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Relevance of Minor Neuropsychological Deficits in Patients With Subjective Cognitive Decline

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Abstract

Background and Objectives

To determine the relevance of minor neuropsychological deficits (MNPD) in patients with subjective cognitive decline (SCD) with regard to CSF levels of Alzheimer disease (AD) biomarkers, cognitive decline, and clinical progression to mild cognitive impairment (MCI).

Methods

This study included patients with clinical SCD and SCD-free, healthy control (HC) participants with available baseline CSF and/or longitudinal cognitive data from the observational *DZNE Longitudinal Cognitive Impairment and Dementia* study. We defined MNPD as a performance of at least 0.5SD below the mean on a demographically adjusted total score derived from the *Consortium to Establish a Registry for Alzheimer's Disease* neuropsychological assessment battery. We compared SCD patients with MNPD and those without MNPD with regard to CSF amyloid-β (Aβ)42/Aβ40, phosphorylated tau (p-tau$_{181}$), total tau and Aβ42/p-tau$_{181}$ levels, longitudinal cognitive composite trajectories, and risk of clinical progression to incident MCI (follow-up $M \pm SD$: 40.6 ± 23.7 months). In addition, we explored group differences between SCD and HC in those without MNPD.

Results

In our sample (N = 672, mean age: 70.7 ± 5.9 years, 50% female), SCD patients with MNPD (n = 55, 12.5% of SCD group) showed significantly more abnormal CSF biomarker levels,

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Glossary

AD = Alzheimer disease; **DELCODE** = *DZNE Longitudinal Cognitive Impairment and Dementia*; **FCSRT** = Free and Cued Selective Reminding Test; **HC** = healthy control; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MNPD** = minor neuropsychological deficits; **NIA-AA** = National Institute on Aging and Alzheimer Association's; **PACC5** = preclinical Alzheimer's cognitive composite; **SCD** = subjective cognitive decline; **SDMT** = Symbol-Digit Modalities Test; **WMS-IV** = Wechsler Memory Scale–Fourth Edition.

increased cognitive decline, and a higher risk of progression to incident MCI (HR: 4.07, 95% CI 2.46–6.74) compared with SCD patients without MNPD (n = 384). MNPD had a positive predictive value of 57.0% (95% CI 38.5–75.4) and a negative predictive value of 86.0% (95% CI 81.9–90.1) for the progression of SCD to MCI within 3 years. SCD patients without MNPD showed increased cognitive decline and a higher risk of incident MCI compared with HC participants without MNPD (n = 215; HR: 4.09, 95% CI 2.07–8.09), while AD biomarker levels did not differ significantly between these groups.

Discussion

Our results suggest that MNPD are a risk factor for AD-related clinical progression in cognitively normal patients seeking medical counseling because of SCD. As such, the assessment of MNPD could be useful for individual clinical prediction and for AD risk stratification in clinical trials. However, SCD remains a risk factor for future cognitive decline even in the absence of MNPD.

Introduction

Some older individuals experience subjective cognitive decline (SCD) while still having an unimpaired performance on standardized, age-, sex-, and education-adjusted neuropsychological tests.[1] Several studies have found that the report of SCD is associated with an increased risk of Alzheimer disease (AD) pathology[2-4] and clinical progression to mild cognitive impairment (MCI) and dementia.[5,6]

Previous studies have also reported that older adults with SCD show a slightly lower average performance in several cognitive domains than those without SCD.[7,8] These results suggest that some individuals with SCD have minor neuropsychological deficits (MNPD), not yet reaching the threshold of MCI, which could be detected on an individual level with standardized neuropsychological tests. We previously reported that lower performances in factor scores measuring verbal memory, executive function, language and global cognition were associated with higher CSF AD biomarker levels in memory clinic patients with SCD, suggesting that the presence of MNPD in SCD could be indicative of developing AD pathology.[9] Based on these findings, we hypothesized that the categorical assessment of MNPD in patients with SCD could enable the identification of individuals who have an elevated risk of AD pathology and future cognitive decline. Previous studies on the association of MNPD with AD biomarkers in individuals with SCD have yielded mixed results,[10,11] and the relevance of MNPD for longitudinal cognitive outcomes in patients with SCD is still unclear. We wanted to address these inconsistencies and open questions in our study.

In this study, we investigate whether dichotomously classified MNPD is related to AD pathology, cognitive decline, and clinical progression to MCI in patients with SCD, with a focus on the adjustment for demographic risk factors. We also compare patients with SCD and HC participants without MNPD to explore whether SCD is associated with an increased risk of AD pathology and symptomatic progression even in the absence of MNPD.

