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Original Article

Distinct trajectories of subjective cognitive decline before diagnosis of neurocognitive disorders: Longitudinal modelling over 18 years

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ABSTRACT

Background: Subjective cognitive decline (SCD) is an established predictor of neurocognitive disorders (NCD) (i.e. mild cognitive impairment and dementia). Yet, its construct remains contentious. Many individuals with SCD do not progress to NCD, leading to an alternative term in the literature – 'functional cognitive disorders' – to describe the SCD experience in these individuals.
Objectives: To examine the distinct differences in trajectories of SCD between those who did and did not eventually develop NCD.
Design: Case-control study.
Setting: Alzheimer's Disease Centers across USA.
Participants: A total of 5,167 participants aged ≥50 years were followed up near-annually to evaluate for SCD and NCD (median follow-up=8.1 years; range=1.0–18.0). *Cases* were defined as those who developed incident NCD during follow-up; *controls* completed ≥10 years of follow-up and had normal cognition throughout follow-up period.
Measurements: SCD was evaluated with a yes/no question based on "perceived decline in memory relative to previously attained abilities". The trajectories of SCD were modelled with mixed-effect logistic regression, using a backward timescale.
Results: Those who developed NCD (*cases*) had new onset of SCD within past 20 years, which became particularly noticeable 13–14 years before diagnosis, and became even more evident in the last 4 years. Those who did not develop NCD (*controls*) reported SCD since younger age, with the probability of SCD remaining constant over time. The distinctive trajectories were consistent across Alzheimer's and non-Alzheimer's disease, and among those with higher baseline rates of SCD due to psychiatric conditions.
Conclusions: SCD exhibits distinctive trajectories among those who do and do not progress to NCD. These distinctive trajectories can inform NCD risk for early interventions, and guide public health messaging to distinguish high-risk SCD from normal ageing. Future SCD scales may possibly need to evaluate symptom changes over a longer, 20-year horizon to better capture the new onset of SCD within this longer timeframe.

1. Background

Subjective cognitive decline (SCD) refers to *subjective* perception of decline in cognition (typically in memory domain) among individuals with *normal cognition* (i.e. in the absence of objective cognitive deficits) [1,2]. It is increasingly common at older ages, with some population-based studies reporting a prevalence of up to 50–80 % among community-dwelling older persons [2]. In recent years, SCD has gained attention as a key predictor for incident neurocognitive disorders (NCD) (i.e. mild cognitive impairment and dementia). As shown in a meta-analysis [3], individuals with SCD were twice as likely to develop NCD, with one-third developing mild cognitive impairment (MCI) or dementia after four years [3]. Most recently, SCD has been highlighted as a useful criterion in diagnosing prodromal NCD [1,2], with the 2018 NIA-AA research framework for Alzheimer's disease [4] incorporating SCD as a transitional stage between normal cognition and early NCD. In 2019, SCD has also been identified as a public health issue by the Centers for Disease Control and Prevention [5], with ongoing national efforts in USA to increase the proportion of individuals with SCD who have discussed their cognitive concerns with healthcare professionals

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[6]. This focus on SCD in public health has an understandable appeal, given the high prevalence of SCD in the population, and the potential for SCD as a practical and low-cost approach [1] to identify high-risk groups for risk modification and early interventions [2,7].

Despite growing interest, the construct of SCD remains contentious. Recent literature has highlighted that many individuals with SCD do not progress to NCD [7,8]. In these individuals, the presence of SCD may be attributed to underlying psychiatric conditions (e.g. depression, anxiety, neuroticism), or medical conditions that could potentially affect cognitive performance (e.g. diabetes, hypertension, heart disease, thyroid dysfunction, nutritional deficiency) [1,2,7]. Such observations have led to the coining of an alternative term in the literature – 'functional cognitive disorders' – to describe a group of overlapping conditions in which subjective cognitive symptoms are present, which are genuine, distressing, and often disabling, but experienced inconsistently and not related to NCD [7]. These observations have also prompted calls for further research to delineate differences in SCD characteristics between those related to functional cognitive disorders and NCD [8], considering the potential iatrogenic harm to patients when SCD in functional cognitive disorders is incorrectly attributed to NCD [7,8].

Given early evidence that the longitudinal characteristics of SCD may potentially be useful in differentiating between those who do and do not progress to NCD [9–11], this study sought to model the trajectories of SCD up to 18 years before the diagnosis of NCD, and compare them with the trajectories of SCD among those who did not develop NCD during follow-up. In particular, this study aimed to address the research question: 'Are there distinct differences in SCD trajectories between those who did and did not eventually develop NCD?'

2. Methods

2.1. Study population

This study is based on participants recruited from approximately 42 Alzheimer's Disease Centers (ADCs) across USA between 2005 and November 2023, as available in the National Alzheimer's Coordinating Center (NACC) database [12]. Majority of participants (88.6 %) visited ADCs primarily to volunteer in research, while the rest visited ADCs to seek clinical evaluation. On an approximately annual basis, participants took part in standardized assessments (which included clinical history, physical examination and detailed neuropsychological testing) to evaluate for incident NCD (i.e. MCI or dementia). The study involved a case-control design, and included participants who fulfilled either of the criteria that defined cases or controls:

a) Cases – Had normal cognition (i.e. no MCI or dementia) at first study visit, had ≥1 year of follow-up, and developed incident NCD during follow-up; or
b) Controls – Completed ≥10 years of follow-up and had normal cognition throughout follow-up period. Of note, this criterion for controls (≥10 years of follow-up with normal cognition) were initially selected to balance the sample size among cases and controls, while ensuring sufficient duration of observations for normal cognition among controls. Meanwhile, a stricter criterion for controls was also evaluated in sensitivity analyses, based on ≥14 years of follow-up with normal cognition (further details are described in Statistical Analyses section).

