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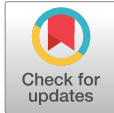
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Featured Article

Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia

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Abstract

Introduction: In this multicenter study on subjective cognitive decline (SCD) in community-based and memory clinic settings, we assessed the (1) incidence of Alzheimer's disease (AD) and non-AD dementia and (2) determinants of progression to dementia.

Methods: Eleven cohorts provided 2978 participants with SCD and 1391 controls. We estimated dementia incidence and identified risk factors using Cox proportional hazards models.

Results: In SCD, incidence of dementia was 17.7 (95% Poisson confidence interval 15.2-20.3)/1000 person-years (AD: 11.5 [9.6-13.7], non-AD: 6.1 [4.7-7.7]), compared with 14.2 (11.3-17.6) in controls (AD: 10.1 [7.7-13.0], non-AD: 4.1 [2.6-6.0]). The risk of dementia was strongly increased in SCD in a memory clinic setting but less so in a community-based setting. In addition, higher age (hazard ratio 1.1 [95% confidence interval 1.1-1.1]), lower Mini-Mental State Examination (0.7 [0.66-0.8]), and apolipoprotein E ϵ 4 (1.8 [1.3-2.5]) increased the risk of dementia.

Discussion: SCD can precede both AD and non-AD dementia. Despite their younger age, individuals with SCD in a memory clinic setting have a higher risk of dementia than those in community-based cohorts.

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Keywords:

Subjective cognitive decline; Dementia incidence; Preclinical Alzheimer's disease; Alzheimer's disease; Vascular dementia; Frontotemporal dementia; Dementia Lewy bodies

1. Introduction

Neurodegenerative changes, eventually leading to dementia due to Alzheimer's disease (AD), begin to accumulate approximately 20 years before clinical symptoms appear [1]. With the lack of curative treatment for dementia due to AD, research is moving toward the prodromal and preclinical stages of AD [2]. Subjective cognitive decline (SCD) refers to the subjective experience of cognitive decline, without objective impairment on cognitive assessment [3]. Compared to individuals without SCD, cognitively normal elderly subjects experiencing complaints have an increased risk of subsequent objective cognitive decline, that is, progression to mild cognitive impairment (MCI) and dementia [4-9]. Therefore, SCD has been suggested to be a possible first symptomatic expression of preclinical AD [2,3].

The conceptual framework on SCD published by the international Working Group (SCD-I) has a focus on SCD as an early harbinger of AD, proposing the SCD-plus criteria as potential risk factors for preclinical AD [3]. However, SCD may also precede other dementia subtypes with a

gradual onset, such as vascular dementia (VaD), dementia with Lewy Bodies (DLBs), or frontotemporal dementia (FTD). Although individuals with SCD have an increased risk of dementia [4-9], the incidence rate of progression from SCD to AD dementia, and especially to non-AD dementia, has not been estimated before.

For cognitively normal individuals, risk factors of dementia include higher age, lower education, and apolipoprotein E (APOE) ϵ 4 status [10,11]. Whether these risk factors influence the risk of progression to AD and non-AD types of dementia in patients with SCD in a similar way remains to be further investigated. The aim of our multicenter study including both memory clinic and community-based cohorts of SCD was to estimate incidence rates of dementia, both for AD and non-AD.

2. Methods

This collaborative project was initiated during a public meeting of the Subjective Cognitive Decline Professional Interest Area during the Alzheimer's Association International Conference in 2015, which was facilitated by the

Table 1
Overview of participating centers and their characteristics

Center	Setting	Definition of SCD	Follow-up information	N, total	N, SCD	N, controls
Alzheimer Disease Neuroimaging Initiative (ADNI) and Indiana Alzheimer Disease Center [41,42]	USA	Memory clinic; multicenter with standardized methods	Normal cognition + MC visit because of complaints (assessed by CCI)	Annual FU	372	126 246
Australian Imaging, Biomarkers and Lifestyle Study (AIBL) [43]	Australia	Community; multicenter with standardized methods	Normal cognition + cognitive complaints question (Mac-Q): Yes	FU interval 18 months	1636	491 161
Amsterdam Dementia Cohort [44-46]	The Netherlands	Memory clinic; single-center	Normal cognition + MC visit because of complaints	Annual FU	463	463 0
Barcelona Hospital Clinic i Universitari	Spain	Memory clinic; single-center	Normal cognition + MC visit because of complaints	Annual FU	75	52 23
German Dementia Competence Network (DCN) [47]	Germany	Memory clinic; multiple single-center studies	Normal cognition + MC visit because of complaints Participant did not meet Jak-Bondi criteria [48]	Annual FU	256	256 0
Development of Screening Guidelines and Clinical Criteria for Pre-dementia AD study (DESCRIPA) [49]	Europe*	Memory clinic; multiple single-center studies	Normal cognition + MC visit because of complaints	Annual FU	245	224 0
Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) [50]	Greece	Community; single-center	Normal cognition + cognitive complaints questionnaire: Yes	Annual FU	531	154 309
INSIGHT pre-AD study, Paris [51,52]	France	Community; single-center	Normal cognition + cognitive complaints questionnaire: Yes	FU after 3 years	318	318 0
Leipzig Longitudinal Study of the Aged (LEILA75+) [53]	Germany	Community; single-center	Normal cognition + cognitive complaints questionnaire: Yes	FU interval 18 months	670	169 501
Sydney Memory and Ageing Study (MAS) [54]	Australia	Community; single-center	Normal cognition + cognitive complaints question: Yes	FU interval 24 months	467	316 151
New York University Langone Medical Center (NYU)	USA	Memory clinic; single-center	Normal cognition + MC visit because of complaints	Annual FU	488	409 0