Methods

In this study, we analyzed data from the observational *German Center for Neurodegenerative Diseases (DZNE) Longitudinal Cognitive Impairment and Dementia Study* (DELCODE), which is conducted in cooperation with 10 university-based memory centers across Germany.[12] All DELCODE participants were required to be at least aged 60 years and fluent in German. Participants were enrolled in the study between April 2014 and August 2018, and annual follow-up assessments are ongoing. Detailed descriptions of the DELCODE assessment protocol, group definitions, inclusion/exclusion criteria, and clinical/biomarker characterization for the complete baseline sample have been published elsewhere.[12,13] In this study, we focused on the patients with SCD (n = 445) and healthy control (HC) participants (n = 235) of the DELCODE cohort and included all participants from these groups with available baseline CSF and/or longitudinal cognitive data in our sample.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by local ethical committees and institutional review boards of all DELCODE study sites. All study participants provided written informed consent.

Participants

The SCD group was recruited from the participating memory clinics and included patients who sought medical support because of a self-experienced decline in their cognitive capacity but did not show test deficits in their standardized

cognitive assessment. The presence of cognitive deficits was evaluated using the *Consortium to Establish a Registry for Alzheimer's Disease* neuropsychological assessment battery (CERAD-NAB). Patients with SCD had to score better than 1.5SD below the demographically adjusted mean on all CERAD-NAB subtests in their assessment at the memory clinic they attended.[12]

A comparison group of HC participants was recruited through local newspaper advertisements. This group included individuals who were cognitively unimpaired and did not have any relevant subjective cognitive concerns. However, volunteers who reported experiencing a subjectively age-appropriate, subtle cognitive decline, that they were not concerned about, were also included in the HC group. HC participants had to score better than 1.5SD below the demographically adjusted mean on all CERAD-NAB subtests at their DELCODE baseline assessment.[12]

Neuropsychological Assessment

The DELCODE neuropsychological assessment battery[9] was applied at baseline and each follow-up assessment. In the present analyses, we used data from the German CERAD battery, Mini-Mental State Examination (MMSE), Free and Cued Selective Reminding Test (FCSRT), Wechsler Memory Scale–Fourth Edition (WMS-IV) Logical Memory Story B, and Symbol Digit Modalities Test (SDMT) to characterize the participants' baseline MNPD status and longitudinal cognitive profiles.

We used the preclinical Alzheimer's cognitive composite (PACC5), a sensitive composite measure for the assessment of early cognitive decline,[14] for the analysis of longitudinal cognitive trajectories. It was calculated as the averaged z-standardized performance in 5 cognitive measures: MMSE total score, FCSRT sum of free and total recall, WMS-IV Logical Memory Story B delayed recall, SDMT correct responses, and the sum of 2 verbal fluency tasks (animals, groceries). Z-scores were derived from the baseline means and standard deviations of cognitively unimpaired DELCODE participants and averaged across the 5 measures.

Operationalization of Minor Neuropsychological Deficits at Baseline

Baseline classifications of MNPD were based on the Chandler CERAD-NAB total score (CTS),[15] an established composite measure calculated from the CERAD test battery, which is widely used in German memory clinics. The CTS is calculated as the sum of 6 CERAD-NAB raw scores: animal fluency truncated at 24 correct responses, Boston Naming Test (15-item version), word list immediate recall, word list delayed recall, word list recognition true positives minus false positives, and figure copying. In total, 233 HC participants and 439 patients with SCD had complete baseline CTS data and were included in our analyses. An age-, sex-, and education-adjusted regression formula, stemming from a model fitted in the German CERAD-NAB normative sample, was used to calculate the demographically adjusted CTS.[16]

Previous research from our group found that a CTS-based MCI criterion, using 1SD below the mean as the threshold to define cognitive impairment, demonstrated good reliability and prognostic validity for the detection of future dementia converters.[17] In this study, we used a lower threshold of 0.5SD below the mean to operationalize MNPD in participants free of MCI at inclusion. Based on the mean and SD reported in the CERAD-NAB normative sample,[16] we set our MNPD cut-off at ≤ 91.8 points on the demographically adjusted CTS.

In a sensitivity analysis, we repeated all of our core analysis steps in the SCD group after excluding participants who scored at least 1SD below the adjusted CTS mean at baseline to assess their influence on the study results. In addition, we examined 2 alternative MNPD criteria that define MNPD based on a required number of low test scores to explore their pattern of associations in our SCD sample (eMethods, links.lww.com/WNL/D144).

Clinical Progression to Incident MCI

Consensus diagnoses of incident MCI were determined in a two-step review process adapted from the diagnostic procedures of the Wisconsin Registry for Alzheimer's Prevention study.[18] For each follow-up assessment, we applied an algorithmic screening procedure to all participants who were cognitively normal at baseline to identify individuals with signs of potential cognitive decline. Those marked by this screening process were reviewed in detail by a team of experienced neuropsychologists (M.W., I.F., S.W., L.K., M.S.), who assessed the conversion status of each participant based on established diagnostic criteria[19,20] (see Figure 1 for an extended description). During the review process, the consensus committee was blind to clinical baseline group assignments, CSF and blood biomarkers, imaging data, and genetic information.

