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Cognitive performance before and after the onset of subjective cognitive decline in old age

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Abstract

Background: Our objectives were (1) to test the association between the report of subjective cognitive decline (SCD) and prospective objective cognitive performance in high age individuals and (2) to study the course of longitudinal cognitive performance before and after the first report of SCD.

Methods: Cognitively normal elderly participants of the German Study on Ageing, Cognition, and Dementia study (N = 2330) with SCD (subjective decline in memory with and without associated concerns) and without SCD at baseline were assessed over 8 years with regard to immediate and delayed verbal recall, verbal fluency, working memory, and global cognition. Baseline performance and cognitive trajectories were compared between groups. In addition, cognitive trajectories before and after the initial report of SCD (incident SCD) were modelled in those without SCD at baseline.

Results: Baseline performance in the SCD group was lower and declined more steeply in immediate and delayed verbal recall than in the control group (no SCD at baseline). This effect was more pronounced in the SCD group with concerns. Incident SCD was preceded by decline in immediate and delayed memory and word fluency.

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Conclusions: SCD predicts future memory decline. Incident SCD is related to previous cognitive decline. The latter finding supports the concept of SCD indicating first subtle decline in cognitive performance that characterizes preclinical Alzheimer's disease.

Keywords: Subjective cognitive decline; Preclinical Alzheimer's disease; Early detection

1. Introduction

Evidence from clinical and epidemiological studies suggests that subjective cognitive decline (SCD) may represent the initial symptomatic manifestation of Alzheimer's disease (AD) before mild cognitive impairment (MCI) [1]. A number of studies found that subjective cognitive decline (SCD) in the cognitively normal elderly is associated with an increased risk of dementia [2–4] particularly in cases where individuals report concern about memory decline [5]. Hypothetically, SCD may represent the self-experience of subtle cognitive decline, before impairment on cognitive tests occurs [1].

Cross-sectional studies in epidemiological samples, however, often did not find an association between SCD and objective memory performance [6–8]. In large cohorts, weak associations between SCD and memory performance in unimpaired elderly individuals have been observed [9–12]. One potential explanation for the small magnitude of the cross-sectional association of SCD with cognitive performance is that SCD relates to individual cognitive trajectories (decline) rather than to cross-sectional abilities.

Only a few studies have addressed the association of SCD with trajectories of cognitive decline. Those with follow-up periods of less than 5 years did not find such associations [13,14]. However, Jorm et al. [15] assessed 331 elderly nondemented individuals over 70 years of age three times over 7.6 years and showed that memory complaints were associated with past memory performance and future memory decline. In that study, anxiety and depression were the strongest predictors of memory complaints. In a population cohort aged 62 to 85 years, (N = 1168), Dik [16] found that baseline memory complaints were associated with a decline in delayed memory, information processing speed, and overall cognition on the Mini-Mental State Examination (MMSE) over 6 years. Hohman et al. [17] repeatedly assessed 98 cognitively normal subjects (mean age = 75 years) with various cognitive instruments including the Cognitive Failures Questionnaire (CFQ) during an average of 11.5 years. Higher CFQ values, aggregated over several follow-ups, were associated with the speed of decline in immediate and delayed verbal memory. This relationship was not present in figural memory or executive function.

These studies with extended follow-up suggest that in elderly subjects SCD may be associated with accelerated memory decline. It is not known, however, how specific concerns (worries) associated with SCD affect the risk of cognitive decline as opposed to SCD without concerns. Also it is not known to what extent the decline in individual cognitive domains occurs before the first report of SCD.

In this study, we examine the relationship of subjective decline in memory, as one particular type of SCD, in association with and without concerns with future and preceding performance in different cognitive domains. We assessed a large cohort of unimpaired elderly subjects over 8 years and conducted growth curve modeling (GCM) of cognitive performance data.

2. Methods

2.1. Sample

The German Study on Ageing, Cognition, and Dementia (AgeCoDe) in primary care patients is an ongoing multicenter prospective study in elderly individuals with a focus on the identification of risk factors and predictors of cognitive decline and dementia. Details about the sampling method and selection process are described in previous publications [5]. A total of 3327 subjects free of dementia at baseline were recruited from general practitioner (GP) registries and assessed with structured clinical interviews and cognitive tests. Main inclusion criteria were ages greater than 75 years, native German language, absence of severe hearing or vision impairments, and residing at home rather than in an institution. The approval of this study was provided by the local ethics committees of the Universities of Bonn, Hamburg, Düsseldorf, Heidelberg/Mannheim, Leipzig, and Munich. All subjects gave written informed consent before the participation in this study.

2.2. Assessment

Subjects were interviewed in their home environment by trained psychologists or physicians at baseline and at all follow-up examinations, which were 18 months apart.

