (SD)	28.92 (1.08)	29.14 (1.04)	28.74 (1.53)	29.33 (0.77)	28.26 (2.00)	28.68 (1.62)	0.20[a]
APOE ε4 carriers, *n* (%)	3 (12.0%)	5 (21.7%)	13 (33.3%)	1 (5.6%)	4 (21.1%)	9 (40.9%)	0.06[b,c]
Aβ_method, PET, *n* (%)	15 (60.0%)	12 (52.2%)	30 (76.9%)	1 (5.6%)	4 (21.1%)	7 (31.8%)	**<0.001**[b,d]
FU years, mean (SD)	2.86 (1.33)	2.91 (1.55)	3.35 (1.39)	3.50 (1.72)	2.87 (1.93)	3.81 (1.40)	0.18[a]

Note: Percentages in table represent proportions within each group. Across the whole sample, there was 17.12% of NC_Aβ−, 15.75% of SCDcom_Aβ−, 26.71% of SCDclin_Aβ−, 12.32% of NC_Aβ+, 13.01% of SCDcom_Aβ+, 15.06% of SCDclin_Aβ+.
Abbreviations: *APOE*, apolipoprotein E; Aβ, amyloid beta; FU, follow-up; MMSE, Mini-Mental State Examination; NC, normal control; PET, positron emission tomography; SCD, subjective cognitive decline; SCDclin, SCD from memory clinic; SCDcom, SCD from community; SILCODE, Sino Longitudinal Study on Cognitive Decline.
[a]Kruskal–Wallis test between groups, post hoc Dunn's tests.
[b]$\chi 2$ between groups.
[c]Post hoc comparison: NC_Aβ+ < SCDclin_Aβ+, and trend for NC_Aβ− < SCDclin_Aβ−, SCDclin_Aβ+, and NC_Aβ+ < SCDclin_Aβ−.
[d]Post hoc comparison: NC_Aβ+ < SCDcom_Aβ+ < SCDclin_Aβ+ < SCDcom_Aβ− < NC_Aβ−, SCDclin_Aβ−.

showed lower baseline cognitive performances ($p < 0.001$) and tended to also show a steeper cognitive decline than the NC_Aβ− group ($p = 0.09$; Model 1, Table S8A).

Regarding dimensional SCD, findings were also confirmed with a significant baseline difference according to the Ecog score (Est = −0.28, SE = 0.06, $p < 0.001$; higher baseline scores were associated with lower cognitive performances) but not according to baseline amyloid status (Est = −0.06, SE = 0.13, $p = 0.63$) or their interaction (Est = 0.006, SE = 0.09, $p = 0.94$). Moreover, a significant three-way interaction between time, Ecog, and amyloid status (Est = −0.09, SE = 0.03, $p = 0.003$) was found in the CLoCODE combined sample (Model 3, Table S9A).

As previously highlighted using amyloid status based on a combination of PET and plasma data, stratified analyses revealed a similar pattern of differences in the DELCODE cohort, except at baseline, where differences between the SCD_Aβ+ and SCD_Aβ− groups were only a trend ($p = 0.07$; Tables S8C and S9C). However, in the SILCODE cohort there were no significant differences in baseline cognition (both models with $p \geq 0.84$), but there were significant interactions between time, Ecog, and amyloid status (Est = −0.13, SE = 0.07, $p = 0.05$; Table S9B) and between time and groups ($p = 0.04$, SCD_Aβ+ > NC_Aβ− ($p = 0.08$), SCD_Aβ− ($p = 0.08$); Table S8B). These slight differences led to a significant interaction between groups and cohorts ($p = 0.009$) in Model 2 only (Table S10A), whereas no interaction was found with cohorts in Model 4 (all $p > 0.15$; Table S10B).

3.4.2 | Amyloid-PET in SILCODE

Analyses conducted in the PET subsample from SILCODE showed the same pattern of differences as the two other sets of analyses, with a significant interaction between time and groups ($p < 0.001$, the NC_Aβ+ group was excluded from this analysis due to few available data; Model 1, Table S11A) and between time, Ecog score, and amyloid status ($p = 0.03$; Model 3), where the SCD_Aβ+ group and Aβ+ participants with higher baseline Ecog scores showed a steeper cognitive decline than the others (Table S11B).

3.5 | Exploration of different SCD recruitment settings in SILCODE

Data from 146 SILCODE participants that had at least two visits and were stratified into six groups according to the recruitment setting combined with the baseline amyloid status (derived from a combination of PET and plasma Aβ42/40 ratio) were analyzed. Details of the demographic and clinical data are shown in Table 2. The mean follow-up time was 3.23 ± 1.55 years. There were no baseline differences regarding age, sex, years of education, MMSE, and follow-up time; there was only a trend for *APOE ε4* carriers ($p = 0.06$, where both SCDclin groups tend to have more *APOE ε4* carriers than NC groups).