Abbreviations: CCI, Cognitive Change Index; FU, follow-up; MC, memory clinic; SCD, subjective cognitive decline.

NOTE: Of the participating cohorts, there were eight single-center studies, two multicenter studies with standardized methods (ADNI and AIBL), and two cohorts composed of data from multiple single-center studies (DCN Germany and DESCRIPA). ADNI and the single site Indiana ADC cohort were combined as both were assessed and included based on the CCI.

*To prevent possible overlap of participants, all cases from the VU Medical Center included in the DESCRIPA data set were not included in analyses (n = 22). See [Supplementary Table](#) for more information.

International Society to Advance Alzheimer's Research and Treatment.

2.1. Setting and recruitment

Eleven cohorts provided data, see [Table 1](#) for an overview of participating cohorts and the number of subjects included. Across studies, there are differences in operationalization of SCD. We deliberately took the case definition of each study as the starting point; [Table 1](#) provides information on center-specific operationalization of SCD. Cohorts were defined as memory clinic setting when patients were referred to the memory clinic by a physician, or actively approached the respective center for evaluation. Cohorts were labeled as community setting when the study was population based, for example, if recruitment was organized via standardized evaluation of eligible participants in a predefined district or when participants were recruited by active (media) appeal.

2.2. Participants

We included SCD participants in the analysis if (1) the participant reported subjective experience of cognitive decline on one or more cognitive domains; (2) the participant had normal baseline cognition, defined by results of cognitive assessment within normal ranges (center-specific), and criteria for MCI or any dementia were not met [12-15], and (3) had at least one follow-up assessment (>8 months from baseline) with repeated evaluation of diagnosis. Controls were provided by the same cohorts but did not endorse inclusion criterion (1). Exclusion criteria were MCI, dementia, alcohol or substance abuse, or any psychiatric or neurological disease possibly causing memory complaints (i.e. epilepsy, Parkinson's disease). In sum, 11 cohorts provided 5521 participants; 2978 cases with SCD and 1391 controls without SCD, see [Fig. 1](#) for an overview of participant selection.

2.3. Outcome measure

The main outcome measure was progression to dementia. Definitions and criteria of specific dementia used in each cohort are provided in the supplement or study design reports. Besides dementia due to AD [13,16], we evaluated the following non-AD dementia: VaD [17], FTD [14], and DLBs [15]. Other less frequent neurodegenerative causes of dementia, such as corticobasal syndrome or progressive supranuclear palsy, were classified as “dementia other.”

2.4. Demographic features of the study population

Sociodemographic features and cognition were assessed in each cohort. Here, we report on age, sex, education, global cognition, and *APOE* $\epsilon 4$ carrier status. Information on years of education was available for 2142 (71.9%) participants. Cognitive function was screened with the Mini-Mental State Examination (MMSE) [18] and available for 2928 (98.3%) participants. *APOE* genotyping was performed according to local procedures and available for 2417 (81.2%) participants. We dichotomized *APOE* $\epsilon 4$ status (0 $\epsilon 4$ alleles vs. 1 or 2 $\epsilon 4$ alleles).

2.5. Statistical analyses

Data were analyzed using SPSS (version 22; IBM, Armonk, NY, USA) and Stata 15 (Stata Statistical Software: Release 15, StataCorp LP). We evaluated baseline characteristics and assessed differences between memory clinics and community cohorts using linear mixed models (continuous variables) or generalized estimating equations (dichotomous variables), taking into account random center effects.

We calculated incidence rates of dementia per 1000 person-years with accompanying 95% Poisson confidence intervals and incidence rates of AD and non-AD dementia separately.