Subjective memory capacity was assessed with the question: "Do you feel like your memory is becoming worse?" The possible answers were "no," "yes, but this does not worry me," or "yes, this worries me." The same question was asked at each of five follow-up visits, which occurred at 18 months intervals.

A 10-item word list learning task and a semantic verbal fluency task from the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) neuropsychological battery [18], was applied at baseline and at all follow-ups. The CERAD 10-item word list consists of three immediate

recall trials. Immediate recall performance equals the sum of recalled words across three presentations of the list. Delayed recall refers to the free recall of the 10-item word list after a delay of approximately 10 minutes filled with other tasks. The CERAD verbal fluency test consists of a 1-minute task for naming animals. The number of correct names given, without duplicates, is used as the score.

In addition, we administered the Structured Interview for the diagnosis of dementia of the Alzheimer type, multi-infarct dementia and dementia of other etiology according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* and *International Classification of Diseases, Tenth Revision (ICD-10)* (SIDAM) [19]. The cognitive assessment of the SIDAM (SISCO) contains the Mini-Mental State Examination (MMSE) [20] and additional items for the assessment of four different areas of cognition: orientation, memory, intellectual abilities, and higher cognitive functions (subscales verbal working memory, constructional abilities, aphasia, and apraxia). For this study, a verbal working memory composite score was used, which consists of seven items, including subtraction calculations (e.g. 9-3 = ?), backward spelling of a word, and backward digit span. The MMSE served as a measure of global cognition in the present analyses.

Depressive symptoms were assessed with the 15-item version of the Geriatric Depression Scale (GDS) [21]. Level of education was categorized as low, middle, or high using the Comparative Analysis of Social Mobility in Industrial Nations educational classification instrument [22]. *apolipoprotein (APOE) ε4* genotyping was performed in all subjects.

At follow-up, dementia was diagnosed according to DSM-IV criteria, applying the diagnostic algorithm of the SIDAM that makes use of the SISCO score as a cognitive measure and impairment in activities of daily living scale (SIDAM ADL scale). The diagnosis of AD-type dementia was made according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria. All diagnoses were made in consensus by the interviewer, experienced geriatric psychiatrists, or geriatricians.

For those subjects, who could not be interviewed in person at follow-up the Global Deterioration Scale [23] and the subscales "Changes in Performance of Everyday Activities" and "Changes in Habits" of the Blessed Dementia Scale [24] were completed by the interviewer with an informant (spouse, relative, caregiver) and/or with the GP. Based on this information the diagnosis of dementia was established.

2.3. Group definitions

Only cognitively normal subjects (n = 2330), performing within 1 standard deviation (SD) of the normative SISCO domain scores, derived in an independent study [25], at baseline were included in the present analyses.

Subjects with a negative response to the SCD question (see section 2.2) served as controls (CO, n = 993), and were compared with subjects reporting a memory decline, either without associated concerns (worries) (SCD-C, n = 965), or with associated concerns (SCD+C, n = 372).

2.4. Follow-up assessment rates

Five follow-up waves with 18 months intervals after baseline are the basis for the present analyses. The number of personal interviews was 2049 (87.9%) at follow-up 1, 1825 (78.3%) at follow-up 2, 1505 (64.6%) at follow-up 3, 1259 (54%) at follow-up 4, and 1037 (44.5%) at follow-up 5.

The main reasons for not obtaining a personal interview were (1) refusal of a personal visit because of several reasons, including, but not limited to bad medical conditions (follow-up 1: 58.7%, follow-up 2: 47.4%, follow-up 3: 47.2%, follow-up 4: 24.2%, follow-up 5: 15.4%) and (2) death (follow-up 1: 32%, follow-up 2: 48%, follow-up 3: 41.5%, follow-up 4:36.7%, follow-up 5: 36.5%). Informant-based information on those participants without personal interview was obtained on 273 participants at follow-up 1, on 222 at follow-up 2, on 316 at follow-up 3, on 197 at follow-up 4, and on 180 at follow-up 5. The combined follow-up rates (personal interview, informant-based information only) were 99.7% at follow-up 1, 87.9% at follow-up 2, 78.2% at follow-up 3, 62.5% at follow-up 4, and 52.2% at follow-up 5. Note that individuals were not followed-up anymore in the case of incident dementia or informant-based information only at one follow-up.

2.5. Statistical analyses and modeling

In the first set of analyses, we modeled cross-sectional and longitudinal group differences (according to SCD status at baseline) in each cognitive domain (verbal immediate and delayed recall, verbal fluency, working memory, global cognition) of those subjects with personal interview including all follow-ups. In addition, we conducted analyses with reduced number of follow-ups to investigate the minimal time span after which differential decline became significant.