No significant differences in baseline cognition were found between the groups ($p = 0.28$; Model 5); however, a significant interaction between time and groups was observed ($p = 0.01$; Figure 3). The SCDclin_Aβ+ group showed a steeper cognitive decline than the other groups (NC_Aβ−, $p = 0.003$; NC_Aβ+, $p = 0.03$; SCDcom_Aβ−, $p = 0.02$; SCDclin_Aβ−, $p = 0.003$), except the SCDcom_Aβ+ group ($p = 0.68$). The SCDcom_Aβ+ group only showed, or tended to show, a steeper cognitive decline than the three Aβ− groups (NC_Aβ−, $p = 0.03$; SCDcom_Aβ−, $p = 0.08$; SCDclin_Aβ−, $p = 0.05$), but not than the NC_Aβ+ group ($p = 0.14$; Table S12).

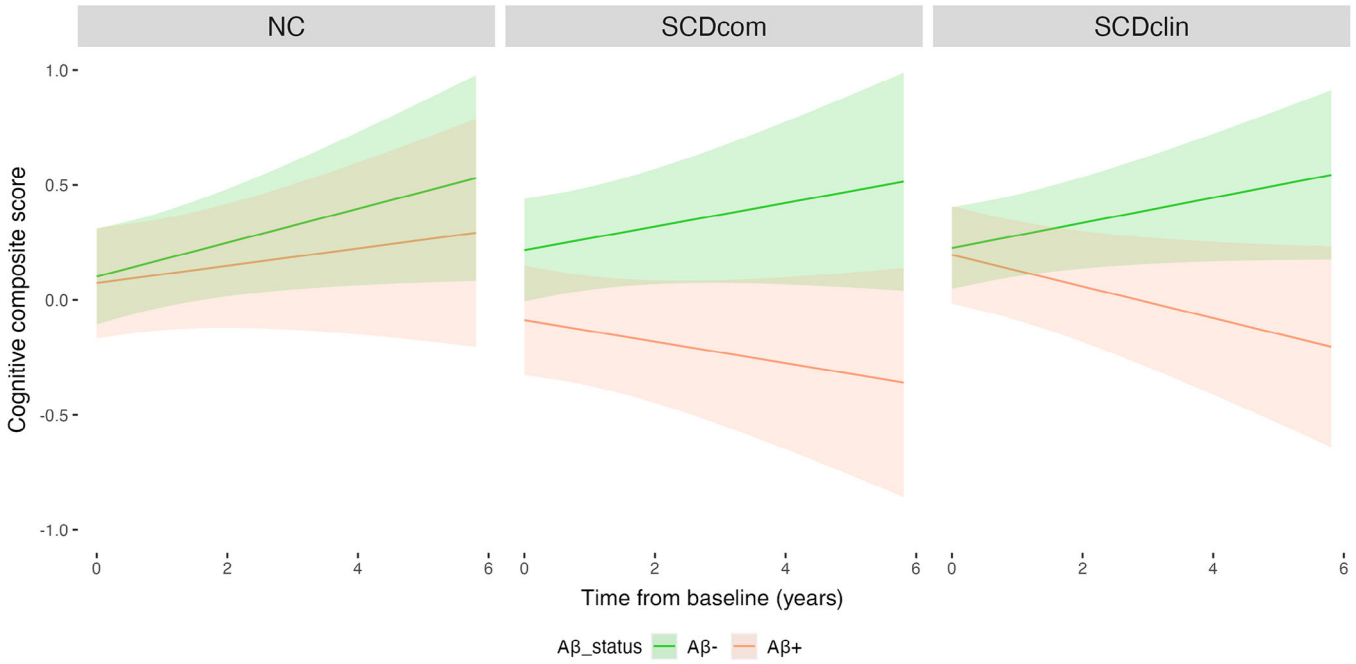

FIGURE 3 Longitudinal cognitive performances according to recruitment setting combined with amyloid status in SILCODE. Plots are derived from linear mixed-effects models (Model 5) looking at two-way interaction between time and six groups based on the combination of recruitment setting (ie, NC, SCDcom, SCDclin) and baseline amyloid status (derived from PET and plasma data combined). Aβ, amyloid beta; Est, estimate; NC, normal control; SCD, subjective cognitive decline; SCDcom, SCD recruited from community; SCDclin, SCD recruited from memory clinic; SE, standard error; SILCODE, Sino Longitudinal Study on Cognitive Decline.