To ensure that cases and controls were relatively comparable in age-groups, the study only included participants who were at least 50 years of age at index time (i.e. year 0 on a backward timescale; see Statistical analyses section for further details on the backward trajectory modelling). All contributing ADCs obtained informed consent from their participants, as well as received approval by their local institutional review boards.

2.2. Measures

SCD was evaluated with a single yes/no question based on whether the participant perceived "a decline in memory relative to previously attained abilities". The use of single question for SCD is not uncommonly adopted in the literature [13]; and in particular, the current version of single question for SCD has been widely validated in previous studies [9,14–17], with demonstrable association with incident NCD over time. The focus on memory domain is also consistent with current literature, particularly in the recently proposed SCD framework, where memory concerns have been suggested to demonstrate better likelihood (than non-memory concerns) in detecting prodromal NCD [1]. Additionally, the same SCD question was evaluated on informants (i.e. informant-reported SCD) as a secondary measure, given that informant-reported SCD was highlighted as a stronger risk of cognitive decline in the SCD framework[1] and in a recent meta-analysis [18]. The other key covariates that were captured are described in **Supplementary Material 1**.

Diagnoses of NCD (i.e. MCI or dementia) were made based on all available information from standardized assessments, with 68.1 % of diagnoses made via consensus conference and remainder made by single clinicians. MCI was diagnosed using the modified Petersen criteria [19]. Dementia was diagnosed using the 2011 NIA-AA criteria [20] from March 2015 onwards (when version 3.0 of Uniform Data Set was introduced in NACC); while before March 2015, the diagnostic criteria for dementia were not specified in NACC, with some ADCs using the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association) criteria [21], DSM-IV (Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition) criteria [22] or other standard criteria for dementia.

2.3. Statistical analyses

In primary analyses, SCD trajectories were modelled using mixed-effect logistic regression, taking reference from the conduct of previous studies on backward trajectory modelling [23,24]. Mixed-effect model offers an advantage of allowing some flexibility in handling longitudinal data – it models the data based on actual dates of observations and does not require longitudinal data to adhere to a strict follow-up protocol. This is especially useful in complex datasets such as the current NACC data, whereby the participants showed some variability *in the total follow-up period* (i.e. some participants had longer follow-up duration than the others), and *in the follow-up schedule* (i.e. although all participants were expected to have annual follow-up, there were some variations in the actual follow-up dates).

The mixed-effect logistic regression included random effects of intercept and time slope, robust standard errors, as well as assumed unstructured covariance. NCD (coded as 0 or 1) was added to the model to test for differences in SCD probabilities between those with and without NCD. Time was coded using a backward scale such that year 0 (index time) was year of incident MCI or dementia for the cases, or end of follow-up for the controls; while the other timepoints indicate the years leading up to index time (e.g. year −10 indicates 10 years before index time). This modelling strategy implies that index time (year 0) was the intercept in the analysis, and the beta associated with NCD term reflects difference in SCD probabilities between those with and without NCD in the years leading up to index time. Time was modelled based on nonlinear terms (time, time-squared, and time-cubed). Interaction term between NCD and time slope (i.e. time, time-squared, and time-cubed) was tested using Wald test, and included in the model in the event of a significant Wald test ($P < 0.05$).

As SCD was captured as two separate variables (i.e. self-reported SCD, and informant-reported SCD), mixed-effect logistic regression was conducted twice – once for self-reported SCD, and in a separate model for informant-reported SCD. The base models adjusted for demographic information, namely, age at index time, sex, ethnicity, years of edu-

cation, and family history of cognitive impairment. The fully-adjusted models additionally accounted for *potential confounders* [25], which are defined as covariates known to predict both the exposure-of-interest (SCD) and the outcome-of-interest (NCD). Based on published literature [1,2,7,14,15], the fully-adjusted models additionally included the following time-dependent covariates: diabetes mellitus, hypertension, hyperlipidemia, history of vitamin B12 deficiency, history of thyroid disease, history of heart disease, history of neurological condition, history of psychiatric condition, current presence of depressive symptoms, and current presence of anxiety symptoms. Output from the models (i.e. predicted probability and odds ratio of SCD) were plotted on graphs to provide clear illustrations on the SCD trajectories.

Secondary analyses were conducted to examine the consistency of results among individuals with higher likelihood of reporting SCD (e.g. those with certain psychiatric or medical conditions) [1,2,7], a subgroup sometimes referred to as individuals with 'functional cognitive disorders' in the literature [7,8]. Predictors of SCD were first identified based on results on the 15 covariates when they were adjusted for in the primary analyses (i.e. in the initial mixed-effect logistic regression). Specifically, covariates were identified as predictors of SCD if they had Bonferroni-corrected $P < 0.05$. Next, a new variable was generated to classify individuals as having higher likelihood of reporting SCD if they had higher than median number of predictors (each predictor was first coded to reflect its overall/ever presence throughout follow-up period; i.e. coded as present if the predictor was reported at any visit during follow-up). This new variable (higher likelihood of reporting SCD) was then included as an interaction term in mixed-effect logistic regression, to identify significant interaction effects ($P_{interaction}<0.05$) between likelihood of reporting SCD and trajectories of SCD.