GCM were estimated with Mplus 7 [26]. A quadratic term was included where it improved the models over fitting only a linear trend [27]. Participant attrition and missing data were addressed with the full information maximum likelihood method [28]. Time was treated with fixed time scores as intervals between measurements were approximately of equal distance. The Akaike Information Criterion, Bayesian information criterion (BIC), sample size adjusted BIC, root mean square error of approximation (RMSEA) [29], chi square fit index, and comparative fit index (CFI) [30] were used as indices of model fit. A CFI value greater than 0.95 and an RMSEA value of 0.04 or less indicate a very good model fit [31,32]. The maximum likelihood with robust standard errors method was used for model estimation, allowing for robust estimation even if the assumption of normal distribution was challenged. We report maximum likelihood parameter estimates and significance values.

Following the general GCM recommendations of McArdle and Grimm [33], we used an unconditional model to estimate the dependent variables without covariates (Model 1). If the amount of variance unexplained by Model 1 remained significant, age, gender, years of education, GDS score (dichotomized at the conventional cut-off score of 6 suggestive of depression), and *APOE* ε4 genotype (yes/no) were added as covariates (Model 2). Because a significant amount of residual variance remained after adding the covariates, Model 3, which included the groups (CO, SCD-C, SCD+C) as predictor variables, was generated. To reduce the complexity of this final model, only variables indicative of a significant trend in Model 2 ($P < .1$) remained in Model 3 [34]. To derive a plot of the three group trajectories, a multigroup analysis with stratification by group was conducted.

The CO group was compared with the SCD+C and SCD-C groups using group contrasts adjusted for significant covariates. Three latent factors—intercept (baseline performance), linear slope (change rate), and quadratic slope (quadratic change rate)—were investigated and tested for significance.

In the second set of analyses, only CO subjects (no SCD at baseline) were included. In those, who reported SCD at some point during follow-up, the initial report of SCD-C or SCD+C was defined as incident SCD. Subjects were classified as incident SCD-C if they did report SCD-C, but did not report SCD+C at any follow-up. They were categorized as SCD+C if they additionally showed a concern regarding memory at any follow-up. Thus, a subject reporting no SCD at baseline, SCD-C at follow-up 1, and SCD+C at follow-up 2 was classified as incident SCD+C, with an onset of SCD at follow-up 1. We modeled the trajectories of each cognitive domain before and after incident SCD. We compare stable CO subjects (who never reported SCD) to subjects with incident SCD-C or SCD+C. The time point of incident SCD at follow-up was recoded as zero to estimate cognitive trajectories. In this analysis, the time point zero is incident SCD. The previous time point was recoded as −1, −2, −3, etc., whereas the time points after the incident SCD were recoded as +1, +2, +3, etc. Each time point represents an interval of 18 months (Fig. 2).

By overlaying the trajectories at time point 0, we obtained group trajectories with up to five time points before and after incident SCD. The stable CO group trajectories during follow-up were randomly assigned to the starting time points by computing a uniformly distributed random integer in the range between one and five, similar to the proportional distribution of incident SCD. Sample sizes at the extremes were not sufficient for statistical modeling ($n < 20$). Thus, the analysis was restricted to three time points before and four time points after incident SCD. The preprocessed data were fitted with piecewise linear growth models [35]. Mean change over time from time point −3 to incident SCD was represented as the linear slope before SCD. Incident SCD to time point +4 was represented as the slope after SCD. The time point zero (incident SCD) was the common intercept of the two slopes. The stable CO group was compared with the incident SCD+C and incident SCD-C groups using group contrasts adjusted for covariates.

To control for false positive results we considered only results with $P < .01$ to be significant.

2.6. Predicting incident dementia hazard

In addition to the cognitive trajectories, Cox proportional hazards regression analysis was performed with SPSS 21 (IBM) to model the risk of incident Alzheimer' dementia and of all dementia types as a function of group membership and of the covariates age, gender, education, depression, and *APOE* ε4 genotype.

3. Results

The three groups differed significantly in terms of gender and education, but not in age, *APOE* ε4 genotype, and MMSE (Table 1). Follow-up rates did not differ between groups (χ^2 (8) = 7.814; $P = .452$ n.s.).

In both sets of analyses, the final models of the cognitive trajectories had a good fit throughout (RMSEA < 0.04, CFI > 0.97) and outperformed the unconditional (Model 1) and covariate (Model 2) models. Further details on model fit can be provided by the corresponding author on request.

3.1. Baseline cognitive performance

All groups differed significantly from each other in delayed recall performance with the CO group performing the best, followed by the SCD-C and SCD+C groups (see Fig. 1 and Table 2). In addition, the adjusted group contrasts between CO and SCD+C, and SCD-C and SCD+C, were significant for immediate recall and for the word fluency task. There were no significant differences in working memory and global cognition between groups.