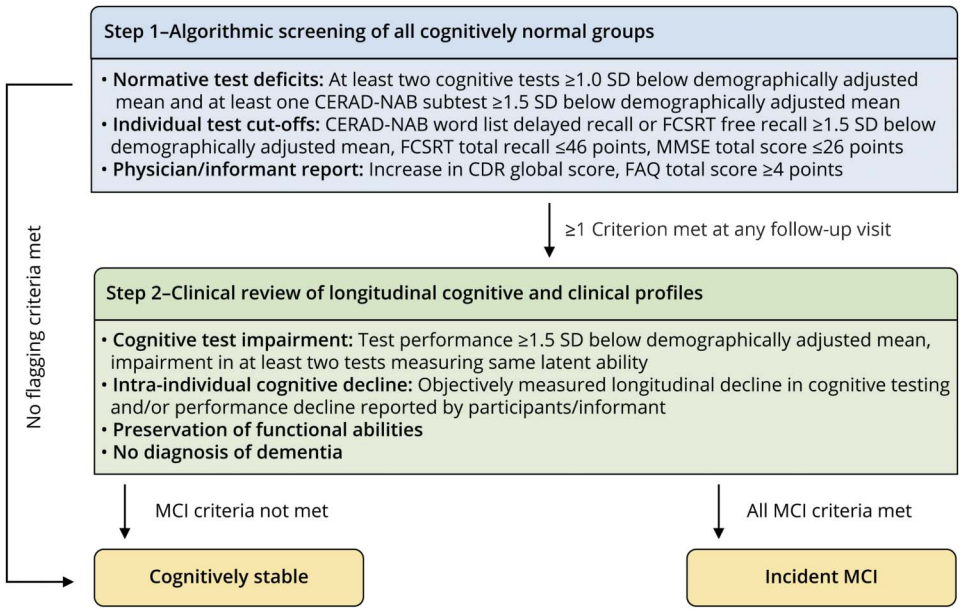
CSF Biomarker Assessment

The acquisition and analysis of CSF in DELCODE followed standardized assessment protocols, which have been described previously.[12] Biomarker levels were determined centrally in one laboratory. We focused on CSF levels of β-amyloid (Aβ)42/Aβ40, phosphorylated tau (p-tau$_{18}$), total tau, and Aβ42/p-tau$_{181}$ to assess group differences in AD pathology. CSF biomarker information was available in a subgroup of our total analysis sample (n = 300, 44.6%).

Statistical Analysis

Analyses were conducted with R version 4.0.3. Statistical significance was set at $p \leq 0.05$. To investigate our main hypothesis, we compared SCD patients with MNPD and those without MNPD regarding baseline CSF biomarkers, longitudinal PACC5 trajectories, and risk of progression to MCI. We also compared patients with SCD and HC participants without MNPD in the same outcome measures to assess

Figure 1 Incident MCI Diagnostic Procedure



Flowchart of the two-step diagnostic procedure that was applied to determine the clinical follow-up status of study participants who were cognitively normal at baseline. CERAD-NAB = Consortium to Establish a Registry for Alzheimer's Disease neuropsychological assessment battery; CDR = Clinical Dementia Rating Scale; FAQ = Functional Activities Questionnaire; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental Status Examination.

whether SCD is indicative of an increased risk of neuropathology and symptomatic progression even in the absence of MNPD. In an exploratory analysis, we conducted the same 3 comparisons between HC participants with MNPD and those without MNPD to explore what pattern of results MNPD show in cognitively normal older individuals without subjective cognitive concerns.

In the study sample with available CSF data, group differences in log-transformed baseline CSF biomarker levels were examined with ANCOVAs adjusted for age and sex. We applied the Holm-Bonferroni procedure to correct for multiple biomarker comparisons.

We analyzed longitudinal PACC5 trajectories with latent process mixed models implemented in the R package *lcmm*.[21] These models adjust for unequal interval scaling in cognitive test outcomes by estimating parameterized nonlinear link functions that describe the relationship between an analyzed cognitive marker and the latent process it measures.[22] Within each analysis sample, we identified the most appropriate link function (linear, beta, or I-spline link function) and modeling of trajectories (linear or quadratic) based on Akaike's information criterion. Maximum likelihood estimation in the latent process mixed model, which calculates parameter estimates under the missing at random assumption, was used to address missing data at follow-up. All mixed models were adjusted for the fixed effects of baseline age, sex, and years of education and their interactions with the slopes of time. Owing to the inclusion of quadratic time slopes, we examined group differences in PACC5 trajectories with multivariate Wald tests for the interactions of the focal grouping variable with the linear and quadratic slopes of time.[21]

Group differences in the risk of progression to incident MCI were examined with Cox proportional hazard regression models adjusted for the covariates baseline age, sex, and years of education. The survival analyses included participants with at least 1 follow-up assessment. Cases with incomplete follow-up data or dropout were censored at their last assessment. For the MCI review process, follow-up data until April 2021 were available, while the PACC5 follow-up data cover the time frame until April 2022. Therefore, the MCI progression analyses on average covered a slightly shorter time frame than the analyzed cognitive trajectories.