Five sensitivity analyses were conducted to evaluate robustness of the results when some parts of the primary analyses were modified. They included:

1) Using a stricter criterion to define the control group, based on a subset of the control group with ≥14 years of follow-up with normal cognition (instead of ≥10 years of follow-up with normal cognition).
2) Focusing only on participants who visited ADCs primarily to volunteer in research (88.3 %). This sensitivity analysis omitted a small proportion of participants (11.7 %) who visited ADCs to seek clinical evaluation, considering that this subgroup of participants can be characteristically different from those who volunteered in research.
3) Splitting NCD cases into 2 separate aetiologies, i.e. Alzheimer's disease (AD) and non-AD. For those diagnosed with NCD in the NACC database, clinicians at ADCs were required to employ their best judgment to further classify presumptive primary aetiology of NCDs based on established criteria for AD [20,21,26], Lewy Body disease [27–29], Frontotemporal lobar degeneration [28,30–35], Vascular disease [36], or other aetiologies of NCDs. In this sensitivity analysis, the NCD term in the analytic model (originally coded as 0 or 1) was recoded as: 0=No NCD; 1=AD; and 2=non-AD.
4) Further adjustment of the following time-dependent covariates in the analyses: obesity (defined by weight in kilograms / squared of height in meters of ≥30), uncorrected hearing loss (i.e. hearing loss without the use of hearing aid), uncorrected vision loss (i.e. vision loss without the use of corrective lenses), current smoking, and current alcohol abuse (with clinically significant impairment in the areas of work, driving, legal or social). While the primary analyses adjusted for known confounders (i.e. known predictors of both SCD and NCD) [25], this sensitivity analysis further examined the consistency of results following the adjustment of other known predictors of NCD.
5) Further simplifying the longitudinal SCD data into three variables based on when SCD occurred during the follow-up period, that is, early-phase SCD (occurring before year −14), middle-phase SCD (occurring between year −14 and year −4), and late-phase SCD (occurring after year −4). Simplified, cross-sectional analyses (based on logistic regression) were then conducted – instead of the original longitudinal analyses (based on mixed-effect logistic regression) – to examine the association between the three variables (early-, middle- and late-phase SCD) and NCD at index time. It is important to note that this analysis could only be performed in the subset of participants with ≥14 years of follow-up (to ensure sufficient information to code the three phases of SCD). While this simplified analysis may not be as robust as mixed-effect models (which takes into account all observed data even for participants with <14 years of follow-up), it was intended to provide a gross indication of whether the results remained consistent when an alternative, much simpler approach was used to analyse the data.

All analyses were conducted in Stata (version 18).

3. Results

Total sample size was 5167, with a median age of 81 (interquartile range, IQR=75–87) and a median education of 16 years (IQR=14–18). **Supplementary Material 2** shows flow diagram on participant selection, while Table 1 presents participant characteristics. At index time, cases were more likely to have diabetes mellitus, hypertension, history of heart disease, history of neurological condition, history of psychiatric condition, current depressive symptoms and current anxiety symptoms. Median follow-up period was 8.1 years for the overall sample (IQR=3.1–12.1; range=1.0–18.0), 4.0 years for cases (IQR=2.1–7.2; range=1.0–18.0), and 12.6 years for controls (IQR=11.1–15.1; range=10.0–18.0). **Supplementary Material 3** further presents the number of observations that were available at each timepoint during the follow-up period. Among cases (n = 3283), 2845 had incident MCI and 438 had incident dementia; of which, 60.7 % had primary aetiology of AD, 8.9 % had Vascular disease, 4.3 % Lewy Body disease, 1.5 % Frontotemporal lobar degeneration, and remainder had NCD due to other or unknown aetiologies.

In primary analyses, nonlinear terms were included in the models as the regression terms were significant for time-squared ($P < 0.001$) and time-cubed ($P < 0.001$). Interaction term between NCD and time slope (i.e. time, time-squared, and time-cubed) was also significant ($P < 0.001$) and was included in the model too. Results from the primary analyses are shown in **Supplementary Material 4** (for base models) and Fig. 1 (for fully-adjusted models). Cases and controls demonstrated distinctive trajectories of SCD over time (Fig. 1a and 1b). Among cases, SCD was generally not present 18 years before index time, became more noticeable by self and informant around 12–13 years before, and became even more evident in last 4 years before diagnosis. Among controls, SCD was present since younger age (i.e. did not represent new onset at older age), with the probability of reporting SCD largely remaining constant over time. Fig. 1c displays odds ratios of reporting SCD among cases, with detailed results presented in Table 2. Informant-reported SCD was more noticeable than self-reported SCD around 9–12 years before diagnosis, became comparable to self-reported SCD around 3–8 years before, and became even more evident than self-reported SCD around 1–2 years before diagnosis.

In secondary analyses, individuals were first classified as having higher likelihood of reporting SCD (i.e. higher likelihood group) when they possessed higher than median number of SCD predictors. Based on results on the covariates that were adjusted for in initial primary analyses (Fig. 2), seven covariates were found to be significant predictors of self-reported SCD: non-White ethnicity, family history of cognitive impairment, history of heart disease, history of neurological condition, history of psychiatric condition, current presence of depressive symptoms, and current presence of anxiety symptoms. Five covariates were identified as significant predictors of informant-reported SCD: male sex, family history of cognitive impairment, history of psychiatric condition, current presence of depressive symptoms, and current presence of anxiety symptoms. Using median-split, individuals were classified as having higher likelihood of self-reported SCD if they had at least 3 of the 7 sig-

Table 1
Demographic information of the study participants at index time[a] (n = 5167), and comparison between those did and did not develop neurocognitive disorders during the follow-up period.

