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FEATURED ARTICLE

Disentangling the relationship of subjective cognitive decline and depressive symptoms in the development of cognitive decline and dementia

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Abstract

Introduction: Subjective cognitive decline (SCD) and depressive symptoms (DS) frequently co-occur prior to dementia. However, the temporal sequence of their emergence and their combined prognostic value for cognitive decline and dementia is unclear.

Methods: Temporal relationships of SCD, DS and memory decline were examined by latent difference score modeling in a high-aged, population-based cohort (N = 3217) and validated using Cox-regression of dementia-conversion. In 334 cognitively unimpaired SCD-patients from memory-clinics, we examined the association of DS with cognitive decline and with cerebrospinal fluid (CSF) Alzheimer's disease (AD) biomarkers.

Results: In the population-based cohort, SCD preceded DS. High DS were associated with increased risk of dementia conversion in individuals with SCD. In SCD-patients from memory-clinics, high DS were associated with greater cognitive decline. CSF Aß42 predicted increasing DS.

Discussion: SCD typically precedes DS in the evolution to dementia. SCD-patients from memory-clinics with DS may constitute a high-risk group for cognitive decline.

KEYWORDS
Alzheimer's disease, depression, latent difference score model, subjective cognitive decline, temporal sequence

Highlights

- Subjective cognitive decline (SCD) precedes depressive symptoms (DS) as memory declines.
- Emerging or persistent DS after SCD reports predict dementia.
- In SCD patients, more amyloid pathology relates to increasing DS.
- SCD patients with DS are at high risk for symptomatic progression.

1 | NARRATIVE

1.1 | Background

Depressive symptoms (DS) and subjectively perceived worsening of cognition in the absence of clinically relevant cognitive impairment (subjective cognitive decline [SCD]) are established risk factors for dementia.[1,2] Moreover, consistent SCD over time[3,4] and increasing DS over time[5,6] are both associated with a particularly elevated dementia risk. However, although both symptoms frequently co-occur,[7,8] their temporal relationship and their association with objective cognitive decline prior to dementia is not sufficiently studied. As a result, there is ambiguity about the typical temporal sequence, and additionally about the causal relationship of SCD and DS. On the one hand, DS can be a non-neurodegenerative cause of SCD due to, for example, negatively biased meta-cognitive judgement of one's own cognitive capacities.[9,10] In this case, DS should predict the development of SCD and should not necessarily indicate increased dementia risk. On the other hand, SCD can be a symptom of an underlying neurodegenerative process, and DS a reaction to experienced changes in cognitive capacities (Figure 1).[8] In this case, DS should follow SCD and should indicate increased dementia risk.[11]

In our study, we aimed to disentangle the relationship of SCD and DS in the pre-dementia phase by studying their temporal sequence and typical development in a population-based cohort of elderly individuals. In addition, we examined the associated risk of dementia in this cohort and of cognitive decline in an additional multicenter memory clinic SCD sample (Figure 2). These analyses aim to improve the understanding of the symptomatic development prior to dementia and the use of SCD and DS as risk indicators.

1.2 | Summary of findings

In a first step, we studied the typical temporal development of SCD and DS and their association with decline in episodic memory in the

RESEARCH IN CONTEXT

1. **Systematic Review**: Studies examining the temporal relationship of subjective cognitive decline (SCD), objective decline, and depressive symptoms (DS) were reviewed using traditional methods. Previously used methods hampered the identification of the temporal order of their occurrence.
2. **Interpretation**: Using an unrestricted latent difference score model, we showed that SCD precedes DS during cognitive decline. In SCD patients, more DS are associated with faster symptomatic progression and with Alzheimer's disease (AD) biomarkers. Thus, DS in individuals reporting SCD might indicate elevated risk for AD, in contrast to the frequently held assumption that reports of SCD are unlikely to herald neurodegeneration if accompanied by DS.
3. **Future Directions**: Future research should confirm the temporal relationship of SCD and DS as this may have implications for optimizing study designs: If SCD would cause DS, conditioning on DS (by, e.g., sample selection or statistical adjustment) could introduce bias when studying outcomes and correlates of SCD.

population-based German study on Ageing, Cognition and Dementia (AgeCoDe) cohort[12] ($N = 3217$ individuals aged > 75 years at baseline, seven equally spaced assessments every 18 months). We used latent difference score models (LDSM),[13,14] a structural equation modeling technique allowing us to evaluate whether the increase of a (leading) variable over time predicts the increase of another (lagging) variable or vice versa. The advantage of our analysis is the unbiased nature of the statistical approach, whereas previous studies applied strong modeling restrictions on temporal relationships,[15] did not assess the longitudinal lead-lag relationships,[10,16–19] or focused on only two variables and not on all three (SCD, DS, objective memory).[20–28] Our results suggest that SCD, DS, and memory decline influence each other over time and develop in a typical temporal sequence: SCD is the initial event, followed by objective memory decline and increasing DS.

Next, we tested whether this temporal ordering of SCD and DS based on assessments at two time points predicts cognitive decline and dementia and may serve as a clinical longitudinal risk indicator. We tested this in the AgeCoDe population-based cohort and in addition in the Dementia Competence Network (DCN) multicenter memory clinic SCD sample. We focused on these two different settings, because the association of SCD with risk of cognitive decline and dementia critically depends on recruitment strategies and prevalence of AD in the respective samples.[29,30]

In the population-based AgeCoDe cohort (subsample of $N = 2593$, up to 12 years of follow-up), we observed that participants who reported SCD at baseline and persistently high or increasing DS after 18 months (first follow-up) were at an increased risk of incident dementia (all-cause dementia and dementia of Alzheimer's type [DAT]) compared to those with SCD at baseline and low or no or decreasing DS. This association was significantly weaker and did not reach statistical significance in individuals *without* SCD at baseline.