To evaluate the clinical relevance and short-term to midterm prognostic value of baseline MNPD for the progression to incident MCI in patients with SCD, we also calculated time-specific estimates of sensitivity, specificity, as well as positive and negative predictive values with the inverse probability of censoring weighting (IPCW) method from the *timeROC* R package.[23]

Although we did not focus on investigating the incremental effect of MNPD beyond other established risk factors in our study, we ran a supplementary Cox regression in the SCD group, which included smoking, alcohol consumption, BMI, hypertension, coronary heart disease, hypercholesterolemia, diabetes, and ApoE-ε4 to assess whether MNPD remained a significant predictor of incident MCI after controlling for these covariates (eMethods).

Data Availability

Data generated and analyzed in this study can be made available on request from qualified investigators for the purpose of replicating procedures and results.

Table 1 Baseline Characteristics of HC Participants and SCD Patients With/Without MNPD

Variable	HC/MNPD−	HC/MNPD+	SCD/MNPD−	SCD/MNPD+		
Demographics	**n = 215**	**n = 18**	**n = 384**	**n = 55**	***F*/χ^2**	***p***
Age (y; mean, SD)	69.03 (5.46)[a,b]	67.17 (3.62)[a,b]	70.68 (5.98)	72.55 (6.13)	8.50	<0.001
Sex (female; n, %)	124 (57.7%)[b]	10 (55.6%)	182 (47.4%)	20 (36.4%)	10.42	0.015
Education (y; mean, SD)	14.64 (2.75)	15.22 (2.65)	14.72 (2.96)	15.69 (2.95)	2.18	0.090
PACC5 (mean, SD)	0.20 (0.53)[a,b]	−0.12 (0.52)[b]	−0.03 (0.64)[b]	−0.71 (0.58)	34.57	<0.001
PACC5 Follow-up time (y; mean, SD)	3.99 (1.98)[a,b]	3.66 (2.09)	3.12 (1.92)	2.79 (1.75)	11.17	<0.001
Time under risk of MCI (y; mean, SD)[c]	3.98 (1.32)[a,b]	3.94 (1.42)[a,b]	3.02 (1.40)[b]	2.24 (1.17)	32.52	<0.001
CSF biomarkers[d]	**n = 83**	**n = 8**	**n = 184**	**n = 25**	***F***	***p***
Aß42/Aß40 (mean, SD)	0.10 (0.02)[b]	0.10 (0.04)	0.09 (0.03)[b]	0.08 (0.03)	3.86	0.010
P-tau$_{181}$ (mean, SD)	51.10 (20.50)[b]	48.50 (10.72)	51.72 (21.12)[b]	67.96 (35.13)	2.77	0.042
Total tau (mean, SD)	377.00 (172.03)	342.64 (109.27)	352.09 (168.87)[b]	485.57 (241.90)	3.02	0.030
Aß42/p-tau$_{181}$ (mean, SD)	17.67 (5.65)[b]	17.51 (6.46)	16.90 (7.27)[b]	12.84 (7.93)	5.17	0.002

Abbreviations: HC = healthy control; MCI = mild cognitive impairment; MNPD = minor neuropsychological deficits (present +, absent -); PACC5 = Preclinical Alzheimer's Cognitive Composite; SCD = subjective cognitive decline.
F statistics reported for one-way ANOVAs of continuous variables. χ^2 statistic reported for sex. CSF biomarkers were log-transformed for significance tests. Holm-Bonferroni corrected post hoc tests (*t*/χ^2) were calculated for variables with significant overall group differences.
[a] Significantly different from SCD/MNPD−.
[b] Significantly different from SCD/MNPD+.
[c] MCI follow-up data missing in 63 individuals (n = 22 HC/MNPD−; n = 2 HC/MNPD+; n = 34 SCD/MNPD−; n = 5 SCD/MNPD+).
[d] CSF biomarker data missing in 372 individuals (n = 132 HC/MNPD−; n = 10 HC/MNPD+; n = 200 SCD/MNPD−; n = 30 SCD/MNPD+).

Results

Participants

Of the 672 study participants who were included in the analyses, 73 met our criterion for MNPD (HC: n = 18, 7.7%; SCD: n = 55, 12.5%; $\chi^2_{(1)} = 3.15$, $p = 0.076$). Descriptive demographic and clinical statistics of the participant and MNPD groups are shown in Table 1.

Baseline CSF data were available in a subset of 300 participants (44.6%). Those with available CSF did not differ significantly from those without CSF data regarding age, education years, and the proportion of individuals with baseline MNPD (MNPD+) but included a higher proportion of men (CSF available: 54.7% male; no CSF available: 46.2% male; $\chi^2_{(1)} = 4.39$, $p = 0.036$) and patients with SCD (CSF available: 69.7% of participants reported SCD; no CSF available: 61.8% of participants reported SCD; $\chi^2_{(1)} = 4.17$, $p = 0.041$).