Variable	Overall sample (n = 5167)	Cases[b] (n = 3283)	Controls[c] (n = 1884)	P value[d]
Age, median (IQR)	81 (75–87)	81 (74–87)	81 (75–87)	0.160
Male sex, n (%)	1826 (35.3)	1239 (37.7)	587 (31.2)	**<0.001**
White ethnicity, n (%)	4263 (82.5)	2665 (81.2)	1598 (84.8)	**<0.001**
Years of education, median (IQR)	16 (14–18)	16 (14–18)	16 (14–18)	**<0.001**
Family history of cognitive impairment, n (%)	3050 (59.0)	1841 (56.1)	1209 (64.2)	**<0.001**
Diabetes mellitus, n (%)	721 (14.0)	500 (15.2)	221 (11.7)	**<0.001**
Hypertension, n (%)	3007 (58.2)	1958 (59.6)	1049 (55.7)	**0.005**
Hyperlipidemia, n (%)	2958 (57.2)	1877 (57.2)	1081 (57.4)	0.890
History of vitamin B12 deficiency, n (%)	334 (6.5)	226 (6.9)	108 (5.7)	0.110
History of thyroid disease, n (%)	1219 (23.6)	782 (23.8)	437 (23.2)	0.610
History of heart disease, n (%)	1492 (28.9)	1055 (32.1)	437 (23.2)	**<0.001**
History of neurological condition, n (%)	1031 (20.0)	906 (27.6)	125 (6.6)	**<0.001**
History of psychiatric condition, n (%)	1297 (25.1)	1103 (33.6)	194 (10.3)	**<0.001**
Current presence of depressive symptoms, n (%)	3179 (61.5)	2199 (67.0)	980 (52.0)	**<0.001**
Current presence of anxiety symptoms, n (%)	780 (15.1)	614 (18.7)	166 (8.8)	**<0.001**

IQR, interquartile range; NCD, neurocognitive disorders.
[a] Index time refers to year 0, which was the year of incident NCD for the cases, or last follow-up visit for the controls.
[b] Defined as participants who developed incident NCD during the follow-up period.
[c] Defined by participants who completed ≥10 years of follow-up and had normal cognition throughout the follow-up period.
[d] Test of difference between cases and controls: chi-square test for categorical variables, and Wilcoxon rank-sum test for continuous variables. Bold-faced p-values are <0.05.

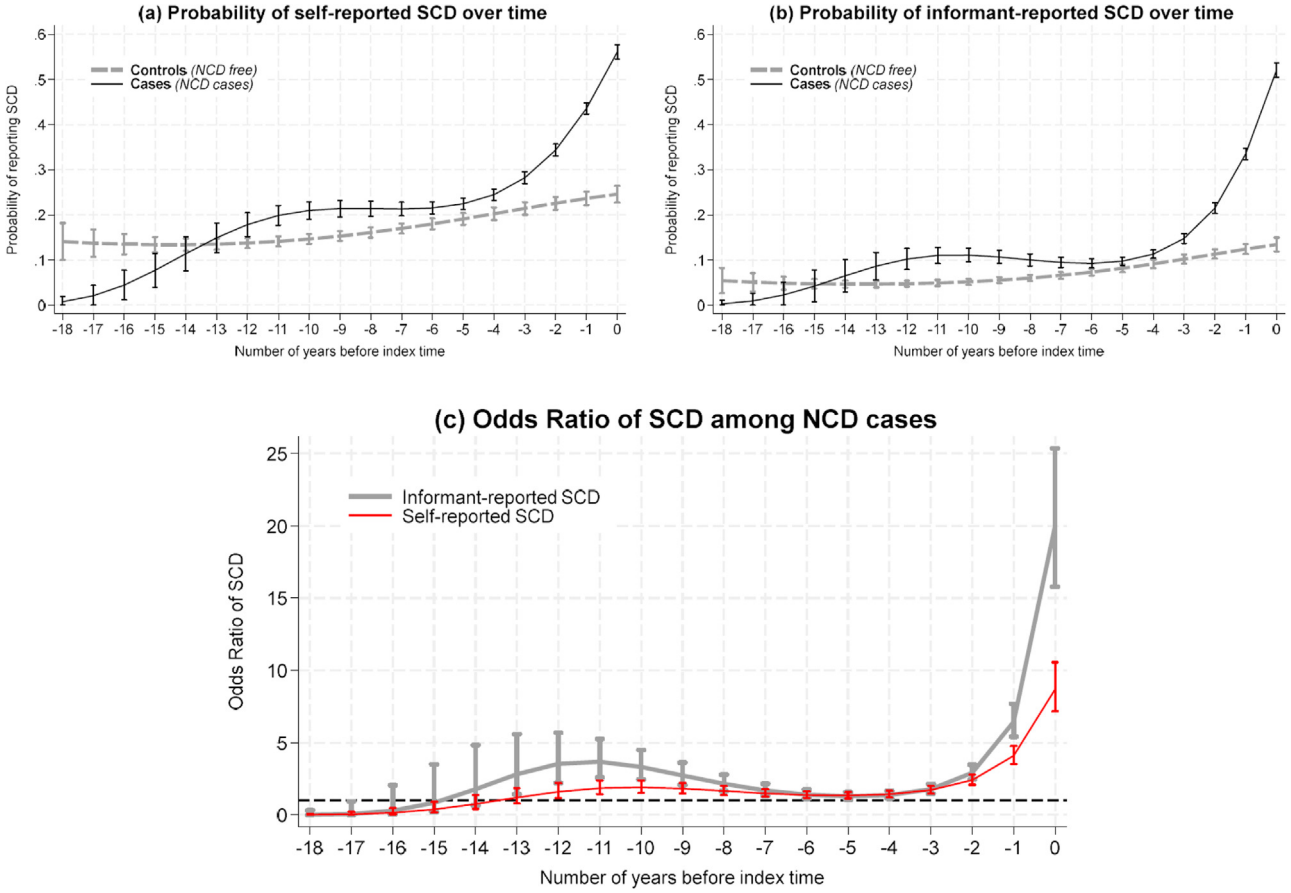

Fig. 1. Predicted probability and odds ratio of reporting subjective cognitive decline prior to the diagnosis of neurocognitive disorders, based on fully-adjusted models. SCD, subjective cognitive decline; NCD, neurocognitive disorders.
Note: Index time refers to year 0, which was the year of incident NCD for the cases, or last follow-up visit for the controls.

Table 2
Predicted probability and odds ratio of reporting subjective cognitive decline at each timepoint prior to the diagnosis of neurocognitive disorders.