In SCD patients from the DCN study[31] ($N = 332$, up to 4 years of follow-up), those with high DS at baseline or increasing/persistently high DS across two time points (12 months apart) showed faster cognitive decline than those SCD patients with low or decreasing DS. We also found that in individuals with SCD and cerebrospinal fluid (CSF) biomarkers ($N = 107$), amyloid beta ($A\beta_{1\text{-}42}$) was associated with an increase in DS over time, providing a link between AD pathology and increase of DS after the onset of SCD.

1.3 | Discussion and next steps

Overall, our results show that SCD typically precedes DS during the development of cognitive decline and dementia. This suggests that DS in individuals reporting SCD are not necessarily independent of neurodegeneration. DS and SCD can both relate to an underlying neurodegenerative process and SCD can specifically contribute to the development of DS (Figure 1). The occurrence of SCD prior to DS in those with cognitive decline refines the understanding of the clinical presentation in the prodromal phase of dementia.[32] As such, the consideration of the temporal order of symptoms may contribute to an even more precise symptomatic staging of individuals with Alzheimer's disease (AD).[32]

Our data also suggest that SCD with subsequent DS identifies a particular high-risk group for cognitive decline and dementia. This may be translated into an easily applicable symptomatic longitudinal risk indicator for use in prevention studies or even in the clinical setting.

An important next step is to examine whether other neuropsychiatric symptoms also follow a specific temporal sequence and whether the temporal sequence of such symptoms may further improve prediction of symptomatic progression. As such, the full spectrum of mild behavioral impairment (MBI),[33] which refers to all neuropsychiatric symptoms in relation to the initial symptomatic phase of AD and dementia, is of high interest. The temporal relationship of all MBI components with SCD and objective decline should be explored, for instance, using our LDSM approach.

Considering SCD, cognitive decline, and DS as parts of a common process (Figure 1) raises additional questions, which should be addressed in the future. In our study, we identified the typical development of SCD, DS, and cognitive decline, but there might also be other temporal and or even qualitative types of symptom patterns that also relate to dementia risk. Methods successfully used in research on brain atrophy patterns[34] could be applied for the identification of these subgroups.

The predictive value of temporal symptom patterns may differ according to contextual factors, such as age and AD prevalence. It

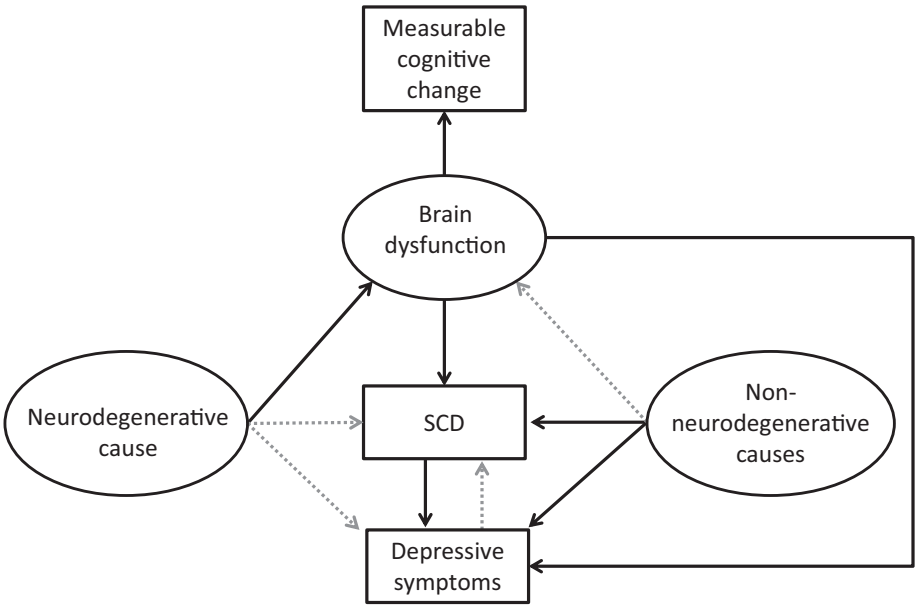

FIGURE 1 This figure summarizes a hypothetical model of the developlment of subjective cognitive decline (SCD), depressive symptoms (DS), and objective cognitive decline based on previous research in the field. It is considered a falsifiable and evolving working model to support further theory formation. The present paper tests some predictions of this model. In the figure, assumed latent causes are shown as circles while measurable variables are shown in rectangles. Directed relationships between variables are shown as arrows and differ in their assumed likelihood: presumably more likely, stronger relationships are shown as black solid arrows while presumably less likely, weaker relationships are shown as gray dotted arrows. It is assumed that SCD and DS can derive from a multitude of *non-neurodegeneration causes* that may not predominantly affect brain function. The likelihood and strength of the influence of these non-neurodegenerative processes on brain dysfunction may depend on the specific cause. However, SCD, measurable cognitive changes, and DS can also derive from brain dysfunction related to a neurodegeneration-related cause and form a common, temporally ordered symptomatic cascade. In addition to this common cause, DS could result as a psychological reaction to actual and subjectively perceived cognitive changes. Therefore, DS in individuals reporting SCD can be considered consistent with the presence of a neurodegenerative process. Accordingly, it can be hypothesized that DS in individuals with SCD relate to biomarkers of neurodegenerative diseases and could indicate increased dementia risk. Furthermore, SCD could predispose the development of DS, that is, a psychological reaction to observed changes (in addition to the common link to brain dysfunction) and should therefore regularly precede DS during their typical development. Nevertheless, DS can precede SCD due to non-neurodegenerative causes (e.g., biased self-assessment of cognition) or neurodegenerative causes but this might be not the usual case. Section 1.2 and 2 summarize the results derived from empirical test of these hypotheses that are consistent with the model shown here. Section 1.3 describes important next steps toward further theory formation

should be explored whether our results generalize to younger age groups (i.e., between 60 and 80) in the general population and populations enriched for other, non-AD neurodegenerative diseases. In addition, the link of longitudinal biomarkers for AD and neurodegeneration with the development of SCD and DS should be assessed in future research, a goal which will be more attainable by using plasma biomarkers. Our observation that the development of DS in SCD patients was associated with amyloid pathology is in line with a recent population-based study.[35] However, it requires further investigation in additional cohorts.

