Subjective cognitive decline and subsequent dementia: a nationwide cohort study of 579,710 people (66 year-olds) in South Korea

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Research

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Abstract

Background: Subjective cognitive decline (SCD) is a potential risk factor for dementia. We aimed to investigate the association between SCD and subsequent dementia in a nationwide population-based cohort in South Korea.

Methods: This cohort included 579,710 66-year-old adults who completed a questionnaire about SCD and were followed-up for a total of 3,870,293 person-years (average 6.68 years per person). Hazard ratios were estimated using the Cox proportional hazards model and compared between subjects with and without SCD.

Results: Compared to subjects without SCD, those with SCD were more likely to develop dementia (incidence per 100,000 person-years: no SCD: 566.14; SCD: 859.35). After adjusting for potential confounding factors, the risk of subsequent dementia significantly increased in subjects with SCD, with an adjusted hazard ratio (aHR) of 1.38 (95% confidence interval [CI] 1.34 to 1.41). The risk of subsequent dementia was greatly increased in subjects with higher SCD scores (aHR=2.77, 95% CI 2.47 to 3.11). A significant association between SCD and dementia was observed in both depressive and non-depressive symptom groups (aHR=1.50, 95% CI 1.42 to 1.57 in subjects with depressive symptoms; aHR=1.33, 95% CI 1.29 to 1.37 in subjects without depressive symptoms; P =0.001).

Conclusions: In the participating 66-year-old population, SCD was significantly associated with an increased risk of subsequent dementia, independent of the presence of depressive symptoms. Our findings suggest that SCD indicates a risk for dementia. Further studies are needed to delineate potential approaches to preventing the development of dementia in individuals with SCD.

Background

Dementia represents one of the most prevalent neuropsychiatric conditions worldwide and is present in approximately 10% of people aged 65 and older [1]. Moreover, the public health burden of dementia is growing more rapidly than any other disease [2]. Research has reported that 26–49% of people worry about developing dementia and identify dementia as their most feared illness, over cancer, heart disease, stroke, and diabetes [3]. Aging is concomitant with increased episodes of forgetfulness, and memory complaints are prevalent in approximately 25–50% of older adults [4]. Previous studies have found that memory complaints may relate to subclinical psychiatric symptoms [4–6], but they can also represent an early indicator of dementia, including Alzheimer's disease (AD) [7–11]. Considering the growing number of patients with dementia and the associated medical and social burden, it is important to characterize at-risk or preclinical states of dementia in order to facilitate early interventions to reduce cognitive impairment in the future.

As part of this effort, considerable progress has been made in investigating the prospective dementia risk associated with subjective cognitive decline (SCD) [12, 13]. SCD refers to a subjective experience of cognitive decline without objective cognitive deficits [13]. Evidences indicate that SCD may be an early

symptom of AD, representing the preclinical stage [8–11], which can progress to mild cognitive impairment (MCI) and dementia in the AD continuum [11–14]. However, SCD is also associated with poor physical health and psychiatric disorders such as depression, which confounds the association with dementia [15, 16]. For example, depression is a major risk factor for dementia, and previous work has indicated that SCD could be linked with subsyndromal depressive symptoms rather than with subsequent dementia [17]. Considerable heterogeneity present across numerous small studies has contributed to conflicting results and has prevented consensus in the field [15–17].

Regarding the recruitment setting, it has been observed that SCD in memory clinic cases increased the risk of dementia [9], whereas SCD in community populations showed less significant or non-significant associations [9, 18]. Given that the concerns and health-seeking behaviors of community-recruited older adults may differ from those of memory clinic patients [9], investigations using a large community sample would improve the accuracy for estimating the SCD-associated risk for incident dementia in the general population.

This study analyzed a nationwide population-based cohort, which includes 51.8% of the 66-year-old adult population in South Korea. We aimed to 1) determine whether the risk of subsequent dementia increases in subjects with SCD compared to those without SCD, 2) to evaluate whether the severity of subjective memory impairment is associated with subsequent dementia, and 3) to examine whether depressive symptoms affect the association between SCD and subsequent dementia.

Methods

Data sources and study cohort

Data were obtained from the South Korean National Health Insurance Service (NHIS) database (supplementary methods) [19]. The NHIS provides mandatory healthcare for 97% of South Koreans under a single-payer model. It further provides the National Screening Program for Transitional Ages (NSPTA), an age-specific national health examination program for all Korean citizens aged 40 and 66 [20]. Our study population consisted of a subset of individuals from the NHIS database who participated in the NSPTA at age 66, between 2009 and 2011. The study population included 51.8% of the total South Korean population (aged 66) during the enrolment period. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital. Because the National Health Insurance Service (NHIS) provided encrypted data to protect private information, the need to obtain informed consent was waived (approval No. X-1901-517-902).