4 | DISCUSSION

This study aimed to confirm the predictive value of SCD combined with baseline amyloid status for longitudinal global cognitive decline in a cross-cultural sample and determine whether this was affected by the methodology used to assess SCD and amyloid status and whether it differed across cultures and recruitment settings. Through combined CLoCODE analyses, and in each of the two cohorts separately, we found that the SCD_Aβ+ group was the only one to consistently show a steeper objective cognitive decline or fewer practice effects over a follow-up period of up to 6 years, compared to the other three groups (including the NC_Aβ+ group, which remained stable or improved slightly). Findings were globally confirmed in analyses (1) using the baseline Ecog score to assess dimensional SCD, (2) using the baseline plasma Aβ42/40 ratio or amyloid-PET separately to determine amyloid status, and (3) using different SCD recruitment settings.

Our study first showed that the SCD_Aβ+ group, using amyloid-PET or plasma Aβ42/40 ratio combined, presented minor cognitive deficits at baseline compared to the other three groups (ie, SCD_Aβ–, NC_Aβ+, NC_Aβ–). This replicated results from a past DELCODE study (restricted sample with CSF and shorter follow-up time)[5] and suggests that SCD_Aβ+ shows slow cognitive decline and may be associated with minor baseline differences, particularly if participants had been in Stage 2 of the AD continuum for years before participating in the study (not recovered in SILCODE where participants were younger).

Furthermore, we found a significant increase in global cognitive performance over time in the entire sample, with a significant interaction between time and the four groups of interest. This indicates that there was a global test-repetition effect in the CLoCODE combined sample. However, this effect differed according to the presence or absence of categorical SCD symptoms (ie, cognitive complaints with concerns/worries) combined with the amyloid status at baseline. Our analyses showed that the SCD_Aβ+ group was the only group showing a steeper global cognitive decline over time (or fewer practice effects in stratified analyses) compared to the other three groups. Conversely, the NC_Aβ+ and SCD_Aβ– groups were not significantly different from the NC_Aβ– reference group, with all three showing slight cognitive improvements. It is noteworthy that diminished practice effects were described previously in Aβ+ participants[70–72] and may be another cognitive feature of Stage 2 of the AD continuum, together with subtle impairments measurable at a single time point.[73] Thus, these practice effects are increasingly viewed as an interesting measure of learning in longitudinal studies. Our study suggests that amyloid does not significantly reduce the practice effects in Stage 1 (as NC_Aβ+ did not differ from NC_Aβ– in any analysis) but only in Stage 2, as indicated by the SCD_Aβ+ group. This implies that learning and practice effects could also be informative regarding the feature of Stage 2 of the AD continuum.

Our additional analyses showed that the interaction of SCD and amyloid pathology with regard to cognitive decline was robust and did not depend on how SCD or amyloid positivity is measured.

In the first subanalysis, we replicated the main findings using dimensional SCD (Ecog score) for all CU older adults, rather than stratifying them according to the presence or absence of concerns/worries (ie, categorical SCD). We showed that Aβ+ participants with higher baseline Ecog scores experienced a steeper cognitive decline (or fewer practice effects) over time. Therefore, our results suggest that using a dimensional SCD measurement combined with amyloid positivity could be sufficient to define Stage 2 of the AD continuum and does not necessarily require the expression of an explicit concern or worry. This is in line with two previous studies conducted in American cohorts.[23,25]

In the second subanalysis, we tested the same model using amyloid positivity defined either by amyloid-PET or the plasma Aβ42/40 ratio separately (instead of combined). Findings were recovered for both categorical and dimensional SCD symptoms, despite the small sample size in PET analyses (restricted to SILCODE) and the downgrading regarding the accuracy of information about amyloid pathology using plasma. These results extend the findings of a previous DELCODE analysis based on a much smaller sample of participants, in which amyloid pathology was determined only in the CSF.[5] Interestingly, the consistency across different measures of SCD and amyloid biomarkers demonstrates that SCD combined with amyloid positivity is a robust and tangible indicator of Stage 2 of the AD continuum, as proposed in the 2018 research framework.[4] It also suggests that a Stage 2 AD risk group could be defined in studies relying solely on plasma biomarkers if combined with an established SCD measure (knowing that AUC > 0.8 using PET in SILCODE [unpublished] and CSF in DELCODE[64]). This may facilitate future studies in regions and for individuals without access to invasive or expensive amyloid measurements, thereby fostering scientific progress.