It will be important to understand the mechanisms underlying the link of SCD and DS to improve strategies for prevention of cognitive decline, such as stress reduction.[36] Interestingly, particularly high levels of DS seem to co-occur with a *decrease* in SCD in our data (Figure 3G–I). Such decreasing awareness of cognitive deficits has been previously described in SCD patients.[37] It is thus tempting to speculate that SCD, as a specific meta-cognitive evaluation, develops into unspecific affective symptoms as cognition and awareness decline. This hypothesis could be tested by longitudinal analyses of measures of symptom awareness[37] in combination with objective cognition and DS.

Finally, our findings on the temporal sequence of SCD, DS, and cognitive decline may also have methodological implications for SCD research. If SCD is a causal driver of DS, the frequent practice of adjusting for DS (either by excluding depressed individuals or by statistically adjusting for DS) could be misleading due to introduction of "collider-stratification bias"[38] (i.e., bias due to conditioning on a common effect, Text S1 in supporting information).

A strength of the study is the observed association of SCD with DS and cognitive decline in two independent samples from two different settings with large sample sizes and longitudinal data over multiple time points. However, the relatively smaller sample size and shorter follow-up in the DCN memory clinic cohort compared to the population-based AgeCoDe cohort did not permit a direct replication of the LDSM. A further limitation is the limited assessment of SCD in AgeCoDe (3-point rating scale, Section 3.1.1) and the memory-focused cognitive outcome measures because associations of SCD with DS can differ across cognitive domains.[25]

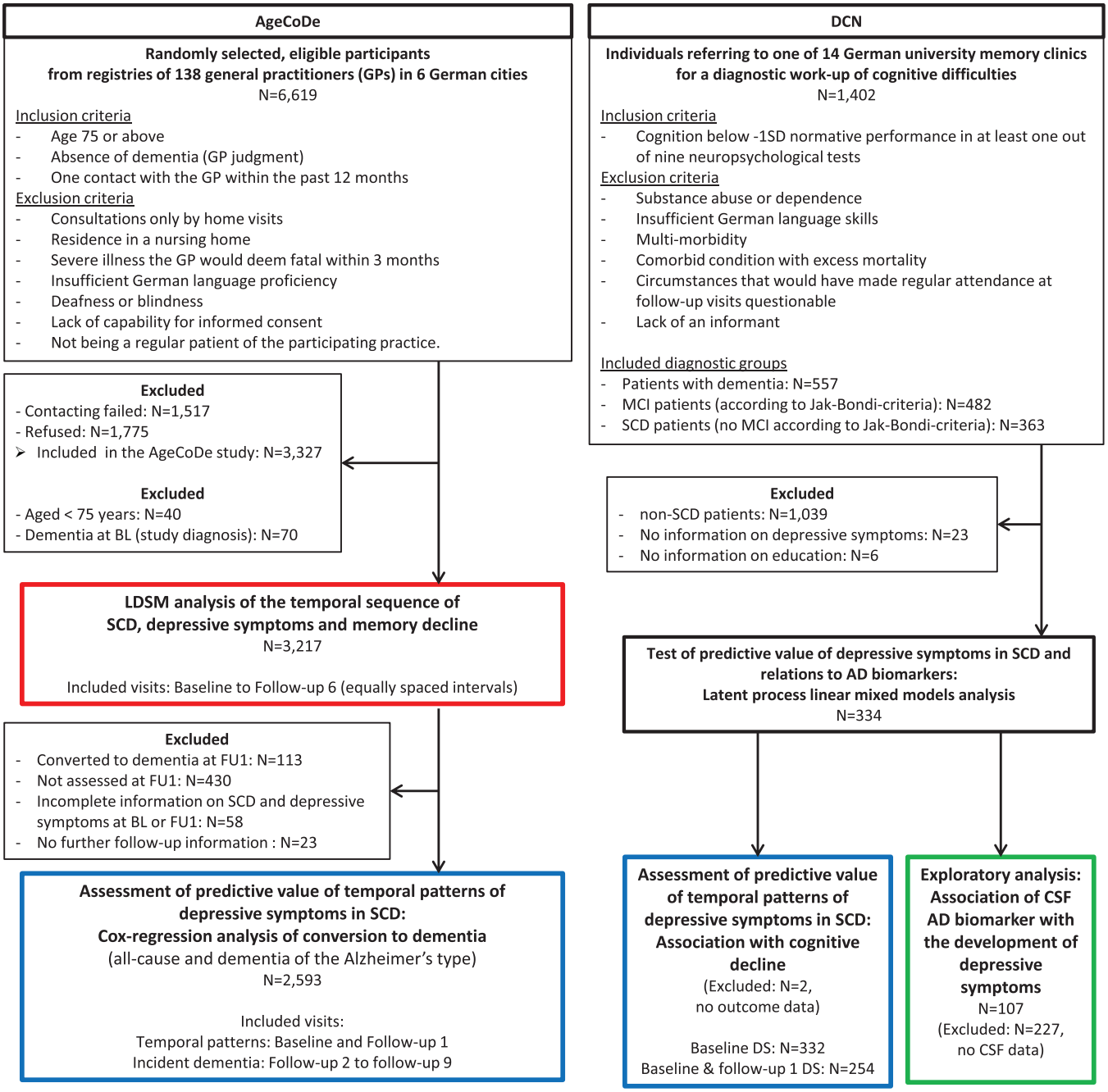

FIGURE 2 Overview of sample selection and performed analyses (boxes printed in bold) for the current study. AD, Alzheimer's disease; BL, baseline; CSF, cerebrospinal fluid; FU1, follow-up assessment 1; LDSM, latent difference score models; MCI, mild cognitive impairment; SCD, subjective cognitive decline