A total of 609 participants (90.6%) had information on their follow-up MCI status (HC/MNPD−: n = 193; HC/MNPD+: n = 16; SCD/MNPD−: n = 350; SCD/MNPD+: n = 50). Individuals with available follow-up data did not differ significantly from those who provided only baseline data regarding their age, sex, and education years or their percentage of patients with SCD and participants with MNPD. During the available follow-up period (M = 3.11 years, SD = 1.68), 10 HC participants from the MNPD− group progressed to MCI (5.2% of those with incident MCI data), while 1 person progressed in the HC MNPD+ group (6.3%). Among the patients with SCD, 58 individuals from the MNPD− group (16.6%) and 24 individuals from the MNPD+ group (48.0%) progressed to MCI.

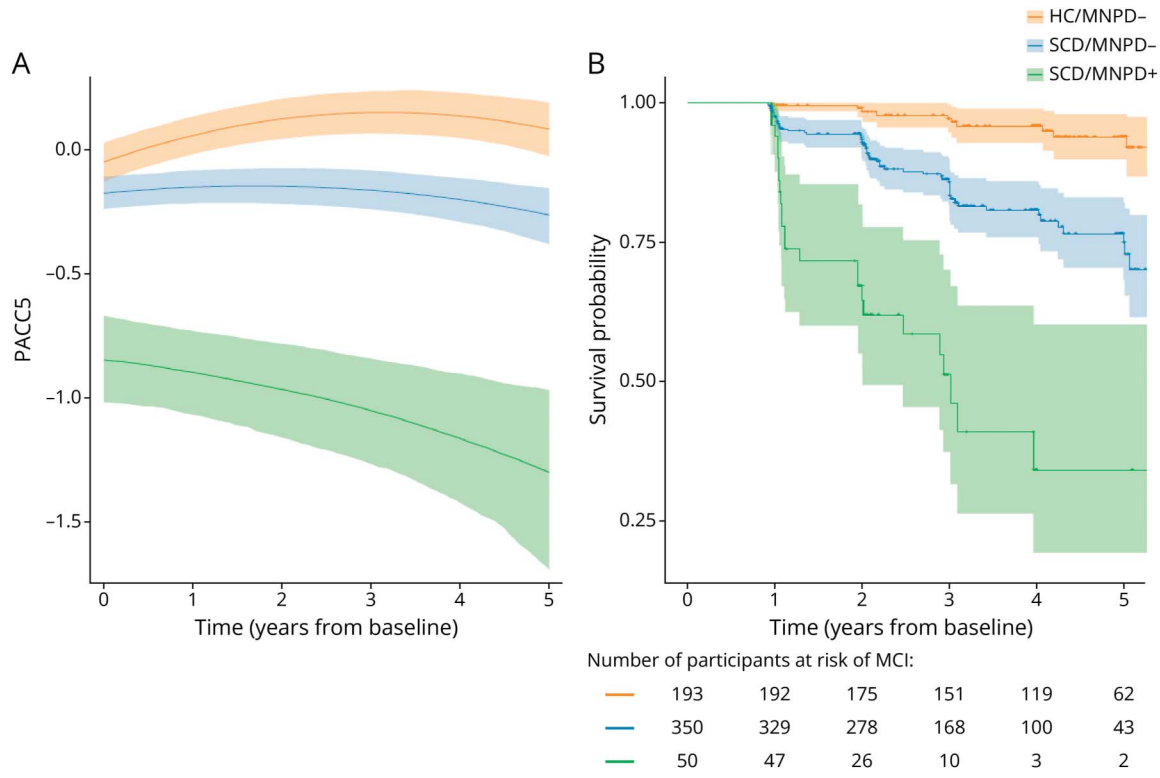
CSF Biomarkers

In the SCD group, patients with MNPD had lower CSF Aβ42/40 ($F_{(1,205)} = 6.16$, $p = 0.014$, $\eta_p^2 = 0.029$) and Aβ42/p-tau$_{181}$ levels ($F_{(1,205)} = 7.29$, $p = 0.008$, $\eta_p^2 = 0.034$) as well as higher levels of p-tau$_{181}$ ($F_{(1,205)} = 5.98$, $p = 0.015$, $\eta_p^2 = 0.028$) and total tau ($F_{(1,205)} = 7.40$, $p = 0.007$, $\eta_p^2 = 0.035$) than SCD patients without MNPD. These differences remained significant with Holm-Bonferroni adjustment. There were no significant biomarker differences between HC participants with MNPD and those without MNPD. In the group of participants without MNPD, patients with SCD and HC participants did not differ significantly in their CSF biomarker levels (eTable 1, links.lww.com/WNL/D144).