Inclusion and exclusion criteria

We included all subjects who had available information on the Pre-screening Korean Dementia Screening Questionnaire (KDSQ-P), a cognitive function questionnaire [21]. Exclusion criteria were as follows: 1) individuals who reported impaired activities of daily living (ADLs) function; 2) individuals with dementia, MCI, or a documented history of dementia medication (donepezil, rivastigmine, galantamine, or

memantine) before the index date, the first day of the follow-up; 3) individuals with a psychotic disorder; 4) individuals with missing or duplicate data on the primary variable of interest or on covariates; 5) individuals with outlier values on analyzed continuous variables (mean ± 4 standard deviations); and 6) individuals who died or dropped out between the time they participated in the NSPTA and the index date. More detailed criteria are described in the supplementary methods.

Primary independent variable of interest: SCD

SCD was defined using the KDSQ-P, a validated self-report questionnaire consisting of five questions [21]. Each item has three possible choices: “no”, “sometimes yes”, or “frequently yes”, scored as 0, 1, and 2, respectively. Overall KDSQ-P scores range from 0 to 10, with higher scores indicating greater degrees of subjective memory impairment. Those who score ≥4 points are advised to seek further evaluation of their cognitive function. All items of the KDSQ-P are presented in Table S1. We defined SCD based on a scoring of 1 or 2 (a positive answer) on the responses to item 2: “Do you think your memory has declined compared to a year ago?”

Primary outcomes

The primary outcome was the incidence of dementia following SCD. Dementia was defined based on the International Statistical Classification of Diseases, 10^{th} revision codes (F00-F03, G30, or G31) and the use of cognitive-enhancing medications. The onset date of dementia was considered to be the first date for which patients were both diagnosed with dementia, and prescribed with dementia medication. Detailed information is described in the supplementary methods.

Covariates

We assessed demographic variables such as sex and income. Lifestyle variables such as smoking status, alcohol consumption habits, and exercise frequency were included as covariates. We further adjusted for healthcare visit frequency, laboratory test results, physical examination results, and the patient’s medical history, including information related to psychiatric disorders, neurological diseases, and medical diseases (Table S2). To assess depressive symptoms, we used a depression screening questionnaire (DSQ, range 0–3), with higher scores indicating more depressive symptoms. Detailed information is presented in the supplementary methods.

Statistical analysis

To investigate the association between SCD and the incidence of dementia, study participants were followed from the index date (January 1 of the year after each participant participated in the NSPTA) until the date of onset of dementia, death, or the end of follow-up (December 31, 2017), whichever occurred first. For all participants, between group differences for continuous and categorical variables were assessed using *t*-tests and Chi-squared tests, respectively. Cox proportional hazard regression analysis was conducted to determine adjusted hazard ratios (aHRs) for SCD in predicting subsequent dementia,

after controlling for covariates. The effect of SCD on subsequent dementia was first analyzed in a sex-adjusted model, and then in three additional models adjusted for various covariates (Models 1 to 3). In the secondary analysis, we used the total KDSQ-P score as an independent variable to evaluate the association between the severity of subjective memory impairment and subsequent dementia. We also used an SCD and depressive symptoms interaction term to test the potential for an interaction effect on subsequent dementia.

The proportional hazards assumption and multicollinearity between all covariates were tested. We performed an additional analysis by sampling the control group using the propensity score matching method based on logistic regression. We also performed survival analyses for sensitivity analysis after excluding the following subgroups: Patients who developed dementia within one year of the index date, patients with dementia other than AD, patients with dementia due to AD, patients with a history of psychiatric disorders, patients with a history of neurological diseases, patients with depressive symptoms according to the DSQ, and patients with a KDSQ-P score ≥4 (the cut-off point for further dementia screening tests) [21]. Detailed information is presented in the supplementary methods.

Statistical analyses were conducted using two-tailed tests, a significance level of 0.05, and 95% confidence intervals (CIs). All analyses were conducted using SAS Enterprise Guide version 7.2 (SAS Institute, Inc.) and R Studio version 1.0.136 (R Studio, Inc., with packages "*Survival*" version 2.43-3 and "*Survminer*" version 0.4.3).