1.4 | Conclusions

We provide evidence that SCD typically precedes DS during the development of cognitive decline and dementia and not vice versa. We also found that SCD in combination with DS is particularly associated with increased dementia risk and with amyloid pathology.

2 | CONSOLIDATED RESULTS AND STUDY DESIGN

To resolve ambiguity regarding origins and outcomes of SCD and DS during cognitive decline, we (1) studied their typical temporal development (Figure 2, red box) and (2) assessed the predictive value of

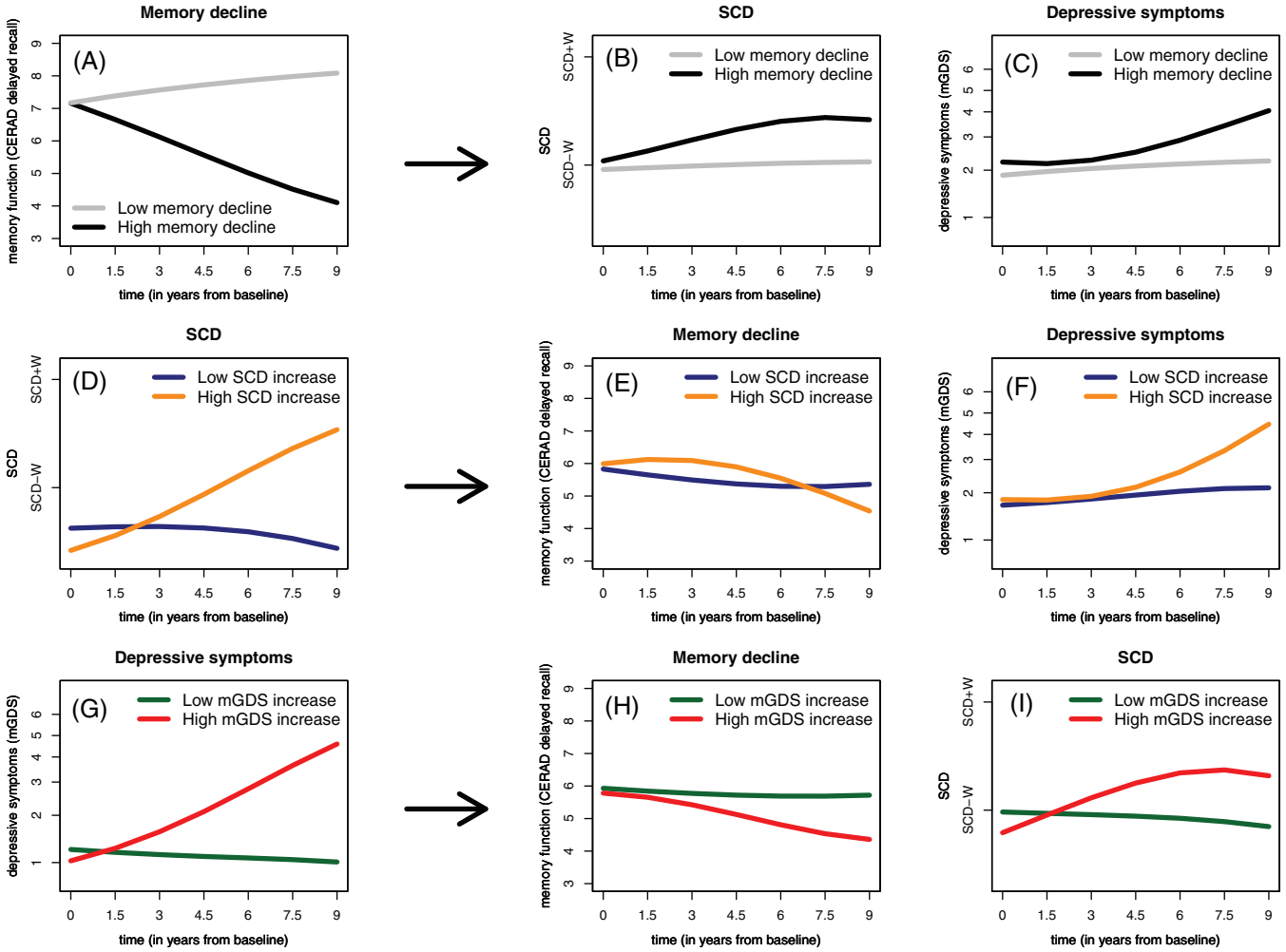

FIGURE 3 Effect of the temporal development of memory decline, SCD, and depressive symptoms on the respective other symptoms. Data are derived from the AgeCoDe study and illustrate the LDSM model. Plots are based on LDSM model parameter estimates. These were used to simulate trajectories of 10,000 hypothetical individuals. First, hypothetical participants with above-median memory function were selected. They were further stratified according to a strong or a weak decline in memory function (defined as above or below median change from baseline to the last follow-up). The resulting averages across all hypothetical participants are shown in the left panel in the top row for memory (A). The resulting average trajectories of SCD (B), and depressive symptoms (C) for these groups are shown in the middle and right panel of the top row, respectively. This procedure was repeated using SCD as the focal variable for sample stratification. Results for SCD (D), memory (E), and depressive symptom (F) trajectories are shown in the middle row. The bottom row shows the results of the procedure with depressive symptoms as the focal variable (G) and the resulting average trajectories for memory decline (H) and SCD (I). The figure illustrates that during objective memory decline, SCD increases earlier than mGDS (B,C). While it takes several years before increasing SCD translates into further cognitive decline and increase of depression (E,F), increasing depression is associated with a parallel change in memory function and SCD (G–I). AgeCoDe, German study on Ageing, Cognition and Dementia; LDSM, latent difference score models; mGDS, modified geriatric depression scale excluding the item on subjectively perceived memory problem; SCD, subjective cognitive decline; SCD−W, SCD without worries about subjectively perceived memory decline; SCD+W, SCD with worries about subjectively perceived memory decline

their temporal patterns for symptomatic disease progression (Figure 2, blue boxes) in participants from the AgeCoDe and DCN. Descriptive statistics are presented in Table 1. All patients gave written informed consent before inclusion in the studies.

2.1 | Sample description: AgeCoDe

AgeCoDe is a prospective longitudinal cohort of dementia-free adults aged 75 or above (Text S2 in supporting information). Participants were randomly selected from medical registers of 138 general practitioners in six German cities. After baseline interviews, participants were reassessed in six follow-up waves (every 1.5 years) and then in three additional follow-ups (every 10 months). Dementia diagnoses were determined in a consensus conference with the interviewer and an experienced geriatrician or geriatric psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria. DAT was established according to National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria (Text S2 in supporting information).

TABLE 1 Baseline characteristics of included participants

	AgeCoDe		DCN			
	total sample ($N = 3217$)		Sample used in cognitive decline analyses ($N = 334$)		CSF biomarker sample ($N = 107$)	
	Mean/*N*	SD/%	Mean/*N*	SD/%	Mean/*N*	SD/%
Age at baseline (mean/SD)	79.7	3.59	66.5	8.72	67.22	8.17
Male sex (*N*/%)	1111	34.5%	198	59.3%	74	69.16%
Education						
Low (*N*/%)	1991	65.5%	–	–	–	–
Middle (*N*/%)	883	27.4%	–	–	–	–
High (*N*/%)	343	10.7%	–	–	–	–
Years of education (mean/SD)	–	–	12.64	3.00	12.42	3.00
CERAD delayed recall at baseline (mean/SD)	5.43	2.23	6.04	2.03	5.79	2.07