Number of years before the diagnosis of NCD	Self-reported SCD				Informant-reported SCD			
	Probability of SCD in cases (95 % CI)[a]	Probability of SCD in controls (95 % CI)[a]	OR of SCD among cases (95 % CI)[a]	P value[b]	Probability of SCD in cases (95 % CI)[a]	Probability of SCD in controls (95 % CI)[a]	OR of SCD among cases (95 % CI)[a]	P value[b]
−18	0.01 (0.00–0.02)	0.14 (0.10–0.18)	0.0 (0.0–0.1)	**<0.001**	0.00 (0.00–0.01)	0.05 (0.03–0.08)	0.0 (0.0–0.3)	**0.009**
−17	0.02 (0.00–0.04)	0.14 (0.11–0.17)	0.0 (0.0–0.2)	**<0.001**	0.01 (0.00–0.03)	0.05 (0.03–0.07)	0.1 (0.0–0.9)	**0.045**
−16	0.04 (0.01–0.08)	0.14 (0.11–0.16)	0.1 (0.0–0.5)	**0.002**	0.02 (0.00–0.05)	0.05 (0.03–0.06)	0.3 (0.0–2.1)	0.211
−15	0.08 (0.04–0.12)	0.13 (0.12–0.15)	0.4 (0.2–0.9)	**0.026**	0.04 (0.01–0.08)	0.05 (0.04–0.06)	0.8 (0.2–3.5)	0.805
−14	0.11 (0.08–0.15)	0.13 (0.12–0.15)	0.7 (0.4–1.4)	0.352	0.07 (0.03–0.10)	0.05 (0.04–0.05)	1.8 (0.6–4.8)	0.265
−13	0.15 (0.12–0.18)	0.14 (0.12–0.15)	1.2 (0.8–1.8)	0.415	0.09 (0.06–0.12)	0.05 (0.04–0.05)	2.8 (1.4–5.6)	**0.003**
−12	0.18 (0.15–0.20)	0.14 (0.13–0.15)	1.6 (1.2–2.2)	**0.004**	0.10 (0.08–0.13)	0.05 (0.04–0.05)	3.5 (2.2–5.7)	**<0.001**
−11	0.20 (0.18–0.22)	0.14 (0.13–0.15)	1.8 (1.4–2.4)	**<0.001**	0.11 (0.09–0.13)	0.05 (0.04–0.06)	3.7 (2.6–5.2)	**<0.001**
−10	0.21 (0.19–0.23)	0.15 (0.14–0.16)	1.9 (1.5–2.4)	**<0.001**	0.11 (0.10–0.13)	0.05 (0.05–0.06)	3.3 (2.4–4.5)	**<0.001**
−9	0.21 (0.20–0.23)	0.15 (0.14–0.16)	1.8 (1.5–2.2)	**<0.001**	0.11 (0.09–0.12)	0.06 (0.05–0.06)	2.7 (2.1–3.6)	**<0.001**
−8	0.21 (0.20–0.23)	0.16 (0.15–0.17)	1.7 (1.4–2.0)	**<0.001**	0.10 (0.09–0.11)	0.06 (0.05–0.07)	2.1 (1.6–2.8)	**<0.001**
−7	0.21 (0.20–0.23)	0.17 (0.16–0.18)	1.5 (1.3–1.8)	**<0.001**	0.09 (0.08–0.11)	0.07 (0.06–0.07)	1.7 (1.3–2.1)	**<0.001**
−6	0.22 (0.20–0.23)	0.18 (0.17–0.19)	1.4 (1.2–1.6)	**<0.001**	0.09 (0.08–0.10)	0.07 (0.07–0.08)	1.4 (1.1–1.7)	**0.002**
−5	0.22 (0.21–0.24)	0.19 (0.18–0.20)	1.3 (1.1–1.6)	**<0.001**	0.10 (0.09–0.11)	0.08 (0.07–0.09)	1.3 (1.1–1.6)	**0.014**
−4	0.24 (0.23–0.26)	0.20 (0.19–0.22)	1.4 (1.2–1.7)	**<0.001**	0.11 (0.10–0.12)	0.09 (0.08–0.10)	1.4 (1.1–1.7)	**0.001**
−3	0.28 (0.27–0.30)	0.21 (0.20–0.23)	1.7 (1.5–2.0)	**<0.001**	0.15 (0.14–0.16)	0.10 (0.09–0.11)	1.8 (1.5–2.1)	**<0.001**
−2	0.34 (0.33–0.36)	0.23 (0.21–0.24)	2.4 (2.1–2.8)	**<0.001**	0.22 (0.20–0.23)	0.11 (0.10–0.12)	2.9 (2.4–3.5)	**<0.001**
−1	0.44 (0.42–0.45)	0.24 (0.22–0.25)	4.1 (3.5–4.8)	**<0.001**	0.34 (0.32–0.35)	0.12 (0.11–0.14)	6.4 (5.4–7.7)	**<0.001**
0	0.56 (0.54–0.58)	0.25 (0.23–0.26)	8.7 (7.2–10.5)	**<0.001**	0.52 (0.50–0.54)	0.13 (0.12–0.15)	20.0 (15.8–25.3)	**<0.001**

SCD, subjective cognitive decline; NCD, neurocognitive disorders; OR, odds ratio, CI, confidence interval.

[a] Results based on output from fully-adjusted models, which accounted for age at index time, sex, ethnicity, years of education, family history of cognitive impairment, as well as several time-dependent covariates, namely diabetes mellitus, hypertension, hyperlipidemia, history of vitamin B12 deficiency, history of thyroid disease, history of heart disease, history of neurological condition, history of psychiatric condition, current presence of depressive symptoms, and current presence of anxiety symptoms.

[b] Bold-faced p-values are <0.05.