Cognitive Trajectories

SCD patients with MNPD had a lower PACC5 performance at baseline (β = −2.00, SE = 0.25, $p < 0.001$) and a steeper decline in PACC5 performance ($\chi^2_{(2)} = 6.47$, $p = 0.039$) compared with those without MNPD (eTable 2, links.lww.com/WNL/D144, Figure 2). HC participants with MNPD had a lower PACC5 performance at baseline (β = −1.33, SE = 0.41, $p = 0.001$) but did not differ significantly from HC

Figure 2 Predicted PACC5 Trajectories and Kaplan-Meier Plots



(A) Predicted PACC5 trajectories over 5 years of follow-up in the SCD groups and HC participants without MNPD at baseline. Plots and 95% confidence intervals were derived from latent process mixed models (see eTable 2, links.lww.com/WNL/D144 for model parameters) and display the predicted group trajectories, with demographic covariates set at male sex, age 70 years at baseline, and 14.75 years of education. Longitudinal PACC5 trajectories differ significantly between the 2 SCD groups ($p = 0.039$) and SCD and HC participants without MNPD at baseline ($p < 0.001$). (B) Kaplan-Meier survival curve estimates and 95% confidence intervals of the risk of progression to incident MCI in the SCD groups and HC participants without MNPD at baseline. Predicted PACC5 trajectories and incident MCI Kaplan-Meier plots of all 4 study groups, including HC MNPD+ participants, are displayed in eFigure 1. HC = healthy control; MCI = mild cognitive impairment; MNPD = minor neuropsychological deficits (present +, absent -); PACC5 = Preclinical Alzheimer's Cognitive Composite; SCD = subjective cognitive decline.

participants without MNPD in their PACC5 decline ($\chi^2_{(2)} = 2.05$, $p = 0.359$, eFigure 1). SCD patients without baseline MNPD had a lower baseline PACC5 performance ($\beta = -0.43$, SE = 0.14, $p = 0.003$) and more pronounced PACC5 decline ($\chi^2_{(2)} = 26.18$, $p < 0.001$) than HC participants without MNPD.

MCI Risk

In the combined total sample, patients with SCD had a higher risk of progression to incident MCI than the HC group (HR: 4.87, 95% CI: 2.57–9.24, $p < 0.001$). SCD patients with MNPD had an increased risk of progression to MCI compared with SCD patients without MNPD (HR = 4.07, 95% CI 2.46–6.74, $p < 0.001$, eTable 3, links.lww.com/WNL/D144, Figure 2). Time-dependent estimates of the prognostic value of baseline MNPD for the progression to MCI in the SCD group are displayed in Table 2. In the HC group, there was no significant difference in the risk of progression to MCI between participants with MNPD and those without MNPD (HR = 1.30, 95% CI 0.16–10.34, $p = 0.806$, eFigure 1). SCD patients without MNPD had an increased MCI risk compared

Table 2 Time-Dependent Prognostic Value of Baseline MNPD for the Progression to MCI in Patients With SCD

Time to outcome	Cases	Surv.	Cen.	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
2 y	40	304	56	39.93 (24.72–55.14)	91.45 (88.29–94.61)	35.60 (21.31–49.89)	92.78 (89.98–95.58)
3 y	62	178	160	32.61 (20.85–44.37)	94.38 (90.99–97.77)	56.95 (38.47–75.43)	86.01 (81.93–90.09)
4 y	74	97	229	31.32 (20.34–42.30)	97.94 (95.12–100.00)	83.29 (63.18–100.00)	81.30 (76.36–86.24)

Abbreviations: Cen. = censored cases; MNPD = minor neuropsychological deficits; NPV = negative predictive value; PPV = positive predictive value; SCD = subjective cognitive decline; Surv. = survivors.
Time-dependent inverse probability of censoring weighting (IPCW) estimates of sensitivity, specificity, and positive/negative predictive values. Results estimate the prognostic value of baseline MNPD for the progression to MCI within 2, 3 and 4 y in patients with SCD.

with HC participants without MNPD (HR = 4.09, 95% CI 2.07–8.09, $p < 0.001$).

Sensitivity Analyses

SCD patients with MNPD still had a significantly increased risk of progression to MCI compared with those without MNPD after controlling for smoking, alcohol consumption, BMI, comorbidities, and ApoE-ε4 as additional covariates (eTable 4, links.lww.com/WNL/D144). In addition, all core results within the SCD group remained significant after the exclusion of 19 patients with SCD who scored at least 1SD below the CTS mean at baseline (eTables 5–7). In our analyses using 2 alternative MNPD criteria, MNPD was a significant predictor of the progression to MCI and showed a similar pattern of results across all the included criteria (eTables 5–7).

Discussion

This study investigated the association of MNPD with cross-sectional AD biomarkers as well as longitudinal measures of cognitive decline and the risk of clinical conversion in memory clinic patients with SCD. As expected, patients with SCD overall had a markedly increased risk of clinical progression compared with HC participants. Importantly, we found that SCD patients with MNPD show increased CSF AD pathology, accelerated cognitive decline, and a higher risk of progression to MCI compared with SCD patients without MNPD. Nevertheless, MNPD-free patients with SCD still showed stronger cognitive decline and an increased risk of incident MCI compared with HC participants without MNPD. However, these groups did not differ significantly in their baseline CSF AD biomarker levels.