We studied the effect of age, sex, MMSE, number of education years, *APOE* $\epsilon 4$ carrier status, and recruitment setting (memory clinic vs. community cohort) on the risk of dementia by using shared-frailty Cox proportional hazards models, taking into account within-group center effects. We conducted simple and multiple Cox regression models and accounted for residual variation in progression risk among studies by including a center-specific random effect. To evaluate whether effects of MMSE and education were generalizable between centers, we added mean MMSE and mean number of education years per center as variables. Finally, we added interaction effects of recruitment setting and variables age, sex, MMSE, and number of education years. We repeated the analyses stratified for AD and non-AD dementia.

For visualization, we constructed Kaplan-Meier curves of progression to dementia in general and for dementia due to AD and to non-AD per decade of age. When calculating the risk of AD, cases progressing to non-AD dementia were censored and vice versa. $P < .05$ was considered to be significant.

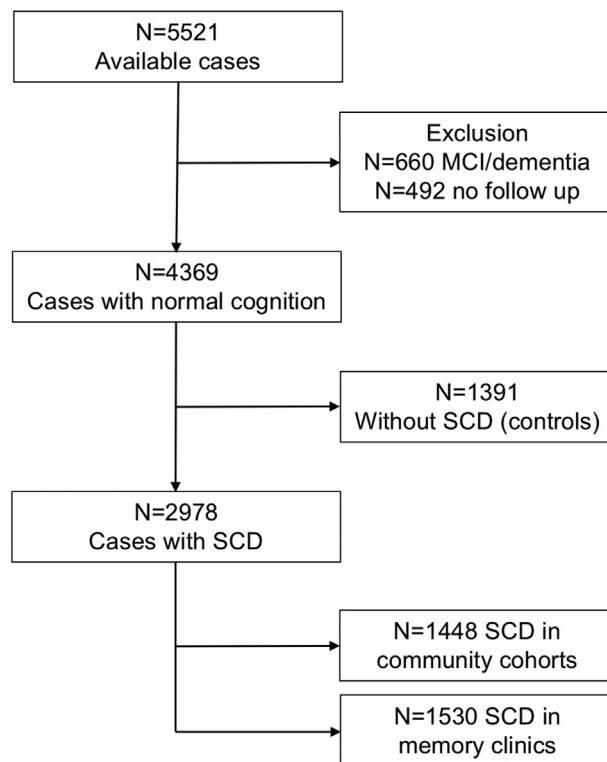


Fig. 1. Flowchart of participant selection. Overview of inclusion of participants. Abbreviations: MCI, mild cognitive impairment; SCD, subjective cognitive decline.

3. Results

3.1. Demographics

Table 2 shows the baseline demographic features of the study population. Individuals with SCD in memory clinic cohorts were on average 10 years younger, and they were less often females, had more years of education, and were more often *APOE* $\epsilon 4$ positive than individuals with SCD in community-based cohorts and controls. Adjusted for random center effects, MMSE scores were lower in controls than in individuals with SCD. For all variables, individuals with SCD from the community were intermediate between SCD from a memory clinic and controls. Center characteristics are provided in [Supplementary Table](#).

3.2. Progression to AD and non-AD dementia

During follow-up, 3.9 ± 2.2 years (range 0.9-12.8 years), 84 (6% of 1391) controls without SCD progressed to dementia, of which 61 (66% of demented) to AD and 23 (33% of demented) and non-AD. Among individuals with SCD, 194 (7% of 2978) progressed to dementia, attributed to AD for 127 (65% of demented) or another type of dementia for 67 (35%). Within the non-AD dementia cohort, 30 (16% of all dementia cases) individuals with SCD progressed to VaD, 8 (4%) progressed to frontotemporal

Table 2
Baseline demographic features of study participants (N = 4369)

Characteristics	All N = 4369	Controls N = 1391	Community N = 1448	Memory clinic N = 1530	P value
Number of cohorts		6	5	6	
Age, year	73 ± 9	77 ± 7	76 ± 6	67 ± 9	.000
Female gender	2611 (60%)	889 (64%)	901 (62%)	821 (54%)	.000
MMSE	28.3 ± 1.7	27.9 ± 1.9	28.4 ± 1.4	28.4 ± 1.6	.000*
Education, year [†]	12 ± 4	11 ± 5	10 ± 4	14 ± 4	.000
APOE ε4 carrier [‡]	888 (28%)	184 (26%)	261 (22%)	443 (36%)	.000
Follow-up, year	3.9 ± 2.2	4.3 ± 2.0	3.9 ± 2.0	3.5 ± 2.3	.000

NOTE: Values are displayed as unadjusted mean ± standard deviation (SD) or N (%). Differences between memory clinic and community cohorts were assessed using linear mixed models (continuous variables) or generalized estimating equations (dichotomous variables) taking into account center random effects.