ADAS-Cog 11 at baseline (mean/SD)	–	–	9.26	3.73	10.21	3.75
mPACC at baseline (mean/SD)	–	–	-0.03	3.27	-0.67	3.18
SCD at baseline						
No SCD (*N*/%)	1341	41.7%	–	–	–	–
SCD without worries (*N*/%)	1337	41.6%	–	–	–	–
SCD with worries (*N*/%)	539	16.8%	–	–	–	–
Depressive symptoms at baseline						
GDS score (mean/SD)	2.25	2.32	–	–	–	–
GDS score excluding SCD item (mean/SD)	2.18	2.26	–	–	–	–
MADRS (mean/SD)	–	–	7.47	6.42	7.46	6.50
Number of conversions to dementia (*N*/%)	748	23.37%	31	9.3%	16	14.9%
Number of conversions to DAT (*N*/%)	511	17.24%	22	6.6%	12	11.21%
Mean observation time (mean/SD)	6.35	3.91	2.19	0.89	2.15	0.90
$A\beta_{1\text{-}42}$ (mean/SD)	–	–	–	–	760.76	309.81
p-tau181 (mean/SD)	–	–	–	–	56.76	28.66
Total tau (mean/SD)	–	–	–	–	379.03	235.17

Abbreviations: Aβ, amyloid beta; AgeCoDe, Ageing, Cognition and Dementia cohort; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CSF, cerebrospinal fluid; DAT, dementia of the Alzheimer's type; DCN, Dementia Competence Network; GDS, Geriatric Depression Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; mPACC, memory-focused Preclinical Alzheimer Cognitive Composite 5; p-tau, phosphorylated tau; SD, standard deviation.

Using a population-based cohort of older individuals allowed us to study the typical development of SCD and DS as well as their predictive value with regard to dementia in the general population.

2.2 | Sample description: DCN

To assess the predictive value of temporal symptom patterns of DS in SCD in a specialist memory clinic setting, 334 cognitively normal SCD patients from the DCN study were included (Text S3 in supporting information). DCN was a multi-center longitudinal observational study (three annual follow-up assessments) including patients referring to 1 of 14 German university memory clinics for diagnostic work-up of cognitive complaints. Patients selected for this analysis were free of dementia and did not show cognitive impairment according to the Jak-Bondi criteria for mild cognitive impairment (MCI),[39] which are recommended to differentiate SCD from MCI.[40] As per DCN inclusion criteria, they had to have at least one "deviant" test result (−1 standard deviation) out of nine cognitive tests. However, such slight deviations in single tests are highly likely to occur even in normative controls.[41]

2.3 | Typical temporal development of SCD and DS in the AgeCoDe cohort

To understand the typical development of SCD and DS during cognitive decline, a trivariate LDSM[13,14] was used (Section 3.1 and Text S4 in supporting information). LDSM are structural equation models that

allow modeling of the trajectory of change in multiple variables while accounting for their dynamic relationship and potential lead–lag relationships. To this end, change from one time point to another (i.e., latent difference score) is modeled in each variable and related to previous levels in each variable (Figure S2 in supporting information). Effects of levels on change were held constant across time to capture the continuous relationship between their developments. In our analysis, SCD was assessed on a three-point rating scale (no SCD/SCD without worries/SCD with worries, Section 3.1.1.), DS was measured using the self-report geriatric depression scale (GDS-15)[42] excluding the item assessing difficulties with memory (mGDS), and objective memory decline was assessed using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list delayed recall.[43]

We found that higher levels of SCD predicted future increase in DS and decline in memory. Worse memory function, in turn, predicted an increase of DS. In contrast, higher DS predicted less decline in memory function and less increase in SCD. In line with this, simulated model-based trajectories of individuals showing a strong decline in memory from previously high levels suggested that SCD increases first, followed by a subsequent increase in DS (Figure 3A–C). Hence, DS typically develops subsequently to SCD if cognition declines.