3.2. Cognitive decline trajectories

Fig. 1 displays the estimated means of cognitive trajectories (see Supplementary Material for observed means) for the three groups.

In delayed recall, the adjusted group contrasts of the linear slope revealed significant differences in decline over time between CO and SCD+C, at a trend level between CO and SCD-C, and between SCD-C and SCD+C (see Table 2 and Fig. 1B).

The adjusted group contrasts for immediate recall also showed significant differences between the CO and SCD-C, CO and SCD+C groups, and SCD-C and SCD+C groups. In global cognition, there were significant differences between CO and SCD-C groups, CO and SCD+C groups, and SCD-C and SCD+C groups. There were no

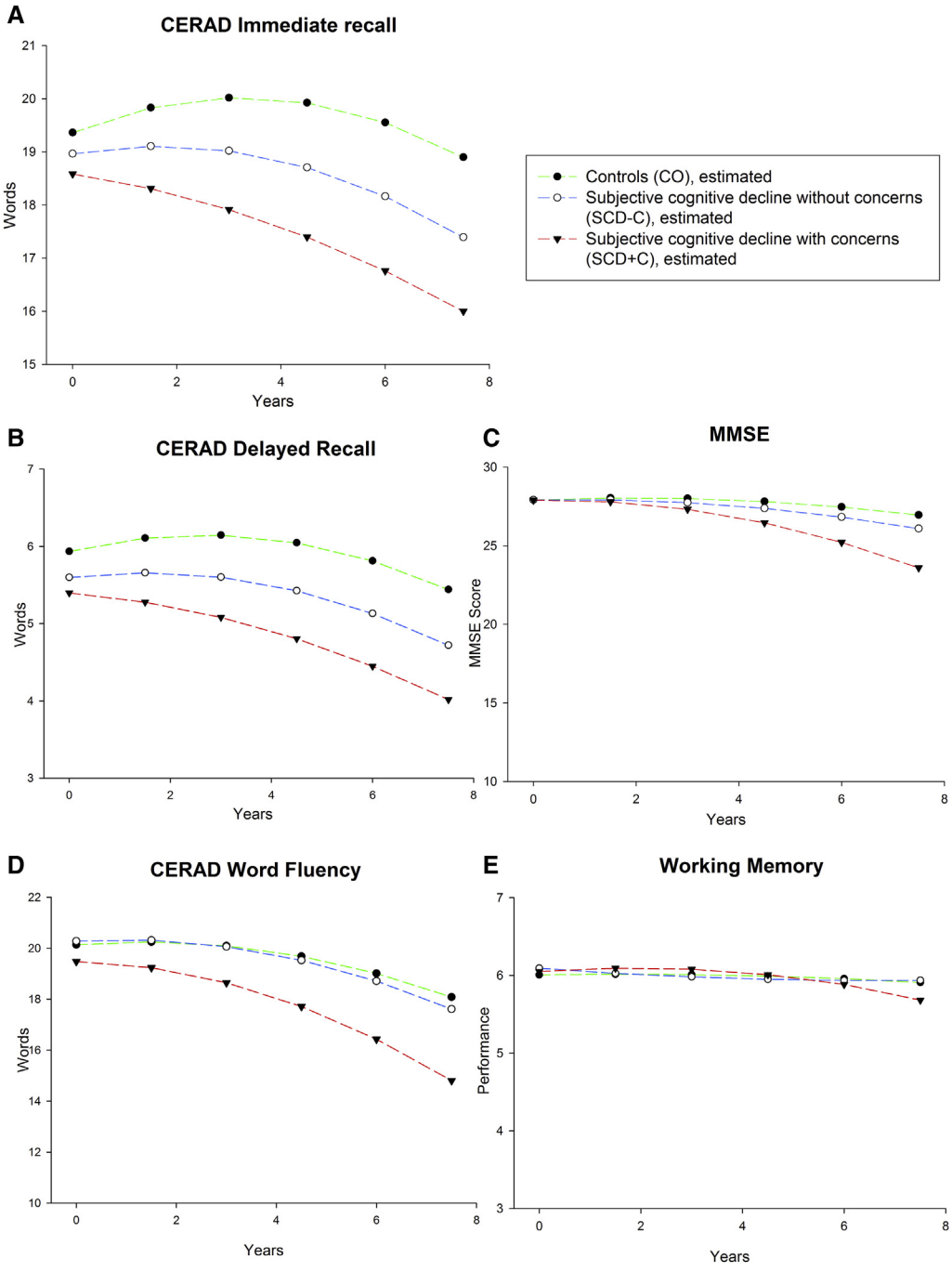

Fig. 1. Trajectories of estimated means for controls (CO), SCD without concerns (SCD-C) and SCD with concerns (SCD+C) controlling for age, gender, education apolipoprotein ε4 -genotype and depression at baseline.

significant differences of slope in the group contrasts for word fluency and working memory.