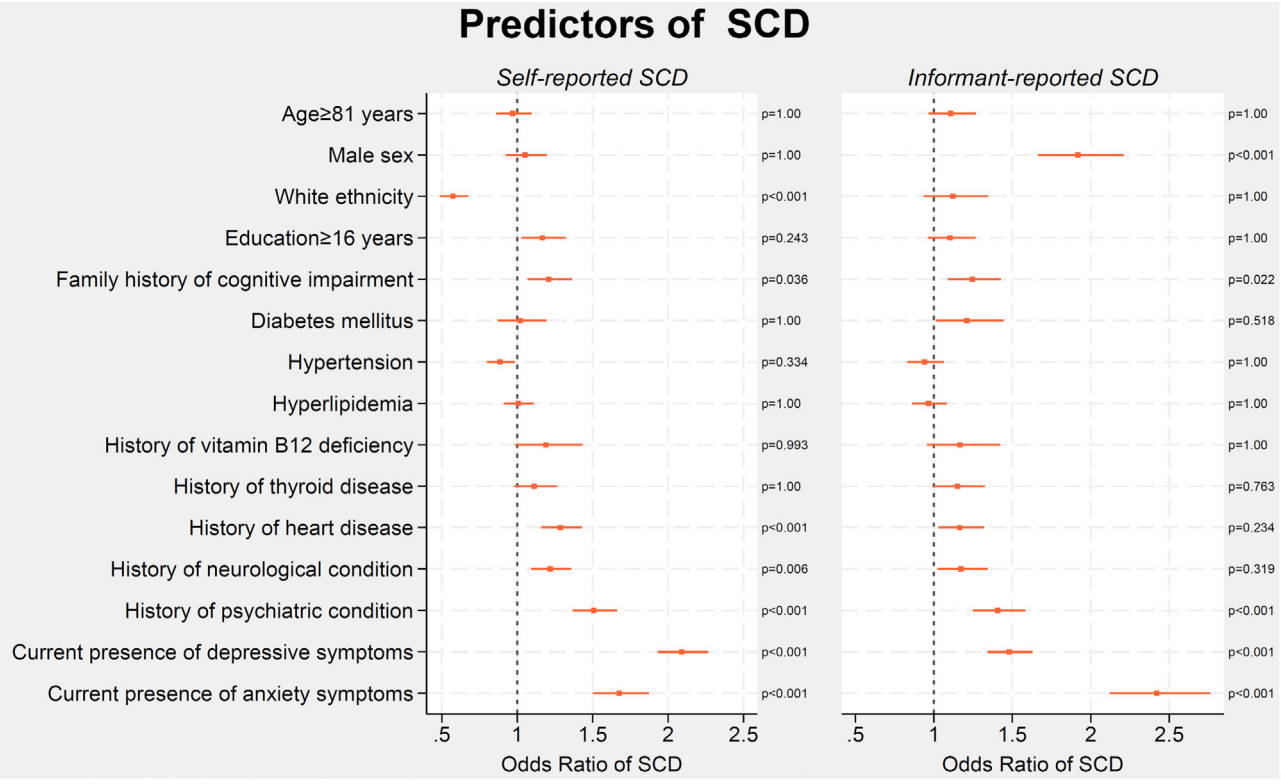

Fig. 2. Predictors of self- and informant-reported subjective cognitive decline. SCD, subjective cognitive decline.
Note: To ease interpretation, age and years of education were recoded as binary variables based on median split. The displayed p-values were Bonferroni-corrected.