It should be noted that none of the combined CLoCODE results reported above differed across cohorts and were mostly replicated in stratified analyses by cohorts (except baseline differences not seen in the SILCODE sample). This suggests that the Stage 2 concept may be robust across countries with different cultural backgrounds, so it applies to Chinese populations as well. Our results contrast with the reduced prevalence of amyloid positivity observed in the SILCODE SCD population (8.37%) compared to the DELCODE SCD population (37.3%) in a previous study carried out on a sample half the size of ours.[74] Here, whether based on PET- or plasma-derived amyloid positivity, the highlighted prevalence (ie, PET-derived: 26.5% SILCODE Aβ+ vs 21.7% DELCODE Aβ+; plasma-derived: 41.1% SILCODE Aβ+ vs 38.0% DELCODE Aβ+) suggests that this difference is not as strong in SCD (eg, probably due to a reduced sample size), but with a prevalence similar to that highlighted in another Chinese study.[75]

In this study, we also explored the effects of different SCD recruitment settings on cognitive decline. In the DELCODE study, all SCD participants were recruited from memory clinics because of concerns/worries expressed to the memory center physician (ie, SCDclin). Only some SCD participants (36%) were recruited in the same way in SILCODE, while others were recruited from the community (ie, SCDcom). This cohort-specific design enabled us to evaluate the impact of the recruitment setting on previous findings using a smaller sample of SILCODE participants. We found no significant differences in baseline cognition between the six groups but showed that Aβ+ participants with SCD (both SCDclin_Aβ+ and SCDcom_Aβ+) had a steeper cognitive decline than all other groups, without any significant differences according to the recruitment setting. The only exception was that the SCDclin_Aβ+ group showed a steeper cognitive decline than the NC_Aβ+ group, whereas this was not significant for the SCDcom_Aβ+ group. Although the distinction between the Stage 1 and 2 concept is more marked in SCDclin patients (the only significant one when comparing them to the NC_Aβ+ group), our results suggest that even in a community sample, the combination of SCD and amyloid positivity might be a red flag for potential future global cognitive decline. This is particularly important in a context where the possibility of assessing memory consultation depends on many factors such as socioeconomic status, availability, cultural context, stigma, and/or individual conditions.[5]

The main strengths of our study are as follows: (1) the large sample size from two different cultures, but with comparable methods of assessment and with long follow-up periods; (2) the inclusion of participants with and without SCD, which allowed us to test the effect of amyloid pathology on cognitive trajectories in both groups; (3) the possibility of testing the impact of different SCD measures (categorical vs dimensional) and amyloid modality (plasma and PET data) on the main findings; and (4) the possibility of exploring the impact of the recruitment setting in a smaller sample.

Despite these strengths, the study also had some limitations. First, different methods were used to define cognitive status across cohorts (CERAD vs Jak&Bondi criteria), and the composite score assessing global cognition in SILCODE, although aggregated across tests from the same cognitive domains, did not perfectly match the PACC5 score used in DELCODE. However, despite this difference, we observed consistent results for the cognitive composites. Second, the proportion of participants with amyloid status derived from PET and plasma differed within cohorts (ie, in DELCODE, only SCD patients had PET data available), and the small sample with PET available in SILCODE did not allow us to test for differences between Stage 1 (ie, NC_Aβ+) and Stage 2 (ie, SCD_Aβ+) of the AD continuum. However, the plasma-only results suggest that the imbalance in amyloid measurement methods across groups and cohorts in the main analysis did not induce bias. Third, the impact of recruitment settings could only be tested in a subsample of the SILCODE study, as DELCODE only included patients with SCD recruited from memory clinics. Therefore, the similarities and differences in SCD recruited in different settings require further investigation and validation in larger sample sizes.

In conclusion, amyloid positivity in individuals with SCD likely reflects Stage 2 of the AD continuum, and this appears to be true across the two countries examined (German and Chinese populations) regardless of the SCD and amyloid measurement used, including in the absence of a memory clinic consultation. Our results suggest that, on average, individuals with combined SCD and amyloid positivity at baseline experience some, yet modest, global cognitive decline over time. The feasible and broadly applicable research definition of Stage 2 of the AD continuum, while not ready for individual diagnosis, now allows for the study of possible interventions to slow disease progression and

for a more targeted study of risk and protective factors specific to this clinical stage.

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CONFLICT OF INTEREST STATEMENT

The authors declare no relevant competing interests. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The SILCODE and DELCODE studies are conducted in accordance with the ethical standards of the Declaration of Helsinki. Both study protocols were approved by their respective ethics committees: the Medical Research Ethics Committee and the Institutional Review Board of XuanWu Hospital, Capital Medical University (registration number for leading center, Beijing: 82020108013) for SILCODE, the ethics committees of the 10 university-based DZNE partner memory centers (registration number for leading center, Bonn: 117/13; local registration number of PET study protocol: 221/13), and the Federal Radiation Protection Authority (Bundesamt für Strahlenschutz) for DELCODE. The CLoCODE study is registered at http://clinicaltrials.gov (ID: NCT04696315). All participants provided written informed consent prior to enrollment.

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SUPPORTING INFORMATION

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