Results

During the 2009-2011 period, a total of 650,861 individuals participated in the NSPTA and had KDSQ-P information available. Of these, we excluded 21,458 individuals who reported impaired ADL function; 12,658 individuals with dementia, MCI, or with a documented history of cognitive-enhancing medication; 18,760 individuals with missing or duplicate data; 14,315 individuals with outlier data; 2,632 individuals with a psychotic disorder; and 1,328 individuals who died or were lost to follow-up between their NSPTA participation date and the index date. A final total of 579,710 subjects were included in the study population for analysis, of which 222,056 (38.3%) experienced SCD (see the flowchart of study participants in Figure S1 in the online supplement). They were followed-up for a total of 3,870,293 person-years (average 6.68 years per person).

Subject characteristics

The clinical and demographic characteristics of the participants at baseline are presented in Table 1. The study population consisted of 266,311 (45.9%) men and 313,399 (54.1%) women. Compared to the non-SCD group, those with SCD tended to be female, did not smoke, consumed more alcohol, exercised more, visited healthcare facilities more frequently, had more medical or medication history, and had higher cholesterol levels and lower fasting glucose, hemoglobin, and blood pressure.

Risk of subsequent dementia according to SCD

Among individuals with SCD, the incidence of dementia was 859.35 per 100,000 person-years, which was higher than individuals without SCD who developed dementia at an incidence of 566.14 per 100,000 person-years (Table 2). The SCD group had a higher cumulative incidence of dementia compared to the non-SCD group (log-rank P<0.001, Figure 1). When adjusted for clinical factors (Model 3), subjects with SCD had an increased risk of subsequent dementia (aHR=1.38, 95% CI 1.34 to 1.41 in Model 3; see Table 2). The aHRs were consistent in both men and women across all Cox regression models tested, despite controlling for various covariates. The propensity score matched analysis also confirmed that the presence of SCD increased the risk of subsequent dementia (aHR=1.39, 95% CI 1.36 to 1.43 in Model 3).

Association between severity of subjective memory impairment and subsequent dementia

Additional questions for SCD in the KDSQ-P were also significantly associated with risk of subsequent dementia (see Table S1 in the online supplement). Subjects, who answered “frequently yes” for each question, had a higher risk for subsequent dementia than those who answered “sometimes yes”. Additionally, the total KDSQ-P score was significantly associated with risk of subsequent dementia (Figure 2). Specifically, subjects with higher KDSQ-P scores tended to have a higher risk of developing subsequent dementia. The risk of dementia in subjects with a score of 9 or 10 was approximately three times higher than in subjects with a score of 0.

Effect of interaction between SCD and depressive symptoms on subsequent dementia

Figure 3 shows the estimated effect of SCD on subsequent dementia after accounting for depressive symptoms. Regardless of the presence of depressive symptoms, SCD was significantly associated with a risk for subsequent dementia. Notably, the effect of SCD on subsequent dementia was particularly prominent in the presence of depressive symptoms (in subjects with depressive symptoms, aHR=1.50, 95% CI 1.42 to 1.57; in subjects without depressive symptoms, aHR=1.33, 95% CI 1.29 to 1.37; interaction P=0.001).

Sensitivity analysis for the association between SCD and subsequent dementia

Even after iteratively removing subgroups from our subjects, the risk of subsequent dementia was consistently associated with SCD (see Table S3 in the online supplement). First, we excluded patients diagnosed with subsequent dementia within one year of the index date to avoid the onset of actual dementia before reporting SCD. In excluding these patients, our analysis demonstrated the robustness of the link between SCD and subsequent dementia in our study cohort (aHR=1.37, 95% CI 1.34 to 1.41 in Model 3). The results were also consistent when subsequent dementia was subdivided into AD (excluding dementia other than AD, aHR=1.38, 95% CI 1.35 to 1.42 in Model 3) and dementia other than AD (excluding AD, aHR=1.37, 95% CI 1.30 to 1.45 in Model 3). The definition and the incidence of dementia other than AD are presented in Table S2. We also observed a significant association between SCD and subsequent dementia after excluding individuals with psychiatric disorders (aHR=1.38, 95% CI 1.34 to 1.43 in Model 3), patients with neurological diseases (aHR=1.43, 95% CI 1.38 to 1.49 in Model 3), patients

with depressive symptoms according to the DSQ (aHR=1.33, 95% CI 1.29 to 1.37 in Model 3), and patients with KDSQ-P scores ≥4 (aHR=1.18, 95% CI 1.14 to 1.21 in Model 3).