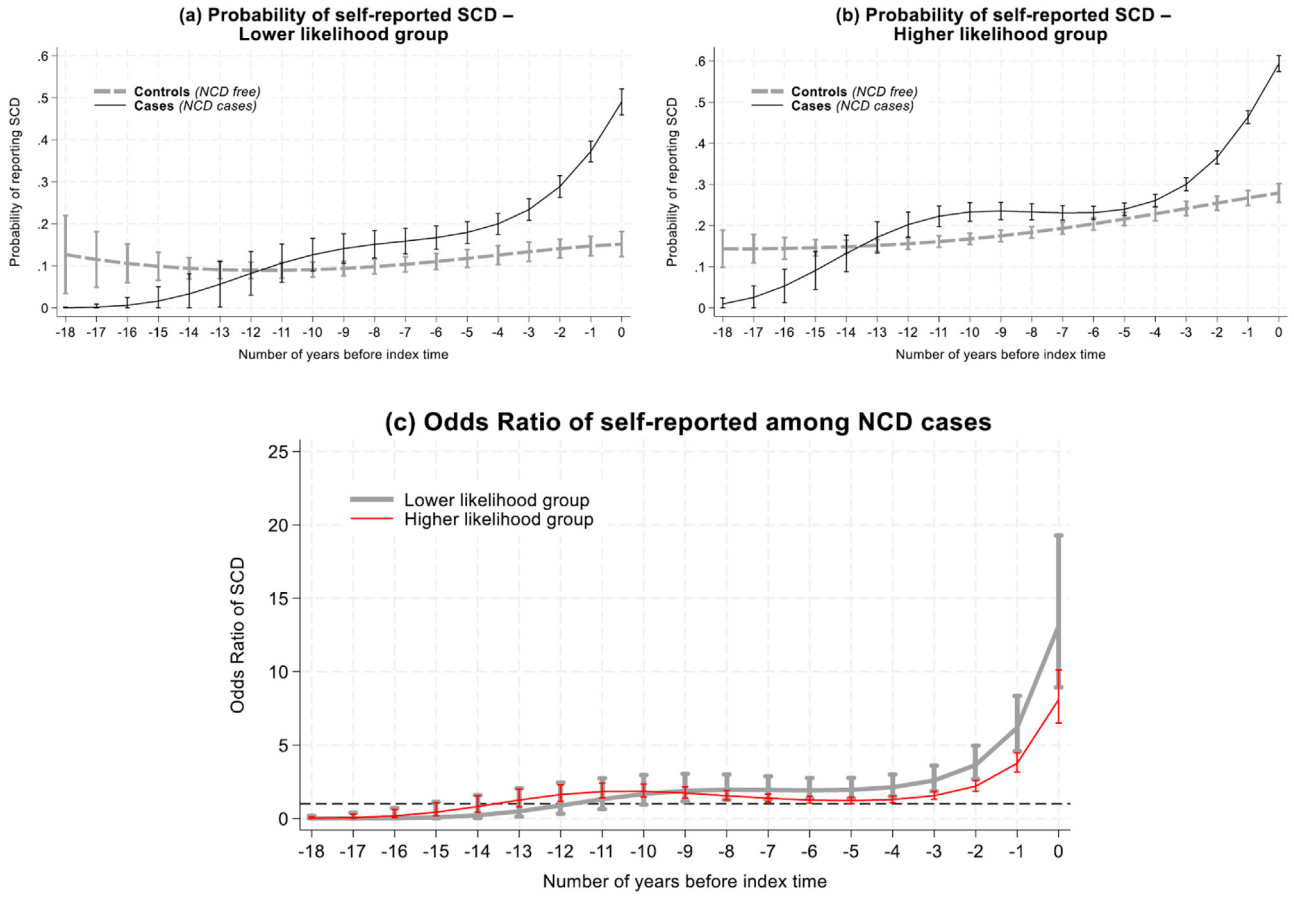

Fig. 3. Predicted probability and odds ratio of self-reported SCD prior to the diagnosis of neurocognitive disorders, stratified by those who have lower or higher likelihood of reporting SCD. SCD, subjective cognitive decline; NCD, neurocognitive disorders.
Note: Based on median split, the higher likelihood group was defined by the presence of at least 3 of the 7 significant predictors of self-reported SCD (i.e. non-White ethnicity, family history of cognitive impairment, history of heart disease, history of neurological condition, history of psychiatric condition, current presence of depressive symptoms during follow-up period, and current presence of anxiety symptoms during follow-up period). The higher likelihood group showed significant interaction with trajectories of self-reported SCD ($P_{interaction}$=*0.048*). Index time refers to year 0, which was the year of incident NCD diagnosis for the cases, or last follow-up visit for the controls.

nificant predictors, and higher likelihood of informant-reported SCD if they had at least at 3 of the 5 significant predictors.

The higher likelihood group demonstrated significant interaction with the trajectories of self-reported SCD ($P_{interaction}$=0.048), but not with the trajectories of informant-reported SCD ($P_{interaction}$=0.398). Results on the interaction between higher likelihood group and self-reported SCD are shown in Fig. 3 and **Supplementary Material 5** – The higher likelihood group maintained similar odds ratio (consistent to the primary analysis); while the lower likelihood group demonstrated even more prominent odds ratios, possibly reflecting a stronger utility of self-reported SCD among the lower likelihood group.

Results remained consistent in the sensitivity analyses when: (1) control group was redefined using a stricter criterion, based on subset with ≥14 years of follow-up with normal cognition (n = 658 in control group; with median follow-up=15.8 years, IQR=15.0–16.5, range=14.0–18.0) (**Supplementary Material 6**); (2) the analyses were reconducted in the subset of participants who volunteered in research (**Supplementary Material 7**); (3) NCD cases were further stratified by primary aetiologies of AD and non-AD (**Supplementary Material 8**); and (4) the analyses adjusted for additional covariates (i.e. obesity, uncorrected hearing loss, uncorrected vision loss, current smoking, current alcohol abuse) (**Supplementary Material 9**; for reference purposes, the distribution of these additional covariates are presented in **Supplementary Material 10**). In the fifth sensitivity analysis (**Supplementary Material 11**), the association with NCD was mainly driven by late-phase SCD (occurring after year −4), which was not unexpected given prior literature on the significance of recent-onset SCD. After excluding late-phase SCD from the model (to remove its strong effects on the model), middle-phase SCD (occurring between year −14 and year −4) then demonstrated marginal association with NCD. Of note, early-phase SCD (occurring before year −14) was consistently not associated with NCD in this sensitivity analysis.

4. Discussion

Consistent with literature, the findings showed that SCD can occur among individuals who do not progress to NCD [7,8], which, cross-sectionally, can be challenging to distinguish with SCD due to NCD [9]. In this context, the current study further added to the literature by demonstrating that the longitudinal trajectories of SCD can be more informative in identifying high-risk groups – those who developed NCD appeared to have new onset of SCD within past 20 years, which became particularly noticeable 13–14 years before diagnosis and became even more evident in the last 4 years; while those who did not develop NCD had SCD symptoms since younger age (i.e. onset >20 years ago), with the probability of SCD remaining constant over time. SCD trajectories remained useful even among individuals with higher baseline rates of SCD (e.g. those with history of psychiatric conditions), although among those with lower baseline rates of SCD, the trajectories of self-reported SCD became even more useful in differentiating those who did and did

not eventually develop NCD. The distinctive SCD trajectories were maintained even across NCD aetiologies of AD and non-AD.

The findings bear a strong resemblance to two previous studies that evaluated the severity of SCD prior to the onset of NCD [10,11]. The study by Verlinden et al. [10] demonstrated that individuals with NCD experienced increasing severity of SCD particularly in the last 4 years before diagnosis, while those without NCD reported SCD that did not worsen in severity over time. Meanwhile, the study by Amieva et al.[11] showed that individuals with NCD had lower severity of SCD 14 years before diagnosis, with the SCD severity rising 8–14 years before diagnosis, stabilizing 4–8 years prior, and increasing further in last 4 years before diagnosis. In contrast, those without NCD maintained stable severity of SCD over time. Of note, these two prior studies utilized SCD severity scores (i.e. continuous variable), and could provide a clearer reflection of the evolution of SCD severity over time.