Models with reduced follow-up time revealed that the rates of decline in all domains were not significantly different before follow-up 4 (respectively, 6 years). Thus, SCD-associated cognitive decline became apparent only 6 years after baseline.

There was no group difference in the quadratic slope in any of the cognitive domains.

3.3. Covariate effects

Covariate effects for the first set of analyses are presented in the Supplementary Material.

3.4. Cognitive performance and incident SCD

Of the 993 individuals free of SCD at baseline, 361 subjects reported SCD without concerns and 146 reported SCD

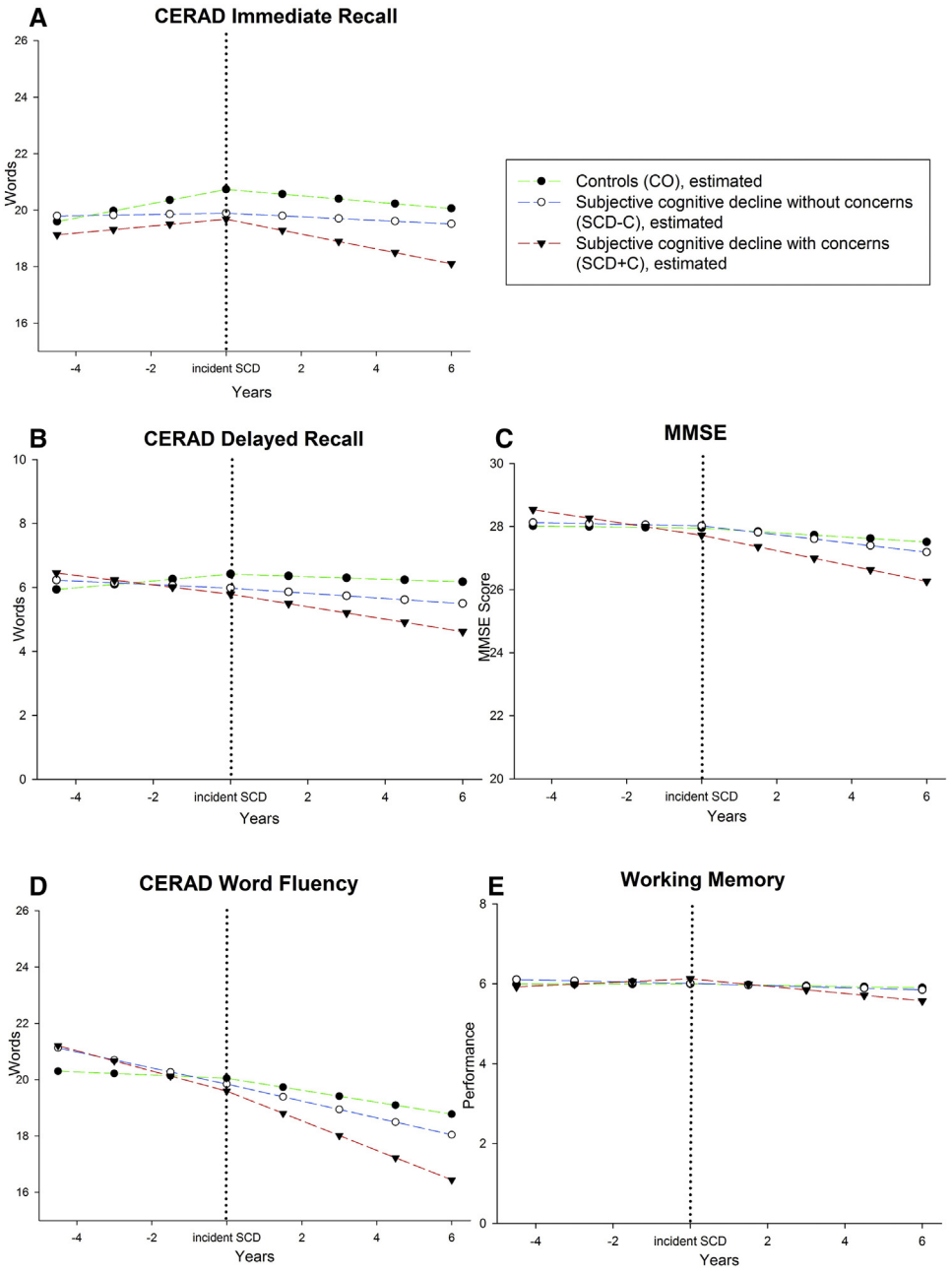

Fig. 2. Trajectories of estimated means for stable controls (CO), converters into SCD without concerns (SCD-C) and converters into SCD with concerns (SCD+C), controlling for age, gender, education apolipoprotein ε4-genotype and depression (at baseline).

with concerns some time during the follow-up period. The median distance of first SCD report from baseline was four assessments (6 years). Fig. 2 shows the cognitive trajectories (estimated means, see Supplementary Material for observed means) before and after incident SCD. Table 3 lists the statistical comparisons.