2.4 | Predictive value of temporal patterns of DS in SCD in AgeCoDe and DCN and association with CSF AD biomarkers

Next, we assessed whether this temporal sequence can be translated into a predictor of cognitive decline and dementia in two different settings (population-based, memory clinic).[29,30] We used reports on depressive symptoms at baseline (BL) and first follow-up (FU1). The time interval between was 18 months in AgeCoDe and 12 months in DCN. We distinguished between (1) persistently low DS (BL DS−/BL DS−), (2) decreasing DS (BL DS+/BL DS−), (3) increasing DS (BL DS−/BL DS+), and (4) persistently high DS (BL DS+/BL DS+). To increase group size, we additionally pooled persistently high and increasing DS groups as well as decreasing and persistently low DS. High (DS+) and low (DS−) DS was operationalized by median split.

In the population-based AgeCoDe cohort, the association of temporal DS patterns (as measured by mGDS at baseline and FU1) with risk of conversion to incident all-cause dementia and DAT (follow-up 2–follow-up 9) was tested by Cox regression analyses using dementia-free participants at FU1 ($N = 2593$, Figure 2).

We found that persistently high levels of DS at baseline and FU1 were associated with increased all-cause dementia risk in the whole group (Table 2, Table S1 in supporting information). However, this association was only significant in individuals with SCD at baseline but not in individuals without SCD. Furthermore, a pattern of increasing DS was associated with increased dementia risk only in individuals with SCD at baseline. Interaction analyses (Section 3.2) confirmed that the co-occurrence of SCD with a pattern of increasing or persistently high mGDS reports is associated with a particularly strong increase in dementia risk compared to decreasing or persistently low mGDS report pattern (Table S2 in supporting information). When using DAT as outcome, results were similar but slightly less pronounced (Section 3.2, Tables S1, S2 in supporting information).

In SCD patients from the DCN study ($N = 334$, up to 4 years of follow-up), DS was assessed using the interview-based Montgomery–Åsberg Depression Rating Scale (MADRS).[44] Due to lower sample size and shorter follow-up compared to AgeCoDe, we used longitudinal cognitive decline as the outcome, which can offer higher statistical power compared to time-to-event (i.e., conversion to dementia) analyses.[45] Specifically, the Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog 11)[46] and a modified version of the memory-focused Preclinical Alzheimer Cognitive Composite 5[47] (mPACC5, Text S3 in supporting information) served as outcome measures. Analyses were performed using latent process mixed models[49] to account for non-equal interval scaling.

Using the same approach to define temporal patterns of DS as in AgeCoDe, we found that a pattern of persistently high or increasing MADRS values was significantly associated with an increased cognitive decline in both outcomes (Section 3.3, Table S3 in supporting information).

In addition, we found that higher levels of DS at baseline predicted increased cognitive decline in both outcomes (Figure 4A, Section 3.3, Table S3). This result is expected because SCD patients from memory clinics are at particular risk of being in a progressed disease stage[29] and, according to our results from AgeCoDe, they should have higher DS, potentially as a consequence of their experience of cognitive decline.

An exploratory analysis revealed an association of lower (i.e., more pathological) CSF $A\beta_{1\text{-}42}$ values with longitudinal increase of MADRS (Figure 4B, Table S4 in supporting information).

3 | DETAILED METHODS AND RESULTS

3.1 | LDSM analysis in AgeCoDe

3.1.1 | Methods

LDSM models were fitted in Mplus version 7.3 using data from the first seven visits providing equally spaced assessment intervals (18 months). SCD was assessed on a 3-point rating scale using the questions "Do you feel like your memory is becoming worse?" with possible answers "no," "yes, but this does not worry me," and "yes, this worries me." We used the CERAD word list delayed recall[43] test to assess the same cognitive domain that was addressed in the SCD question, namely memory. DS were measured using the mGDS, that is a modified 15-item version of the self-report GDS-15[42] excluding the item on memory difficulties. SCD and mGDS were modeled as categorical variables, CERAD word list recall was modeled as a continuous variable using the mean- and variance-adjusted weighted least square estimator (WLSMV) and the theta parameterization. A latent slope and intercept factor was included and regressed on age, sex, and education. Missing data were handled using multiple imputation (Text S4 in

TABLE 2 Associations of patterns of DS reports with conversion to all-cause dementia depending on SCD status at baseline

	Whole cohort ($N = 2593$)			No SCD at baseline ($N = 1085$)			SCD at baseline ($N = 1508$)		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Persistently low DS[a]	Ref	–	–	Ref	–	–	Ref	–	–
Decreasing DS[b]	1.12	0.83–1.50	.456	0.95	0.54–1.65	0.843	1.18	0.83–1.68	.348
Increasing DS[c]	1.18	0.91–1.52	.222	0.68	0.39–1.21	0.195	**1.40**	**1.04–1.88**	**.028**
Persistently high DS[d]	**1.48**	**1.23–1.79**	**$4.8*10^{-5}$**	1.25	0.88–1.78	0.214	**1.54**	**1.23–1.94**	**$2.1*10^{-4}$**
Persistently high or increasing DS[e]	**1.35**	**1.15–1.60**	**$3.1*10^{-4}$**	1.05	0.77–1.44	0.749	**1.45**	**1.19–1.77**	**$2.0*10^{-4}$**