*When taking into account center random effects, MMSE is lower in controls versus community cohorts versus memory clinic cohorts ($P < .001$), whereas unadjusted means are shown in the table.

[†]Data available for 77% (memory clinic 98%, community 44%, controls 88%).

[‡]Data available for 72% (availability memory clinic 82%, community 81%, controls 51%).

lobar degeneration (FTLD), 9 (5%) to DLB, and 20 (10%) to another type of non-AD dementia. Fig. 2 shows the percentages of dementia diagnoses in community cohorts and memory clinics. In a multilevel model, we compared percentages of dementia diagnoses in community and memory clinic cohorts and found that individuals with SCD in community-based cohorts more often received a diagnosis of VaD (23% community vs. 9% memory clinic [$P = .01$]). By contrast, diagnoses of DLB and FTLD were more frequently made in a memory clinic setting (DLB 8% memory clinic vs. 1% community ($P = .070$); FTLD: 8% memory clinic versus 0% community, model did not converge). The percentage of a diagnosis of AD did not differ between recruitment settings (67% vs. 63%, $P = .55$), nor did the number of cases with “dementia other” (memory clinic 8% vs. community cohort 13% [$P = .34$]).

3.3. Incidence rate of dementia

Among individuals with SCD, the incidence rate of dementia was 17.7 (95% Poisson confidence interval

15.2-20.3) per 1000 person-years. The incidence rate per 1000 person-years for dementia due to AD was 11.5 (9.6-13.7) and for non-AD dementia 6.1 (4.7-7.7). In controls without SCD, the incidence rate of dementia was 14.2 (11.3-17.6); 10.1 (7.7-13.0) for AD and 4.1 (2.6-6.0) for non-AD. Table 3 shows the incidence rates of dementia in memory clinics (20.0 [16.4-24.1]) and community cohorts (15.4 [12.3-19.0]) per decade and for AD and non-AD dementia separately. Incidence rates increased with age, as visualized in Figs. 3 and 4. Multivariate Cox proportional hazards models showed that compared to controls without SCD, individuals with SCD in memory clinic cohorts are at a clearly increased risk of dementia (Table 4). The increased risk of dementia in community-based cohorts did not reach significance. In addition, higher age, lower MMSE, and APOE ε4 carrier status were independent predictors of incident dementia. We evaluated center random effects for MMSE and education in the Cox proportional hazards models, which did not specifically alter results, concluding that findings were generalizable for MMSE and education.

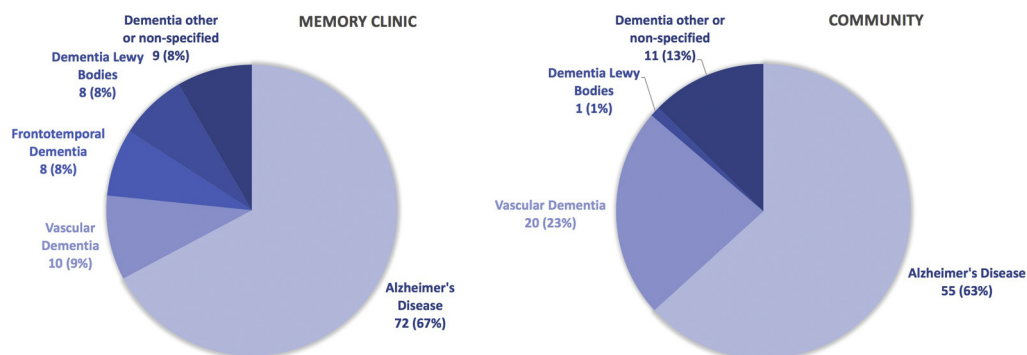


Fig. 2. Type of dementia diagnosis in memory clinic and community settings. Dementia diagnoses per type of recruitment setting. Total number of dementia diagnoses: memory clinic n = 107, community n = 87. Results are represented as N (%).