Discussion

In this nationwide population-based study of 579,710 66-year-old adults, subjects with SCD were more likely to develop subsequent dementia than those without SCD over a follow-up period of up to eight years. The association between SCD and subsequent dementia was robust across sex, subtype of dementia (AD or other than AD), history of psychiatric disorders or neurological diseases, and presence of depressive symptoms. The severity of subjective memory impairment was also associated with risk of subsequent dementia. Furthermore, the significant association between SCD and dementia was independent of the presence of depressive symptoms.

The positive association between SCD and subsequent dementia found in our study is generally consistent with previous studies. A recent population-based study (N = 2,710) reported an aHR in SCD similar to that of our study (aHR = 1.18, 95% CI 1.03 to 1.33) [18]. Moreover, the prevalence of SCD in our study was 38.3% (222,056 in 579,710), which is comparable to prevalence estimates of previous community-based studies that ranged from 22.1–56.0% [4]. However, the rate of incident dementia and risk of subsequent dementia in the SCD group compared to the non-SCD group in our study were lower than in previous studies. In a recent multi-center cohort study of 4,369 participants, the incidence rate of dementia in patients with SCD was reported to be 17.7 per 1,000 person-years [9], which is higher than our result of 8.6 per 1,000 person-years. Discrepancies between our results and those of previous SCD studies may be due to the heterogeneity of the study populations [9, 11]. Reports have indicated that, when compared to community populations, patients who visited memory clinics had a higher conversion rate from normal cognition to MCI [22], from SCD to AD [9], and from MCI to AD [23]. The higher conversion rate observed in memory clinic samples has been attributed to the subjects' greater likelihood of experiencing the early signs of neurodegenerative disease and of spontaneously reporting memory complaints [8, 9, 13, 22, 23]. More importantly, decreased functional abilities were found in memory clinic attendees at the baseline, which indicates a significant risk for dementia [22, 23]. In contrast to previous studies, our study consisted of subjects obtained from a population-based setting, and thus better illustrates the robust association between SCD and subsequent dementia in the general population. Additionally, in accordance with the suggested features of SCD, including onset at 60 years or older and only lasting a few years [13], the homogeneity of age in our study subjects represents the strength for observing the association between SCD and subsequent dementia.

Our analysis showed a higher rate of conversion from SCD to dementia in women than men (6.5% vs. 4.8%) but no sex difference in the aHR (aHR = 1.38, 95% CI 1.33 to 1.42 for women; aHR = 1.38, 95% CI 1.32 to 1.44 for men; Table 2). Some studies reported women to be more susceptible than men to conversion from SCD to dementia [24, 25], whereas others found no significant sex difference [7, 9, 18]. Some have reported a tendency for women to report SCD worries with a higher sensitivity to subtle cognitive symptoms relating to dementia progression when compared to men [26]. However, in our study,

after adjusting for various clinical factors and sociodemographic variables, it appears that the risk of dementia associated with SCD was comparable in both sexes.

Our results also highlight the positive linear association between the severity of subjective memory impairment and subsequent dementia (Fig. 2). This finding suggests that the more severe the subjective memory complaints, the greater the risk of subsequent dementia. KDSQ-P, a validated pre-screening tool for dementia [21], includes items measuring subjective memory and instrumental ADLs using multiple response types. In a recent review of self-report measures used in the SCD working group, most measures included multiple items (mean = 18.8 items) [27]. Moreover, many of them ask about specific memory (70.7%) and functional decline (41.6%) to assess SCD [27]. The use of a general question to identify the presence of SCD and a variety of additional questions regarding specific subjective memory impairment may also clarify the effect of well-defined features of SCD on subsequent dementia.

In this study, the SCD group with depressive symptoms had a greater risk for subsequent dementia than the group without depressive symptoms, with a significant interaction effect (Fig. 3). Although depressive symptoms are regarded as a crucial factor for subsequent dementia due to their association with cognitive disorders [6, 12, 15, 28], previous studies have found a minimal effect of mood scores on the association between SCD and further cognitive decline [7, 18, 29]. This is possibly attributable to the limited size of the studies. Our results imply that SCD and depressive symptoms not only act as independent risk factors for dementia, but also contribute to its development through their interaction.