At the time point of incident SCD, those with incident SCD+C had poorer delayed recall than stable CO. A similar trend was observed for incident SCD-C. There was a significant difference in the slope of delayed recall performance between groups. Although the stable CO increased their performance (possibly due to test repetition effects), the other groups showed a decline in delayed recall preceding their incident SCD (CO vs. SCD-C, CO vs. SCD+C).

A similar pattern was observed for immediate recall: At incident SCD, those with incident SCD+C had poorer immediate recall performance than those with stable CO. The same was observed for incident SCD-C. The immediate recall slopes before incident SCD differed

Table 1
Sample description for groups with and without subjective cognitive decline at baseline

	Groups				Group differences between the three groups	Significant post-hoc tests
	CO	SCD-C	SCD+C	Total sample		
n	993	965	372	2330		
Rate of follow-up in % at follow-up1	85.7	88.8	83.5		χ^2 (8, N = 2330) = 7.814, P = .452, n.s.	
Rate of follow-up in % at follow-up2	73.1	76.6	72.9			
Rate of follow-up in % at follow-up3	58.4	62.7	58.0			
Rate of follow-up in % at follow-up4	47.6	51.3	48.5			
Rate of follow-up in % at follow-up5	36.6	40.6	35.8			
MMSE: mean (SD)	27.97 (1.49)	27.95 (1.51)	27.88 (1.55)	27.95 (1.51)	*P = .672*	
Age in years: mean (SD)	79.39 (3.40)	79.73 (3.56)	79.72 (3.60)	79.58 (3.50)	*P = .065*	
Female, n (%)	661 (66.6)	566 (58.7)	263 (70.7)	1490 (63.9)	χ^2 (2, N = 2330) = 22.04, $P < .0001$	*,‡
Level of education					χ^2 (4, N = 2330) = 16.26, $P < .003$	*,†,‡
Low, n (%)	675 (68.0)	618 (64.0)	262 (70.4)	1555 (66.7)		
Middle, n (%)	241 (24.3)	233 (24.1)	67 (18.0)	541 (23.2)		
High, n (%)	77 (7.8)	114 (11.8)	43 (11.6)	234 (10.0)		
APOE ε4+, n (%)	195 (19.6)	201 (20.8)	78 (21.0)	0.20 (20.3)	χ^2 (2, N = 2330) = 0.54, P = .765	
Incident Alzheimer's dementia within five follow-ups: n	51	88	53	192		
Risk, incident Alzheimer's dementia[§] hazard ratio, *P*-value (CI)	1.0	**1.64** *P = .005* (1.16–2.32)	**2.89** *P = .000* (1.96–4.26)	-		
Incident dementia within five follow-ups: n	88	129	87	304		
Risk, incident dementia[§] hazard ratio, *P*-value (CI)	1.0	**1.41** *P = .014* (1.07–1.85)	**2.63** *P < .001* (1.95–3.55)	-		

Abbreviations: CO, controls (without subjective cognitive decline); SCD-C, SCD (subjective cognitive decline) without concerns; SCD+C, SCD with concerns; SD, standard deviation; *APOE* ε4, apolipoprotein ε4; FU, follow-up interval was 18 months; MMSE, Mini-Mental State Examination; CI, confidence interval; n.s., non-significant.

NOTE. Covariates: age, sex, education (low, medium, high), depressive symptoms (Geriatric Depression Scale scores <6 points or ≥6).

Bolded text indicates significant hazard ratio. Italicized text indicates significant *P*-values.

*CO vs. SCD-C.

†CO vs. SCD+C.

‡SCD-C vs. SCD+C.

§CO group = reference group.

significantly between CO and SCD-C, but not between CO and SCD+C.

For word fluency, there were no significant intercept differences at incident SCD, but before incident SCD there were significant differences in the slopes between the stable CO group and the incident SCD-C and incident SCD+C groups.

There was no significant difference in decline between the groups in working memory either in the intercept at incident SCD or in the slope before incident SCD.

In global cognition, there was a significant difference in performance at incident SCD between SCD-C and SCD+C. Incident SCD+C was preceded by a significant decline in global cognition before incident SCD compared with CO, and also compared with SCD-C.