Table 3
Incidence rates of dementia in general, and dementia due to AD and non-AD

Groups with age-bins	Number of person years	Incidence rate/1000 person-years (95% Poisson confidence intervals)		
		Dementia	AD	Non-AD
Controls (n = 1391)				
All		14.2 (11.3-17.6)	10.1 (7.7-13.0)	4.1 (2.6-6.0)
Age category				
<60	55	0	0	0
60-70	859	2 (0-8)	2 (0-8)	0
70-80	3379	7 (5-11)	4 (2-7)	3 (2-6)
80-90	1547	33 (25-43)	25 (18-34)	8 (4-14)
>90	81	74 (27-161)	62 (20-144)	12 (0-69)
Community (n = 1448)				
All	5647	15.4 (12.3-19.0)	9.7 (7.3-12.7)	5.7 (3.9-8.0)
Age category				
<60	12	0	0	0
60-70	904	2 (0-8)	2 (0-8)	0
70-80	3222	11 (8-15)	6 (4-9)	5 (3-8)
80-90	1509	32 (24-42)	23 (16-32)	9 (5-16)
>90	47	60 (12-175)	20 (1-111)	40 (5-145)
Memory clinic (n = 1530)				
All	5355	20.1 (16.4-24.1)	13.4 (10.5-16.9)	6.5 (4.6-9.1)
Age category				
<60	1271	6 (2-11)	2 (0-6)	4 (1-9)
60-70	1952	17 (12-24)	11 (7-16)	6 (3-11)
70-80	1571	32 (24-42)	22 (15-30)	10 (6-16)
80-90	447	26 (20-58)	31 (17-52)	4 (1-15)
>90	12	0	0	0

Abbreviation: AD, Alzheimer's disease.

NOTE: Results are displayed as incidence rates (95% Poisson confidence interval) per 1000 person-years. Analyses stratified for AD and non-AD types of dementia, age category, and recruitment setting.

Stratified for AD or non-AD outcomes, the increased risk of dementia in individuals with SCD was particularly attributable to incident non-AD dementia. Lower MMSE increased the risk of both AD and non-AD dementia (Table 4), while higher age was associated with an increased risk of non-AD dementia. There was no significant effect of sex, education, or APOE in the stratified analyses.

4. Discussion

In this multicenter study including both memory clinic and community-based cohorts of SCD, we evaluated incidence rates of dementia, both for AD and non-AD. We found an overall dementia incidence rate in individuals with SCD of 17.7 per 1000 person-years, compared to 14.2 in controls without SCD. Particularly, in memory clinic patients with SCD, the risk of non-AD dementia is strongly increased. In line with incidence studies of dementia subtypes [19,20], roughly one of 3 incident dementia in individuals with SCD cases was due to non-AD. Of note, non-AD dementia in memory clinics often comprised FTD or DLB, while in community-based cohorts, VaD was relatively more common. Other determinants of incident dementia included higher age, lower baseline cognition, and APOE ε4 carriership.

Our data clearly showed that recruitment setting modifies the risk of progression from SCD to dementia. It is well known that recruitment setting (i.e. memory clinic vs. community) affects studies in SCD [3,21,22]. However, the number of studies directly comparing recruitment setting is small [9,23–25]. A previous meta-analysis suggested that the annual conversion rate from SCD to dementia did not differ between memory clinics and community cohorts [9], and likewise at first sight, our memory clinic cohorts also had only slightly higher incidence rates (20.1/1000 person-years) compared with community cohorts (15.4/1000 person-years). However, heterogeneity between studies has repeatedly been mentioned in SCD studies [9,21], and a recent study showed that progression to MCI is more common in individuals with SCD recruited at a memory clinic than in a community-based setting [26]. We also observed great heterogeneity between cohorts in study design, center, and patient characteristics, and to allow meaningful pooling of data, we used a multilevel statistical approach, carefully taking into account center differences. Particularly, memory clinic cohorts were on average a decade younger, explaining their overall lower incidence. When we stratified by age, our data revealed that in every age bin, incidence of dementia is higher in the memory clinic than in the community-based