Several studies have already shown that cognitively unimpaired individuals with MNPD, operationalized with differing criteria and cut-offs, have an increased risk of AD biomarker abnormalities[24-26] and progression to MCI or dementia[24-27] as well as increased brain atrophy[27,28] compared with those without MNPD. However, few studies have investigated the effect of MNPD in older individuals with SCD and those that did focused solely on cross-sectional biomarker analyses.[10,11] Our study extends these findings by demonstrating that SCD patients with MNPD show increased cognitive decline and an elevated risk for progression to MCI. Previous studies investigating the association of MNPD with AD biomarkers in individuals with SCD have yielded inconsistent results. In line with our study, one research group reported elevated amyloid PET in SCD patients with MNPD, who were recruited from a network of Korean memory clinics.[11] In contrast to these findings, another study examined cognitively normal Alzheimer's Disease Neuroimaging Initiative (ADNI) participants and reported no significant amyloid or tau PET differences between MNPD groups in individuals with subjective memory concerns.[10] These inconsistent biomarker results might be explained by differences in the study settings and SCD criteria of the investigated cohorts. ADNI does not include a separate *clinical* group of participants with SCD, that is, individuals recruited into the cohort because of a subjectively perceived cognitive decline, which prompted them to seek medical attention. Instead, participants with SCD are identified based on a self-report questionnaire and constitute a subgroup of the cognitively normal sample.[10] However, past research suggests that the recruitment setting is an important moderator of SCD study results. For instance, the risk of amyloid pathology[29] and progression to MCI and dementia[5,6] seems to be higher in patients with clinical SCD, who were recruited from a specialized medical setting, than in community volunteers reporting SCD. The current findings on MNPD show a similar pattern, suggesting more pronounced differences between MNPD groups in clinical SCD samples.

Considered together with previous findings, our results strongly suggest that MNPD in patients with clinical SCD provide important information that should not be disregarded. In patients with SCD, subtle test deficits seem to be an early cognitive sign of neurodegeneration and may offer a cost-efficient and noninvasive approach to identify individuals with an increased risk of underlying AD pathology and cognitive decline. The assessment of MNPD could thus provide a method of risk stratification in future SCD research and clinical contexts, supplementing biomarker assessments for the identification of underlying diseases. In our study, the presence of MNPD in patients with SCD indicated a 35.6% probability of developing incident MCI within 2 years and an estimated probability of 83.6% of developing MCI within 4 years. SCD patients with MNPD therefore constitute a high-risk group for clinical progression that requires a close monitoring of symptomatic worsening. On the other hand, the absence of MNPD ruled out a progression from SCD to MCI within 2 years with a probability of 92.8%, while a progression to MCI over 4 years could still be ruled out with a probability of 81.3%. Considering that most SCD patients without MNPD did not develop MCI or dementia in this time frame, an assessment of MNPD may be a useful approach to identify patients who can be reassured about their low risk of clinical progression. However, a single assessment of MNPD has a limited predictive ability because of longitudinal cognitive change. Some of our study participants likely developed MNPD only after their baseline assessment and then quickly progressed to MCI. This probably influenced our low and decreasing sensitivity of MNPD for future MCI, which might improve through repeated assessments of MNPD, for example, after 2 or 3 years when MCI conversions reach a moderate level in our MNPD− sample.

Our results are also relevant from a theoretical perspective. Other research groups have previously posited that subtle cognitive deficits determined from a single cross-sectional assessment could help to detect transitional cognitive changes[24,30]—a defining characteristic of AD stage 2 in the National Institute on Aging and Alzheimer Association's (NIA-AA) clinical staging scheme of biologically defined

AD.[31] According to the current NIA-AA research framework, objectively measured transitional cognitive changes can be detected using longitudinal cognitive testing. Previous studies have also shown that longitudinally measured cognitive decline is predictive of AD biomarker abnormalities and the progression to MCI in cognitively normal individuals.[30,32] Our findings show that the cross-sectional assessment of MNPD can also capture useful information on an individual's cognitive state and risk of future decline. Our results further suggest that the combined assessment of the 2 established markers of potential transitional decline (i.e., SCD and cross-sectional MNPD) is not redundant because subtle cognitive deficits are still predictive of future MCI in individuals with SCD.

Furthermore, some authors conceptualize AD as a clinical-biological entity, which should only be diagnosed if both a specific clinical phenotype of AD (i.e., MCI or dementia) and a biomarker evidence of AD pathology are present.[33] In this perspective, SCD in patients without MCI is not considered sufficiently specific or predictive for future impairment to be classified as such an AD-defining clinical phenotype. However, our data now raise the possibility that the combination of an assessment of SCD with cognitive testing could offer a suitable approach to identify high-risk groups for clinical progression. Research on the combination of SCD and MNPD with the assessment of depressive symptoms[34] or broader neuropsychiatric concepts, such as mild behavioral impairment,[35] may further promote the identification of clinical phenotypes of AD that precede the onset of MCI.