We observed that SCD was likely to be an incipient symptom of both AD and non-AD related dementias (see Table S3 in the online supplement). Previous studies have reported inconsistent results regarding the association between SCD and non-AD dementia, such as vascular dementia, Lewy body dementia, and frontotemporal lobar degeneration [7, 9]. Although the typical symptoms of dementia differ according to the case, memory dysfunctions may represent an early symptom in all forms of dementia [30]. Importantly, memory dysfunctions can have diverse manifestations including difficulties with episodic and semantic memory and encoding, retrieval, and recognition. Our results suggest that SCD can broadly be used as a risk indicator for a myriad of cognitive disorders such as AD and non-AD dementias.

The major strength of our study was the use of the largest nationwide representative cohort dataset to date that relates SCD to subsequent dementia. We analyzed 579,710 eligible subjects, extracted from over 50 million entries in the NHIS database. Clinical cohorts in SCD research have relatively small to modest numbers of selective participants, ranging from 42 to 4,500 [9, 27]. In addition, studies which have assessed the risks associated with subjective memory complaints have used diverse and inconsistent characteristics, including the number of participants (17 to 2,901), age (18 to 87), follow-up periods (1 to 15 years), operational criteria for defining SCD, and methods of assessing dementia [5, 11, 27]. Consequently, when these studies are combined for meta-analysis, the significant heterogeneity between studies may add considerable noise towards estimating the association between SCD and dementia. As an additional strength, our results are based on the mandatory national healthcare screening service, which is more reflective of the general population, and might be more robust and

generalizable than studies conducted through memory clinics. In this study, measuring SCD in a large homogeneous community population with comprehensive information enabled us to investigate SCD and risk for both AD and non-AD dementia with a wide range of clinical covariates, extended time frame, consideration of depressive disorder and subclinical symptoms, and comparison with peers of the same age without SCD.

This study also has several limitations. First, the main weakness is the lack of objective cognition test results. Normal performance on standardized cognitive tests is one of the research criteria for SCD [13]. To reduce bias related to this limitation, we excluded subjects with pre-existing cognitive decline from the analysis, namely subjects with impaired ADLs, a documented history of dementia, MCI, or with a prescription for dementia medication. Second, although we comprehensively adjusted for various confounds, we did not consider the years of education, occupational attainment, family history, imaging biomarkers, or other potentially relevant confounds. Third, the operational definition of AD may be susceptible to misdiagnosis or underdiagnosis, although the rate of AD in our study population was similar to the rates reported in epidemiological studies conducted in South Korea [31]. Finally, because the study population included individuals from only a single country, our findings may not be generalizable to people of other backgrounds.

Conclusions

In conclusion, our study that uses a population-based cohort is the largest to date, and demonstrates the importance of SCD as an early, independent risk factor for dementia. These findings thus provide strong evidence for the role of SCD in characterizing the initial high-risk stage of dementia. As a growing public health issue, SCD should be further investigated as a risk-factor for dementia. Giving additional attention to SCD as a risk factor for dementia could facilitate more focused surveillance from the public and healthcare professionals. However, it may not be appropriate for the public to view SCD as a disease state that should be actively treated. Instead, an approach focused on prevention for people with SCD, including lifestyle modifications or providing education on dementia, could be promising. Future studies should further explore the clinical and neurobiological nature of SCD as an early sign of dementia.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital. Because the National Health Insurance Service (NHIS) provided encrypted data to protect private information, the need to obtain informed consent was waived (approval No. X-1901-517-902).

Consent for publication

Not applicable

Availability of data and materials

This study is based on National Health Insurance Service (NHIS) registry data in South Korea (NHIS-2019-1-211). Because these data belong to the NHIS, the authors are not permitted to share them, except in aggregate (as, for example, in a publication). However, interested parties can obtain the data on which the study was based by submitting a research protocol to the NHIS (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do). The analytic/statistical codes are available from the corresponding author (wjmyung@snubh.org, WM), upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YCL and HL conceived and designed the study, acquired and analyzed the data, interpreted the study findings, and drafted the manuscript. JMK conceived and designed the study; defined the exclusion criteria and exposure, outcome, and covariate categories; interpreted the study findings; and drafted the manuscript. KK, SK, TYY, EML, CTK, and DKK designed the study; defined the exclusion criteria and exposure, outcome, and covariate categories; interpreted the study findings; and drafted the manuscript. HHW, FJ, and WM conceived and designed the study, interpreted the study findings, supervised and directed the conduct of the study, and critically reviewed the manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. HHW and WM are the guarantors of the work. YCL, JMK and HL contributed equally to this work as co-first authors. HHW (wonhh@skku.edu) and WM (wjmyung@snubh.org) contributed equally to this work and should be considered as co-corresponding authors. All authors read and approved the final manuscript.