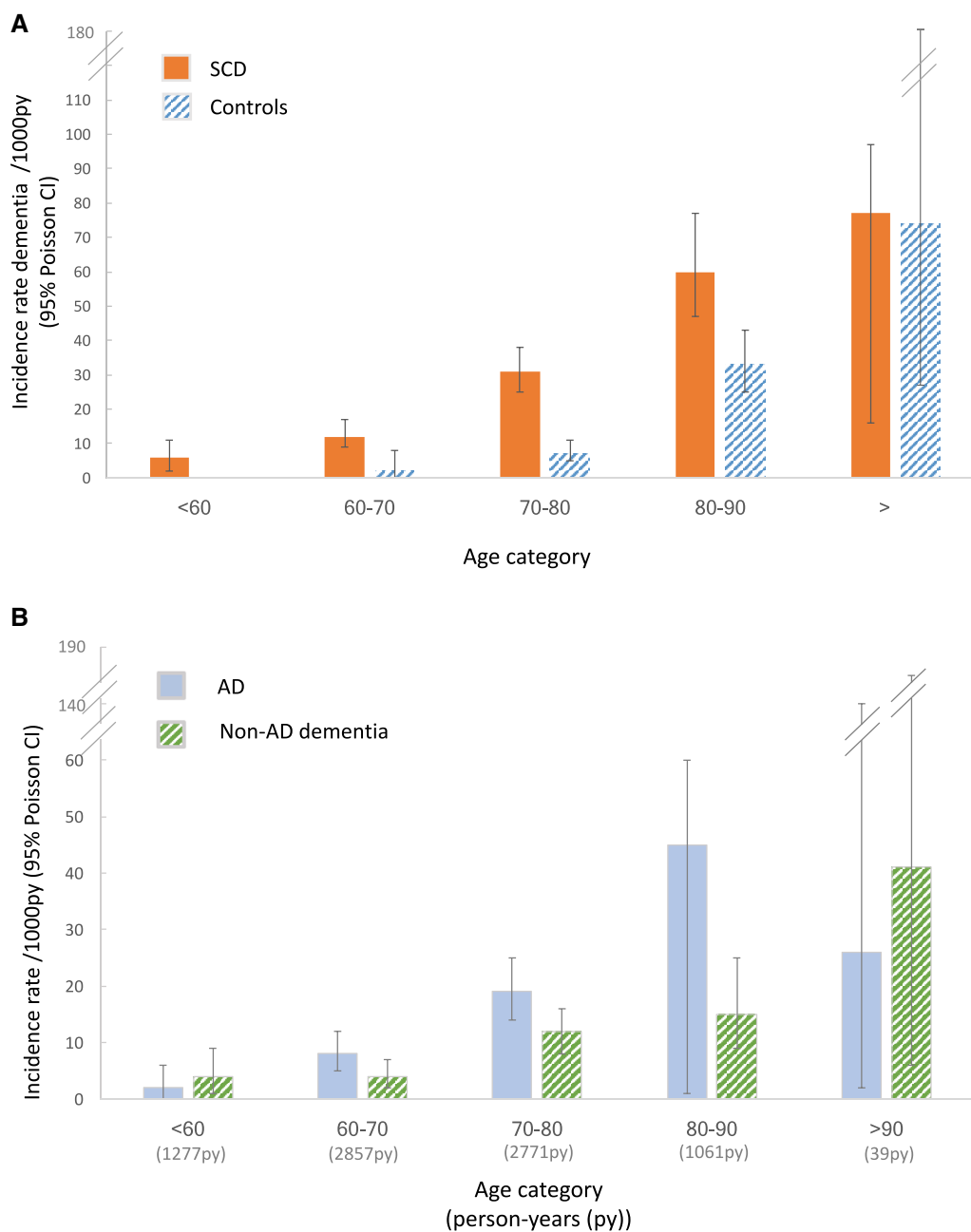


Fig. 3. Incidence rates of dementia and AD and non-AD dementia. (A) Incidence rates of dementia per decade in individuals with SCD and controls. (B) Incidence rates of AD and non-AD dementia per decade. Results are presented as incidence rates per 1000 person-years (95% Poisson confidence intervals) per decade. Abbreviations: AD, Alzheimer's disease; CI, confidence interval; SCD, subjective cognitive decline.

cohorts of individuals with SCD. The only exception was the oldest age bin >90 years, where data in memory clinics were simply lacking, and the incidence of dementia in community-based cohorts was high. Our data illustrate that memory clinic patients who actively seek help for their perceived cognitive problems, indeed, are more likely to experience the first (preclinical) signs of a neurodegenerative disease [23,24].

Our findings provide evidence that SCD is not only a potential harbinger of AD but also of other dementia. Two-third of incident dementia in individuals with SCD was attributable to AD dementia, whereas approximately one-third was attributable to another type of dementia. The relative frequencies of individuals with SCD progressing to FTLD, DLB, and VaD seemed comparable with previous dementia incidence studies [19,20,27–29]. In memory clinic