Note: Data are from the AgeCoDe study. Significant associations are printed in bold. Analyses were controlled for age, sex, and education.
[a]Persistently low DS is defined as mGDS below median at baseline and follow-up 1.
[b]Decreasing DS is defined as mGDS above median at baseline and mGDS below at follow-up 1.
[c]Increasing DS is defined as mGDS below median at baseline and mGDS above at follow-up 1.
[d]Persistently high DS is defined as mGDS above median at baseline and follow-up 1.
[e]Effect of persistently high or increasing DS compared to persistently low or decreasing DS.
Abbreviations: AgeCoDe, Ageing, Cognition and Dementia cohort; CI, confidence interval; DS, depressive symptoms; HR, hazard ratio derived from Cox regression analysis; mGDS, subjective difficulties with memory; Ref, reference group; SCD, subjective cognitive decline.

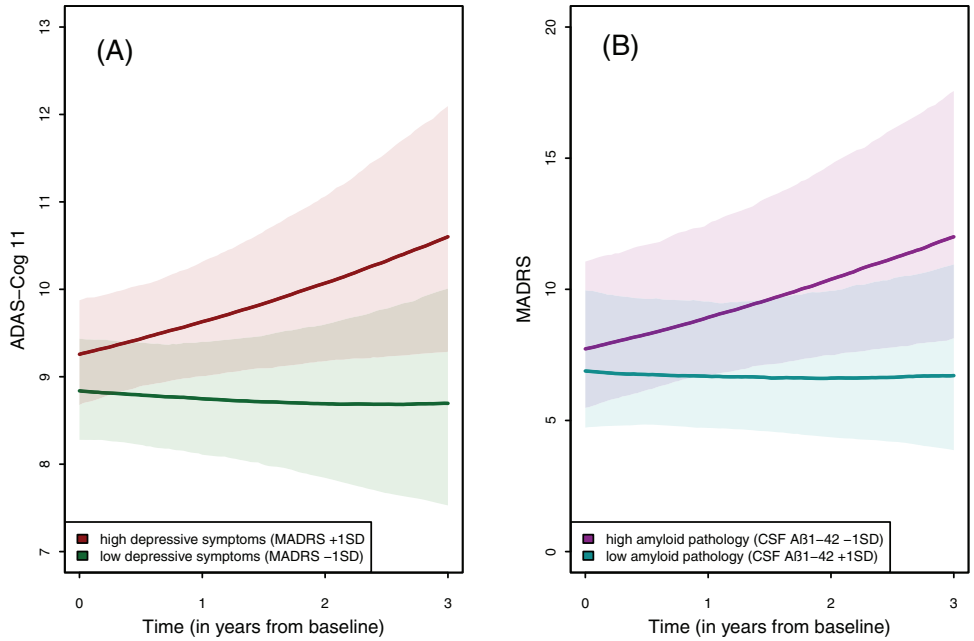

FIGURE 4 Association of baseline depressive symptoms with cognitive decline (A) and baseline amyloid pathology with change in depressive symptoms (B) in memory clinic SCD patients. A, Results from the latent process mixed model associating depressive symptoms (as measured by the MADRS) at baseline with cognitive decline over time (as measured by the ADAS-Cog 11). Plotted trajectories correspond to individuals with MADRS values above (high depressive symptoms) versus below (low depressive symptoms) one standard deviation from the sample mean. Higher ADAS-Cog 11 values indicate worse cognitive function. Shaded areas show 95% confidence intervals of the predicted trajectories. B, Results from the latent process mixed model associating amyloid pathology (as measured by CSF $A\beta_{1\text{-}42}$) at baseline with change in depressive symptoms over time (as measured by the MADRS). Plotted trajectories correspond to individuals with CSF $A\beta_{1\text{-}42}$ values above (low amyloid pathology) and below (high amyloid pathology) one standard deviation from the sample mean. Higher MADRS values indicate more depressive symptoms. Lower CSF $A\beta_{1\text{-}42}$ values indicate more amyloid pathology. Shaded areas show 95% confidence intervals of the predicted trajectories. Aβ, amyloid beta; ADAS-Cog 11, Alzheimer's Disease Assessment Scale Cognitive subscale; CSF, cerebrospinal fluid; MADRS, Montgomery–Åsberg Depression Rating Scale; SCD, subjective cognitive decline

supporting information). For the assessment of model fit we considered a root mean square error of approximation (RMSEA) ≤ 0.05, comparative fit index (CFI) ≥ 0.95, and Tucker–Lewis index (TLI) ≥ 0.95 as a good fitting model. Further modeling details are elaborated in Text S4 in supporting information.

To illustrate model predictions, we simulated model-based trajectories for each variable (on the latent variable scale) for 10,000 hypothetical individuals. To demonstrate the association of an increase in a selected variable on the other two, we extracted trajectories from those hypothetical individuals showing below median levels in SCD

and DS or above median levels of memory performance, respectively. To differentiate between different magnitudes of change over time, we further stratified by median change from baseline to the last measurement in the selected variable. We plotted the average level of all three variables at each time point to show the effect of the occurrence of a selected symptom on the other two. Results are shown in Figure 3.