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Abbreviations

AD, Alzheimer’s disease; ADL, activities of daily living; aHR, adjusted hazard ratio; CI, confidence interval; DSQ, depression screening questionnaire; HDL, high-density lipoprotein; KDSQ-P, Pre-screening Korean Dementia Screening Questionnaire; LDL, low-density lipoprotein; MCI, mild cognitive impairment; NHIS, National Health Insurance Service; NSPTA, National Screening Program for Transitional Ages; SCD, subjective cognitive decline; SD, standard deviation.

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Tables

Table 1. Descriptive characteristics of the study population

	Total (N=579,710)	Non-SCD group (n=357,654)	SCD group (n=222,056)	P-value
Sex				<0.0001
Male	266,311 (45.9%)	173,795 (48.6%)	92,516 (41.7%)	
Female	313,399 (54.1%)	183,859 (51.4%)	129,540 (58.3%)	
Income				<0.0001
Medicaid aid	33,023 (5.7%)	19,101 (5.3%)	13,922 (6.3%)	
Group 1 (1^{st} to 6^{th} ventiles)	125,064 (21.6%)	82,491 (23.1%)	42,573 (19.2%)	
Group 2 (7^{th} to 14^{th} ventiles)	178,625 (30.8%)	110,550 (30.9%)	68,075 (30.7%)	
Group 3 (15^{th} to 20^{th} ventiles)	242,998 (41.9%)	145,512 (40.7%)	97,486 (43.9%)	
Lifestyle factors				
Smoking status				<0.0001
Never smoked	406,103 (70.1%)	250,238 (70.0%)	155,865 (70.2%)	
Ex-smoker	95,502 (16.5%)	57,647 (16.1%)	37,855 (17.0%)	
Current smoker	78,105 (13.5%)	49,769 (13.9%)	28,336 (12.8%)	
Alcohol consumption				<0.0001
No drinking: rarely	508,547 (87.7%)	314,324 (87.9%)	194,223 (87.5%)	
Light drinking: 3–4 times per week	38,840 (6.7%)	23,954 (6.7%)	14,886 (6.7%)	
Heavy drinking: almost every day	32,323 (5.6%)	19,376 (5.4%)	12,947 (5.8%)	
Exercise frequency				<0.0001
Exercise	327,775 (56.5%)	200,723 (56.1%)	127,052 (57.2%)	
No exercise	251,935 (43.5%)	156,931 (43.9%)	95,004 (42.8%)	
Healthcare visit frequency *				
First quartile	144,858 (25.0%)	93,542 (26.2%)	51,316 (23.1%)	
Second quartile	144,945 (25.0%)	89,583 (25.1%)	55,362 (24.9%)	
Third quartile	144,988 (25.0%)	88,208 (24.7%)	56,780 (25.6%)	
Fourth quartile	144,919 (25.0%)	86,321 (24.1%)	58,598 (26.4%)	
Past medical history				
Psychiatric disorders				
Depression	48,653 (8.4%)	26,676 (7.5%)	21,977 (9.9%)	<0.0001
Bipolar affective disorder	1,891 (0.3%)	1,059 (0.3%)	832 (0.4%)	<0.0001
Substance use disorder	3,522 (0.6%)	2,035 (0.6%)	1,487 (0.7%)	<0.0001
Panic disorder	2,315 (0.4%)	1,298 (0.4%)	1,017 (0.5%)	<0.0001
Obsessive-compulsive disorder	671 (0.1%)	370 (0.1%)	301 (0.1%)	0.001
Personality disorder	237 (0.0%)	142 (0.0%)	95 (0.0%)	0.619
Other psychiatric disorder	140,212 (24.2%)	81,764 (22.9%)	58,448 (26.3%)	<0.0001
Neurological diseases				
Cerebrovascular disease	80,212 (13.8%)	46,895 (13.1%)	33,317 (15.0%)	<0.0001