Unlike the two prior studies [10,11], the current study utilized a binary response (yes/no) for SCD measurement and generated predicted probabilities in the results. In contrast to SCD severity scores from the prior studies [10,11], the predicted probabilities in this study may be less intuitive to interpret. Predicted probabilities can be interpreted at the group level to reflect the proportion of individuals who are likely to report SCD at each timepoint (e.g. in the last 4 years before MCI/dementia diagnosis, around 20–50 % of individuals in this group would have endorsed the symptom of self-reported SCD, as seen in Fig. 1a). At the same time, predicted probabilities can also be interpreted at the individual level to reflect a person's likelihood of reporting SCD at specific timepoints (e.g. in the last 4 years before MCI/dementia diagnosis, individuals are increasingly more likely to report SCD).

Despite the key difference in methodology, the current findings still align closely with those of the previous studies [10,11], plausibly suggesting that the predicted probabilities from the current study may reflect SCD severity over time. If the findings could be true, they possibly suggest three phases in the evolution of SCD symptoms prior to NCD diagnosis – onset of SCD in the initial years, stable symptoms over the next 5–10 years, and further worsening of SCD in last few years before diagnosis. In a way, these findings parallel the literature on objective cognitive assessments, where the diagnostic criteria for NCD often emphasize the need to consider premorbid abilities and longitudinal changes when interpreting impairments in objective cognitive assessments, distinguishing them from cognitive deficits in neurodevelopment disorders which are longstanding and do not worsen over time [37].

Potentially, the findings may have research, clinical and public health implications. In current research practice, existing SCD scales often evaluate for symptom changes over a 10-year horizon (e.g. in the Everyday Cognition Scale, and the Informant Questionnaire on Cognitive Decline in the Elderly) [38,39], which is in line with previous reports that SCD is detectable 5–10 years before NCD [40,41]. Yet current findings also suggest the need for SCD scales to cover a longer horizon – possibly over 15–20 years – to better capture the new onset of SCD within this longer timeframe. In clinical settings, patients who present with SCD may benefit from careful clinical evaluation of the longitudinal symptoms of SCD. Those with longitudinal characteristics suggestive of high-risk SCD (i.e. new onset of SCD within the past 20 years, with further worsening in the past years) can then be directed to further patient counselling, disease monitoring and preventive interventions [42–44]. Such approach is in line with growing interests to identify high-risk individuals for early interventions, given current understanding that interventions to preserve brain functions are more beneficial when provided early and before irreversible neuronal cell death has occurred [16,45,46]. From the public health perspective, although SCD has been identified as a public health issue [5,6], it can sometimes be difficult for laypersons to tell whether a cognitive concern is a part of normal ageing, or reflects a genuine issue that should prompt further health-seeking behaviour. The findings on SCD trajectories may possibly guide the crafting of public health messaging on SCD, particularly focusing on the onset and progression of SCD over time to identify those who are at high risk of NCD.

Several limitations should be considered. First, a large majority of participants in this study were of White ethnicity and had high educational attainment (median education of 16 years). Although efforts were done to stratify results for non-White ethnicities and those with lower educational attainment (e.g. Figs. 2 and 3), the results of this study may not fully represent these subgroups of individuals and would benefit from further validation. Second, the SCD measure in this study only focused on the memory domain. While this may not be an uncommon practice in current literature [47,48], such SCD measure may not have captured the full range of cognitive concerns, especially in the non-memory domains [49]. Third, SCD was measured based on a binary (yes/no) response. Hence, the predicted probabilities from the analyses should mainly be interpreted as the likelihood a person experiencing SCD at each timepoint. Although the SCD trajectories bore much similarity with two previous studies on SCD severity [10,11], readers should exercise caution in interpreting the predicted probability as a reflection of SCD severity. Fourth, the control group was not defined using disease biomarkers, and hence may still include some individuals with preclinical NCD who could possibly develop NCD if follow-up duration is extended. Arguably, this limitation may not be as critical, considering the rather distinctive trajectories in cases and controls, the reasonably long follow-up duration for most participants in the control group (median follow-up=12.6 years; IQR=11.1–15.1), and the consistency of results in sensitivity analysis when controls were defined by even longer period of observations (median follow-up=15.8 years; IQR=15.0–16.5). Moreover, with a median age of 81 years in the control group, it is probably less likely for individuals in this group to progress to NCD after ≥11–15 years of follow-up with normal cognition. Fifth, the number of participants with 14 to 18 years of follow-up were relatively smaller, compared to those with shorter duration of follow-up (**Supplementary Material 3**). Although mixed-effect models could account for such variation in the duration of follow-up, readers should still exercise caution in interpreting the findings related to early-phase SCD (i.e. those occurring before year −14; due to the relative smaller number of observations during this time period), and treat the findings related to this time period as preliminary and requiring further validation. Sixth, inasmuch as the analyses adjusted for many covariates, there are still other potential confounders (i.e. known predictors of both SCD and NCD) [25] that were not captured in NACC and hence could not be adjusted for (e.g. folate deficiency, personality traits and distressing life events) [2,50–52].

In conclusion, SCD may have distinctive trajectories among those who do and do not progress to NCD – those who progress to NCD seem to have new onset of SCD within past 20 years, which becomes more noticeable in last 4 years before diagnosis; while those who do not progress to NCD report SCD since younger age with plausibly no worsening over time. In research practice, the findings possibly suggest the need for SCD scales to evaluate for symptom changes over a longer, 20-year horizon to better capture the new onset of SCD within this longer timeframe. From the clinical and public health perspective, the findings on distinctive trajectories can facilitate stratification of NCD risk to tailor early interventions, as well as guide public health messaging to distinguish bona fide SCD from normal ageing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Tau Ming Liew reports financial support was provided by National Medical Research Council. Tau Ming Liew reports financial support was provided by Prime Minister's Office. Tau Ming Liew reports a relationship with Lundbeck LLC that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Tau Ming Liew: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Ethical standards

All contributing Alzheimer's Disease Centers obtained informed consent from their participants, as well as received approval by their local institutional review boards.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100123.

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