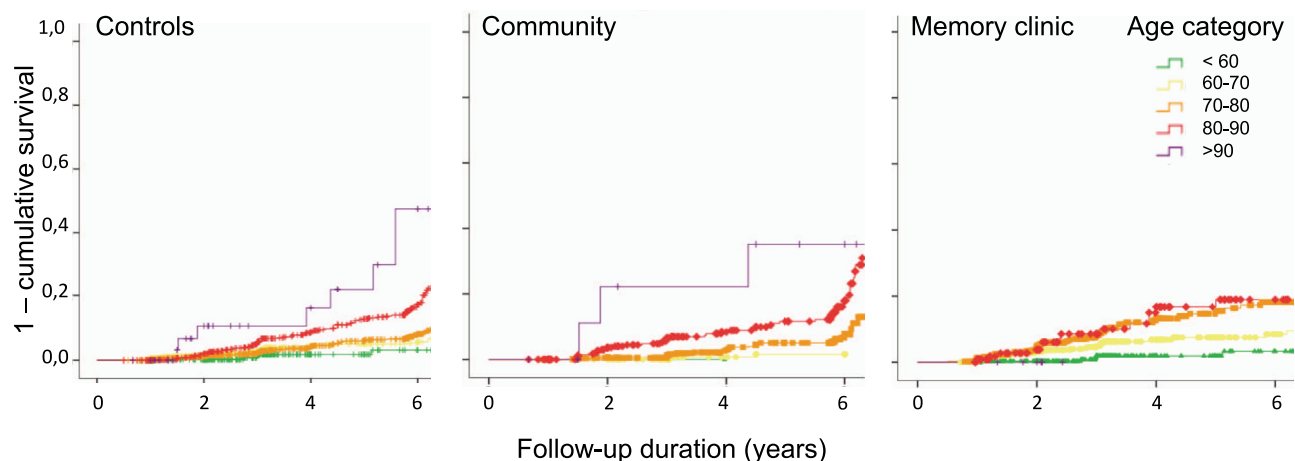


Fig. 4. Kaplan-Meier curves of cumulative risk of dementia in controls and individuals with subjective cognitive decline in memory clinic and community cohorts. Kaplan-Meier curves of the cumulative risk of progression to dementia per decade, stratified for recruitment setting.

cohorts, DLB and FTLD were more frequently diagnosed than in community cohorts. By contrast, VaD was more often diagnosed in the older community cohort individuals with SCD. This difference could be a reflection of differing operationalization of diagnostic criteria for dementia, which may be handled differently between settings [30], for example, VaD in memory clinic settings often requires neuroimaging criteria, whereas in community-based settings such a diagnosis may be based on clinical presentation only. Diagnosis of DLB or FTLD requires careful neurological examination by an expert neurologist, available mostly in specialized clinics rather than in community settings. Also, individuals with early VaD or DLB might be referred for evaluation to general neurology, instead of a memory clinic, as patients complain rather of neurological symptoms, such as parkinsonism or gait change, than memory decline. Furthermore, individuals

with FTLD may be less likely to participate in voluntary studies because of disease characteristics [31].

The large majority of individuals with SCD in both memory clinic and community-based cohorts did not progress to any type of dementia, but rather remained cognitively normal. Despite the growing interest in SCD as a putative first syndrome stage of AD, the group of individuals seeking help where a neurodegenerative disorder can be excluded as cause of their problems also merits our attention. From studies in the field of MCI and early studies in SCD, it is clear that, for example, cerebrospinal fluid biomarkers have particularly good negative predictive value, illustrating that their optimal clinical use is for reassurance of individuals with normal biomarkers [32,33]. Alternative causes of SCD could be subclinical psychiatric disorders, personality traits, or surmenage. Individuals with SCD who are unlikely to progress to AD or non-AD

Table 4

Associations between determinants and the risk of dementia in general and dementia due to AD and non-AD in a combined SCD sample (n = 4369)

Determinant	Dementia		AD		Non-AD	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Controls	ref	ref	ref	ref	ref	ref
SCD—community	2.1 (0.6 – 7.7)	1.5 (0.4 – 5.8)	1.8 (0.8 – 4.1)	0.7 (0.3 – 1.9)	4.6 (1.1-19.0)	2.2 (0.5-9.7)
SCD—memory clinic	10.0 (2.9 – 34.0)	10.4 (3.4 – 32.0)	1.7 (0.8 – 3.6)	2.0 (1.0 – 4.1)	12.7 (3.1-51.4)	7.1 (1.8-27.3)
Age, years	1.1 (1.1 – 1.1)	1.1 (1.1 – 1.1)	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.0)	1.09 (1.05 – 1.12)	1.07 (1.02 – 1.11)
Female gender	1.1 (0.9 – 1.4)	1.0 (0.7 – 1.5)	1.0 (0.9 – 1.04)	1.0 (0.9 – 1.1)	0.8 (0.5 – 1.3)	0.6 (0.3 – 1.0)
MMSE ^h		0.7 (0.65 – 0.8)		0.95 (0.92 – 0.98)		0.8 (0.7 – 0.9)
Education, years*		1.0 (0.97 – 1.1)		1.0 (0.98 – 1.01)		1.0 (0.9 – 1.1)
APOE ε4 status [†]		1.8 (1.3 – 2.5)		1.0 (0.9 – 1.1)		1.1 (0.6 – 2.1)

Abbreviations: AD, Alzheimer's disease; SCD, subjective cognitive decline.