Epilepsy	8,622 (1.5%)	4,807 (1.3%)	3,815 (1.7%)	<0.0001
Migraines	43,466 (7.5%)	25,304 (7.1%)	18,162 (8.2%)	<0.0001
Headaches	70,207 (12.1%)	40,791 (11.4%)	29,416 (13.2%)	<0.0001
Sleep disorder	63,769 (11.0%)	36,635 (10.2%)	27,134 (12.2%)	<0.0001
Head injury	64,698 (11.2%)	39,459 (11.0%)	25,239 (11.4%)	<0.0001
Medical diseases				
Diabetes mellitus	154,977 (26.7%)	94,346 (26.4%)	60,631 (27.3%)	<0.0001
Myocardial infarction	8,504 (1.5%)	5,245 (1.5%)	3,259 (1.5%)	0.981
Congestive heart failure	31,952 (5.5%)	19,222 (5.4%)	12,730 (5.7%)	<0.0001
Liver disease	146,020 (25.2%)	88,392 (24.7%)	57,628 (26.0%)	<0.0001
Renal disease	5,669 (1.0%)	3,476 (1.0%)	2,193 (1.0%)	0.564
Peptic ulcer disease	259,797 (44.8%)	155,929 (43.6%)	103,868 (46.8%)	<0.0001
Thyroid gland disorder	40,236 (6.9%)	23,104 (6.5%)	17,132 (7.7%)	<0.0001
Asthma	123,850 (21.4%)	74,598 (20.9%)	49,252 (22.2%)	<0.0001
Cancer	41,290 (7.1%)	24,845 (6.9%)	16,445 (7.4%)	<0.0001
Medication history				
HMG-CoA reductase inhibitors	128,527 (22.2%)	77,725 (21.7%)	50,802 (22.9%)	<0.0001
Diabetes medication	84,015 (14.5%)	51,878 (14.5%)	32,137 (14.5%)	0.735
Antihypertensive medication	288,262 (49.7%)	178,093 (49.8%)	110,169 (49.6%)	0.180
Antidepressants	31,079 (5.4%)	17,216 (4.8%)	13,863 (6.2%)	<0.0001
Benzodiazepines and sleeping pills	92,444 (15.9%)	53,108 (14.8%)	39,336 (17.7%)	<0.0001
Antiplatelet medication	140,615 (24.3%)	86,071 (24.1%)	54,544 (24.6%)	<0.0001
Depression screening questionnaire score, mean (SD)	0.34 (0.79)	0.23 (0.67)	0.53 (0.92)	<0.0001
Laboratory findings				
Cholesterol level, mean (SD), mg/dL				
LDL cholesterol	117.47 (35.58)	117.26 (35.55)	117.81 (35.64)	<0.0001
HDL cholesterol	53.63 (13.64)	53.57 (13.61)	53.73 (13.68)	<0.0001
Triglycerides	134.31 (70.64)	134.80 (70.97)	133.54 (70.10)	<0.0001
Fasting glucose	101.89 (20.96)	102.11 (21.10)	101.52 (20.73)	<0.0001
Hemoglobin	13.59 (1.40)	13.63 (1.40)	13.54 (1.39)	<0.0001
Physical examination findings				
Body mass index	24.29 (2.98)	24.31 (2.99)	24.25 (2.98)	<0.0001
Systolic blood pressure	128.74 (15.43)	129.05 (15.44)	128.22 (15.41)	<0.0001
Diastolic blood pressure	78.01 (9.73)	78.18 (9.73)	77.73 (9.73)	<0.0001

* The fourth quartile group had the highest frequency of medical visits.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCD, subjective cognitive decline; SD, standard deviation; HMG-CoA: 5-hydroxy-3-methylglutaryl-coenzyme A

Table 2. Cox regression analysis for the association between subjective cognitive decline and subsequent dementia

	Non-SCD group	SCD group
Total population	357,654 (61.7%)	222,056 (38.3%)
Dementia events	13,501 (3.8%)	12,766 (5.8%)
Person-years	2,384,745	1,485,548
Incidence (events/100,000 person-years)	566.14	859.35
Sex-adjusted HR (95% CI)	[Reference]	1.48 (1.44-1.51)
aHR in Model 1 (95% CI) *	[Reference]	1.46 (1.43-1.50)
aHR in Model 2 (95% CI) †	[Reference]	1.42 (1.39-1.46)
aHR in Model 3 (95% CI) ‡	[Reference]	1.38 (1.34-1.41)
Men	173,795 (48.6%)	92,516 (41.7%)
Dementia events	5,480 (3.2%)	4,399 (4.8%)
Person-years	1,147,608	611,069.20
Incidence (events/100,000 person-years)	477.52	719.89
aHR in Model 1 (95% CI) *	[Reference]	1.49 (1.43-1.55)
aHR in Model 2 (95% CI) †	[Reference]	1.44 (1.39-1.50)
aHR in Model 3 (95% CI) ‡	[Reference]	1.38 (1.32-1.44)
Women	183,859 (51.4%)	129,540 (58.3%)
Dementia events	8,021 (4.4%)	8,367 (6.5%)
Person-years	1,237,137	874,478.80
Incidence (events/100,000 person-years)	648.35	956.80
aHR in Model 1 (95% CI) *	[Reference]	1.45 (1.40-1.49)
aHR in Model 2 (95% CI) †	[Reference]	1.41 (1.37-1.45)
aHR in Model 3 (95% CI) ‡	[Reference]	1.38 (1.33-1.42)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; SCD, subjective cognitive decline.