Unlike in the SCD group, HC participants with MNPD did not differ significantly from those without MNPD in any of our study outcomes. These results stand in contrast to several previous studies, which reported that cognitively normal older individuals with MNPD show increased levels of neuropathology and accelerated cognitive decline.[10,25,27,28] The small number of HC participants with MNPD (n = 18) reduced the statistical power of our analyses and may explain the findings, especially in the CSF analysis. However, it is tempting to speculate that the low frequency of MNPD in HC participants and the lack of significant differences may also indicate that the assessment of MNPD is particularly informative in individuals with SCD. One source of the discrepancies to previous findings could be the comparatively stringent exclusion criteria used in the recruitment of DELCODE participants. HC individuals were not included in the study if they reported signs of SCD they considered worrisome or unusual for their age.[12] This probably excluded most individuals showing MNPD because of actual age-associated cognitive *decline* from our HC sample. Instead, the MNPD+ HC group may mainly include individuals who have shown a stable cognitive performance in the lower normative percentiles for their entire adult lives.

While the relevance of subtle cognitive deficits in cognitively normal individuals has been studied in previous publications, a clear consensus on their operationalization does not seem to exist. Some authors use cognitive composite scores to identify MNPD,[26,27] while other, frequently used criteria require low scores in a certain number of cognitive tests to classify someone as MNPD+.[11,24,36] In our sensitivity analyses, MNPD was a significant predictor of the progression to MCI and showed a similar pattern of results across all the applied MNPD criteria. This suggests that the clinical relevance of MNPD in patients with SCD does not depend on a specific operationalization of the construct.

Finally, despite faring better than SCD patients with MNPD, patients with SCD above the threshold of subtle deficits still showed stronger cognitive decline and had an increased risk of incident MCI compared with control participants with a similar cognitive performance level at baseline. The lack of significant CSF biomarker differences between these groups may, again, be due to the reduced sample size in these analyses. However, the 2 groups also did not show strongly pronounced descriptive biomarker differences. It is possible that the group of SCD patients without MNPD includes individuals in an early stage of AD-related SCD, who perceive subtle cognitive changes early in the neurodegenerative process, but have not yet developed a degree of amyloid or tau pathology that is detectable in group comparisons. Previous results show that a longitudinal increase in PET amyloid is associated with concurrent memory decline in individuals who were amyloid negative and cognitively normal at baseline,[37] suggesting that cognitive decline is an early consequence of amyloid accumulation that can already be detected and reported in individuals below the threshold of amyloid pathology. In addition, other pathologic processes that we did not investigate in our current analyses could have driven the longitudinal differences between the 2 groups. For example, in one large multicenter study of memory clinic patients with SCD, approximately a third of incident dementia cases were attributable to non-AD pathologies.[5] Similarly, some individuals in our sample of MNPD-free patients with SCD might have exhibited cognitive decline that was driven by vascular, Lewy body, and other types of non-AD pathology. The pathologic background of the increased risk of symptomatic progression in SCD patients without MNPD should be further investigated, ideally in larger samples with biomarker data. Especially the longitudinal analysis of biomarkers measuring AD pathology and neurodegeneration could provide an avenue to a deeper understanding of the cognitive group differences we observed.

In our study, we examined a large and well-characterized cohort of participants with AD biomarkers and extensive longitudinal neuropsychological data. The inclusion of memory clinic patients, who sought medical help because of their cognitive concerns, allowed us to investigate the clinical relevance of MNPD in a sample that reflects current and future patient populations. However, this study is not without limitations. The small number of HC participants with MNPD, which was further reduced in the CSF

biomarker analysis and across subsequent follow-up assessments, limited our ability to detect group differences and did not allow us to draw reliable conclusions from the comparison of the HC groups. Our study participants are on average highly educated and European, which limits the generalizability of our results to other populations. In addition, the CSF sampling rate at baseline was 44.6%, and the availability of longitudinal CSF data was further limited. This reduced the power of our baseline biomarker analyses and did not allow us to compare longitudinal biomarker trajectories between the participant groups.

In summary, our results show that SCD patients with subtle cognitive test deficits have increased levels of AD pathology as well as an increased risk of cognitive decline and clinical progression. These findings show that MNPD can indicate a high-risk group for AD pathology and dementia among patients seeking medical counseling because of their subjective cognitive concerns. They also show that absence of MNPD does not rule out clinical progression in patients with SCD. Our results shed new light on the intertwined subjective and objective transitional decline in preclinical AD. Pending further research and replication, they may help clinicians to gauge and communicate individual risk in patients with SCD.

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Disclosure

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Continued

Appendix *(continued)*

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