In none of the studied cognitive domains, there was a group difference in slope after incident SCD.

3.5. Cox regression of SCD as a predictor of incident dementia

In addition to the GCM analyses, we performed a Cox regression analysis to assess the risk of baseline SCD on future dementia of AD-type and of all cause dementia. For AD-type dementia, SCD+C showed a 2.89 times increased risk ($P < .001$) and SCD-C showed a 1.64 times increased risk ($P = .005$) for over five follow-ups in comparison with CO. For dementia of all cause, SCD+C showed a

Table 2
Results of the growth factor estimates with regard to baseline groups

	Immediate recall		Delayed recall		Word fluency		Working memory		MMSE	
	Estimate	*P*-value	Estimate	*P*-value	Estimate	*P*-value	Estimate	*P*-value	Estimate	*P*-value
Intercept										
CO vs. SCD-C	−0.352	.080	**−0.073**	**.004**	0.015	.947	0.040	.315	−0.010	.869
CO vs. SCD+C	**−0.389**	**.000**	**−0.252**	**.000**	**−0.313**	**.034**	0.026	.376	0.064	.125
SCD- vs SCD+C	**−0.504**	**.020**	**−0.271**	**.029**	**−0.713**	**.020**	0.019	.732	0.132	.118
Slope										
CO vs. SCD-C	**−0.352**	**.008**	−0.093	.060	0.018	.915	−0.017	.218	**−0.110**	**.005**
CO vs. SCD+C	**−0.410**	**.000**	**−0.157**	**.000**	−0.130	.238	−0.008	.359	**−0.180**	**.000**
SCD- vs. SCD+C	**0.412**	**.024**	**−0.182**	**.044**	−0.267	.233	−0.007	.742	**−0.246**	**.000**
Quadratic slope										
CO vs. SCD-C	0.027	.354	0.051	.358	−0.029	.404	*		*	
CO vs. SCD+C	0.035	.079	0.014	.142	−0.027	.246				
SCD- vs SCD+C	0.033	.393	0.014	.451	−0.024	.606				

Abbreviations: CO, controls (without subjective cognitive decline); SCD-C, SCD (subjective cognitive decline) without concerns; SCD+C, SCD with concerns; MMSE, Mini-Mental State Examination.

NOTE. In all cognitive domains, *P*-values are corrected for age, gender, education, depression, and apolipoprotein ε4 genotype.

Bold text indicates significant group contrasts.

*Only linear slope was fitted to the data.

2.63 times increased risk ($P < .001$), whereas SCD-C showed a 1.4 times increased risk ($P = .014$).

4. Discussion

Overall, our results show that a report of subjective memory decline, a specific form of SCD, in cognitively normal elderly may predict future objective memory decline and incident dementia. Furthermore, incident subjective memory decline may also reflect past cognitive decline.

As expected, SCD at baseline predicted accelerated decline in episodic memory over 8 years, and the decline was more pronounced in SCD+C. This confirms prior reports [15–17]. The other cognitive decline measures were largely unrelated to the subjective report on memory, suggesting some degree of specificity regarding the association of subjective and objective decline.

Apart from different cognitive trajectories, we also found baseline differences in episodic memory between groups, particularly in the SCD+C group. As expected, greater age, male gender, lower education, depressive symptoms, and having the *APOE* ε4 genotype were associated with poorer baseline cognition, but the effects of SCD were independent from these covariates. Known effects on cognitive decline were replicated in our study. In line with Caselli et al. [36], *APOE* ε4 had an effect on delayed recall, but

Table 3
Results of the growth factor estimates with regard to incident SCD

	Immediate recall		Delayed recall		Word fluency		Working memory		MMSE	
	Estimate	*P*-value	Estimate	*P*-value	Estimate	*P*-value	Estimate	*P*-value	Estimate	*P*-value
Intercept—incident SCD										
Stable CO vs. converters into SCD-C	**−0.724**	**.034**	−0.338	.060	−0.321	.440	−0.005	.949	0.111	.413
Stable CO vs. converters into SCD+C	**−0.615**	**.005**	**−0.332**	**.003**	−0.287	.308	0.027	.633	−0.148	.106
Converters into SCD-C vs. converters into SCD+C	−0.490	.242	−0.329	.139	−0.268	.589	0.082	.451	**−0.389**	**.009**
Slope before SCD										
Stable CO vs. converters into SCD-C	**−0.370**	**.005**	**−0.234**	**.001**	**−0.399**	**.012**	−0.035	.378	0.006	.922
Stable CO vs. converters into SCD+C	−0.161	.105	**−0.174**	**.001**	**−0.265**	**.020**	0.018	.587	**−0.137**	**.006**
Converters into SCD-C vs. converters into SCD+C	0.038	.850	−0.108	.279	−0.120	.612	0.070	.300	**−0.267**	**.003**
Slope after SCD										
Stable CO vs. converters into SCD-C	0.149	.449	−0.004	.970	−0.137	.518	0.013	.803	−0.027	.796
Stable CO vs. converters into SCD+C	−0.025	.827	−0.095	.101	−0.252	.055	−0.045	.237	−0.063	.384
Converters into SCD-C vs. converters into SCD+C	−0.189	.342	−0.184	.065	−0.301	.138	−0.096	.115	−0.118	.273