3.1.2 | Results

LDSM model showed a good fit to the data (RMSEA = 0.031, CFI = 0.978, TLI = 0.977). In the LDSM model, higher SCD predicted a decline in memory function (Est [standard error (SE)] = −0.543 [0.107], $P = 4.2^{*}10^{-7}$) and increase in mGDS (Est [SE] = 0.412 [0.155], $P = .008$). Lower memory function predicted an increase of mGDS (Est [SE] = −0.092 [0.039], $P = .020$). Higher mGDS, in turn, predicted less increase in SCD (Est [SE] = −0.225 [0.104], $P = .031$) and less decline in memory function (Est [SE] = 0.154 [0.078], $P = .048$).

Model-predicted trajectories show that a stronger decrease of memory function in individuals with above-average memory function at baseline is associated with an increase in both SCD and mGDS (Figure 3A–C). Importantly, SCD increases earlier than mGDS (Figure 3B,C). Furthermore, the model suggests that it takes several years before increasing SCD translates into further cognitive decline and increase in mGDS (Figure 3E,F). In contrast, an increase of mGDS is paralleled by an ongoing change in memory function and SCD that slows down over time (Figure 3G–I).

3.2 | Sensitivity analysis and interaction analysis using Cox regression in AgeCoDe

3.2.1 | Methods

Cox regression analyses were performed using the survival R package. We tested differences in association of DS pattern with incident dementia between individuals with and without SCD reports at baseline based on interaction analyses. Here, individuals with a persistently high or increasing pattern were pooled in one group and individuals with a persistently low or decreasing pattern of DS were pooled to increase group size and ease interpretation of the interaction analyses. Importantly, pooled groups showed similar associations with dementia risk in the main analysis (Table 2). Interaction was assessed on the multiplicative scale (hazard ratio [HR] of the product term of SCD and DS patterns in Cox regression) as well as on the additive scale (i.e., relative excess risk due to interaction [RERI] as implemented in the epiR R package).[48]

To test the potential influence of analytic decisions on our results, sensitivity analyses were performed by repeating analyses excluding cognitively impaired individuals at FU1, using conversion to DAT as the outcome (non-DAT conversions coded as censored) and by defining high and low DS based on the GDS-15 cut-off indicating clinically relevant depressive symptomatology (GDS-15 ≥ 6).[42]

3.2.2 | Results

Table S1 in supporting information summarizes the results from the sensitivity analysis, which were highly similar to the results from the main analysis (Table 2). However, when excluding individuals with a cognitive impairment at FU1 or when using DAT as the outcome of the Cox regression, the pattern of increasing DS in individuals reporting SCD did not reach significance, probably due to lower sample size in these analyses. When using an established cut-off for "presence of a depressive symptomatology" (original GDS ≥ 6) to define high and low DS, persistently high DS were associated with increased dementia risk in individuals without SCD at baseline.

Results from the interaction analyses (Table S2 in supporting information) provided evidence for interaction on both the additive scale (RERI [95% confidence interval (CI)] = 0.57[0.16–0.97]), and the multiplicative scale (HR [95% CI] = 1.47 [1.02–2.12]). However, interaction tests were no longer significant when using DAT as outcome or when using the cut-off for "presence of a depressive symptomatology" to define high DS. This could again be attributed to lower sample size or slightly more SCD-independent association of DS with dementia risk in case of a stronger elevation of DS, respectively.

3.3 | Latent process mixed model analyses in DCN

3.3.1 | Methods

We used one-class, univariate latent process mixed models as implemented in the R package lcmm[49] to assess the effect of the interaction of time with DS or CSF biomarkers on the cognitive outcomes. Non-equal interval scaling of the cognitive measures was taken into account by modeling a beta-link function. We included a random intercept and a random slope of time and controlled for fixed effects of age, sex, education, and their interaction with time. DS at baseline (as measured by MADRS) and CSF AD biomarkers ($A\beta_{1\text{-}42}$, phosphorylated tau [p-tau]181, total tau; Text S3 in supporting information) were entered as continuous variables. Of note, 78 individuals did not have DS reports available at FU1 of DCN and were thus excluded from the analysis of two time point DS patterns.

Because we performed analyses using two outcomes, different coding schemes of DS and multiple biomarkers, we performed Benjamini–Hochberg multiple-testing correction[50] on all associations of DS or CSF biomarkers with change in either cognition or DS.

3.3.2 | Results

Table S3 in supporting information provides the results of the mixed model analyses on the association of DS with cognitive decline in the

ADAS-Cog 11 or mPACC5 (Text S3 in supporting information). Across both outcomes, analyses revealed significant associations of increased levels of DS at baseline (ADAS-Cog 11: Est [SE] = 0.022 [0.007], $P = .001$; mPACC5: Est [SE] = −0.015 [0.007], $P = .035$). Associations of baseline DS level with ADAS-Cog 11 but not mPACC5 were significant after multiple testing correction. In addition, a pattern of persistently high or increasing DS was significantly associated with cognitive decline (ADAS-Cog 11: Est [SE] = 0.282 [0.093], $P = .002$; mPACC5: Est[SE] = −0.220 [0.094], $P = .020$). These associations withstood correction for multiple testing. Analyzing individual temporal patterns of DS again indicated an association of persistently high pattern of DS and an increasing pattern of DS with cognitive decline, although associations appeared to be less consistent across outcomes and not all associations were significant after multiple testing corrections.

Table S4 in supporting information presents the results on the association of CSF AD biomarkers with longitudinal change in DS. Only the association of $A\beta_{1\text{-}42}$ with change in DS (Est [SE] = −0.001 [< 0.001], $P = .019$) was significant after correction for multiple testing. A nominally significant association of higher p-tau181 values with baseline MADRS (Est [SE] = 0.011 [0.005], $P = .049$) was observed.

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CONFLICTS OF INTEREST

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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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