NOTE: Results are presented as hazard ratios (95% confidence interval) and reflect the risk of progression from SCD to dementia in general and dementia due to AD and non-AD. Model 1: age and gender adjusted. Model 2; additionally adjusted for MMSE, education in years, and APOE ε4 status (due to missing data in MMSE, education, and APOE, model 2 has less observations). HRs were calculated per determinant in univariate models and combined in multivariate models.

^hHigher scores reflect better performance.

*Data available for 77%.

[†]Data available for 72%.

dementia could be reassured and might benefit from counseling and/or lifestyle interventions, aiming to promote a healthy brain.

We evaluated which determinants contributed to an increased risk of progression from SCD to dementia and found that higher age, lower baseline MMSE, *APOE* ϵ 4 status, and recruitment setting resulted in an increased risk of dementia, which is consistent with the literature [9,34,35]. We found that higher age contributed relatively more to the risk of AD than non-AD dementia in individuals with SCD. A possible explanation could lie in the fact that some non-AD dementia, such as FTLN, are relatively more often diagnosed at a younger age, thus reflecting less contribution of a higher chronologic age in the risk of non-AD dementia in comparison with AD dementia [31]. The effect of MMSE on the risk of clinical progression also seemed stronger for AD than for non-AD. The MMSE is mainly designed as a global cognitive screening tool and most sensitive for disturbances in memory and orientation [18]. Because the memory domain is relatively less affected in non-AD dementia, it is conceivable that MMSE is less sensitive for non-AD dementia [36]. *APOE* ϵ 4 status was associated with an increased risk of dementia, which appeared to be attributable to the risk of AD but not to non-AD, which is in agreement with the literature [37,38].

The limitations of the study include the substantial heterogeneity in cohort characteristics. The heterogeneity includes differences in demographics of participants among centers and substantial inherent center characteristics such as the definition of SCD, the administered SCD questionnaires, the use of (magnetic resonance imaging, positron emission tomography, or cerebrospinal fluid) biomarkers in the diagnostic process, and the outcome measures (differences in dementia criteria used). Furthermore, recruitment setting has been shown to be a moderator of SCD results, as discussed previously. Nonetheless, we were able to combine these cohorts by using a multilevel statistical approach, using shared-frailty Cox models and taking into account random center effects. Our results underline the importance of the harmonized research criteria for SCD, which have been put forward by the SCD-I working group [3,39]. In this study, we had no information available on different domains of cognitive complaints, such as memory domains versus nonmemory domains. As one-third of dementia diagnoses were non-AD, evaluation of SCD in nonmemory domains using questionnaires and also qualitative assessment is of interest to better understand the underlying pathology of SCD [40]. Also, we had no comprehensive cognitive test battery or biomarker data available for a large part of our cohort, and we cannot exclude the possibility of misdiagnosis in a number of cases. Future studies should include a wider range of cognitive tests and biomarkers to further evaluate the process of differentiating between AD and non-AD types of dementia. We did not take into account all available SCD cohorts, but this collaborative study did originate from the International

Society to Advance Alzheimer's Research and Treatment's SCD Professional Interest Area, including all centers that wanted to contribute data. The strengths of the study, therefore, include the large sample of SCD patients, with participating centers from around the world. Furthermore, this is the first time that the incidence of non-AD dementia is evaluated in the context of SCD.

Members of the international SCD Working Group (SCD-I) have published a conceptual framework on SCD research to facilitate harmonization of SCD research [3,39]. The framework, however, is focused on the detection of preclinical AD and not so much on the preclinical stages of other dementia. The risk of preclinical AD has been suggested to be specifically modified by self-reported memory decline [7], and a large overview of SCD measures indicated that most instruments indeed evaluate memory-specific decline [3,21]. However, as approximately one-third of progressing patients in our SCD sample progressed to another type of dementia than AD, the importance of nonmemory characteristics needs to be considered when evaluating SCD.

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Supplementary Data

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RESEARCH IN CONTEXT

1. Systematic review: We evaluated literature on incidence numbers of subjective cognitive decline (SCD) and risk factors of progression from SCD to dementia, with a particular focus on both AD and non-AD types of dementia.
2. Interpretation: This large collaborative study including 2978 participants with SCD, indicated that SCD is a prodrome of both AD and non-AD dementia. Risk factors for progression from SCD to dementia included higher age, lower MMSE, apolipoprotein E, and recruitment setting, specifically memory clinic setting.
3. Future directions: As we evaluated risk factors for progression from SCD to dementia, we concluded that these risk factors, in particular recruitment setting, should be taken into account while interpreting and comparing future study results. Future studies may include biomarker data while assessing risk factors of progression from SCD to dementia.

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