Abbreviations: CO, controls (without subjective cognitive decline); SCD-C, SCD (subjective cognitive decline) without concerns; SCD+C, SCD with concerns; MMSE, Mini-Mental State Examination.

NOTE. In all cognitive domains, *P*-Values are corrected for age, gender, education, and apolipoprotein ε4 genotype.

Bold text indicates significant group contrasts.

not on MMSE. Age had a significant effect on the level and shape of the trajectories, in line with Gomeni et al. [37], depression had an effect on baseline, but no effect on verbal memory decline, in line with Royall et al. [38]. Education was associated with better baseline performance in all measures.

A novel finding of this study is that, in subjects free of SCD at baseline, incident SCD was preceded by objective memory decline. For delayed recall and also for verbal fluency, the slope of decline in the 4.5 years before incident SCD was stronger in the SCD-C and SCD+C group. Subtle objective decline therefore precedes, and possibly also gives rise to, the report of SCD, supporting the concept that SCD may indicate a subtle decline in cognitive function [1]. This temporal sequence was evident in group analyses but would probably not be detectable on an individual basis.

It is not possible with the present data to exactly determine the time lag between objective and subjective decline. The answer to this question will, however, also depend on the relative sensitivity of the objective and subjective decline assessments used.

Amieva et al. [39] showed that cognitive complaints, assessed with a questionnaire, increased on an average 7 to 8 years before the diagnosis of Alzheimer's dementia, whereas verbal fluency started to drop 12 years before diagnosis. Amieva et al. did not focus on the SCD individuals themselves but their findings are in line with the sequence proposed by this paper. Stewart et al. [40] found that hippocampal atrophy over 4 years preceded incident SCD and this could also be a cause of the memory decline preceding SCD in the current sample.

We here focused on prevalent SCD and incident SCD. However, like other phenotypical classifications (e.g. MCI), SCD is unlikely to be absolutely stable over time. It will be an interesting issue for further research to study the determinants and consequences of SCD stability over time.

In subjects without SCD at baseline or during follow-up, there is a slight increase in memory test scores over the years, probably due to test repetition effects [41]. However, these test repetition effects appear to be outpaced by memory decline in the SCD groups. Reduced test repetition effects in the CERAD word list learning task have also been described before in patients with mild AD [42].

The strengths of our study include the large sample size, the multicentre design, and long follow-up time, the availability of *APOE* ε4 genotyping and application of GCM. The limitations of our study include the lack of brain imaging. Our data do not allow us to elucidate the brain changes that underlie incident SCD. However, elderly help-seeking subjects with SCD (but without mild cognitive impairment) show signs of brain atrophy in the entorhinal cortex [43] and hippocampus [44], glucose metabolism changes [45], and increased Pittsburgh Compound B Positron Emission Tomography beta-amyloid load [46]. Many of these characteristics are indicative of and consistent with the preclinical stages of AD. In addition, SCD has been associated with AD-like pathology in autopsy studies [47,48].

In sum, this study shows that a report of memory decline in old age is partly related to ongoing (past and future) memory decline, and is not merely a depressive interpretation of normal age-related cognitive loss. Furthermore, our data suggest that at the group level, subjects begin to report incident SCD after their memory starts to deviate from normal. This would be consistent with the "self-experience of decline" hypothesis of SCD in the context of preclinical AD.

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RESEARCH IN CONTEXT

1. Systematic review: Subjective cognitive decline (SCD) in memory appears to be a risk factor for future cognitive decline and dementia. The association with trajectories of decline in individual cognitive domains and potentially SCD-preceding cognitive decline are not well studied. The authors investigated a large epidemiological cohort from Germany to address these questions.
2. Interpretation: Subjective decline in memory and related concerns (SCD+C) are related to subtle decline in memory performance. They are risk factors for future decline in memory functions. Before the onset of SCD, memory decline already occurred.
3. Future directions: The study further supports the concept of SCD as a risk factor for cognitive decline and an indicator of very first impairment of cognitive performance in elderly. These results can aid in designing future prevention trials.

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