Figures

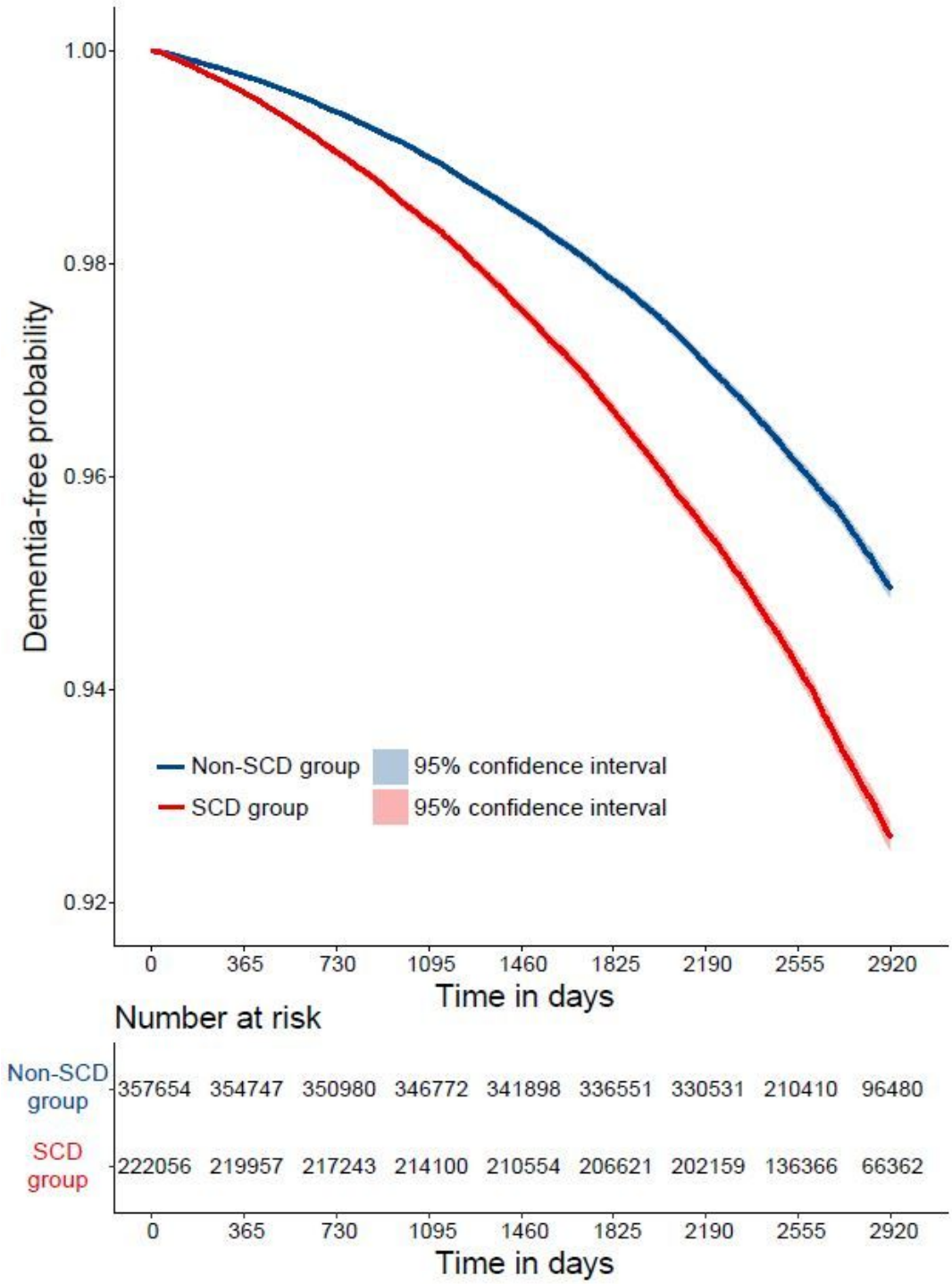
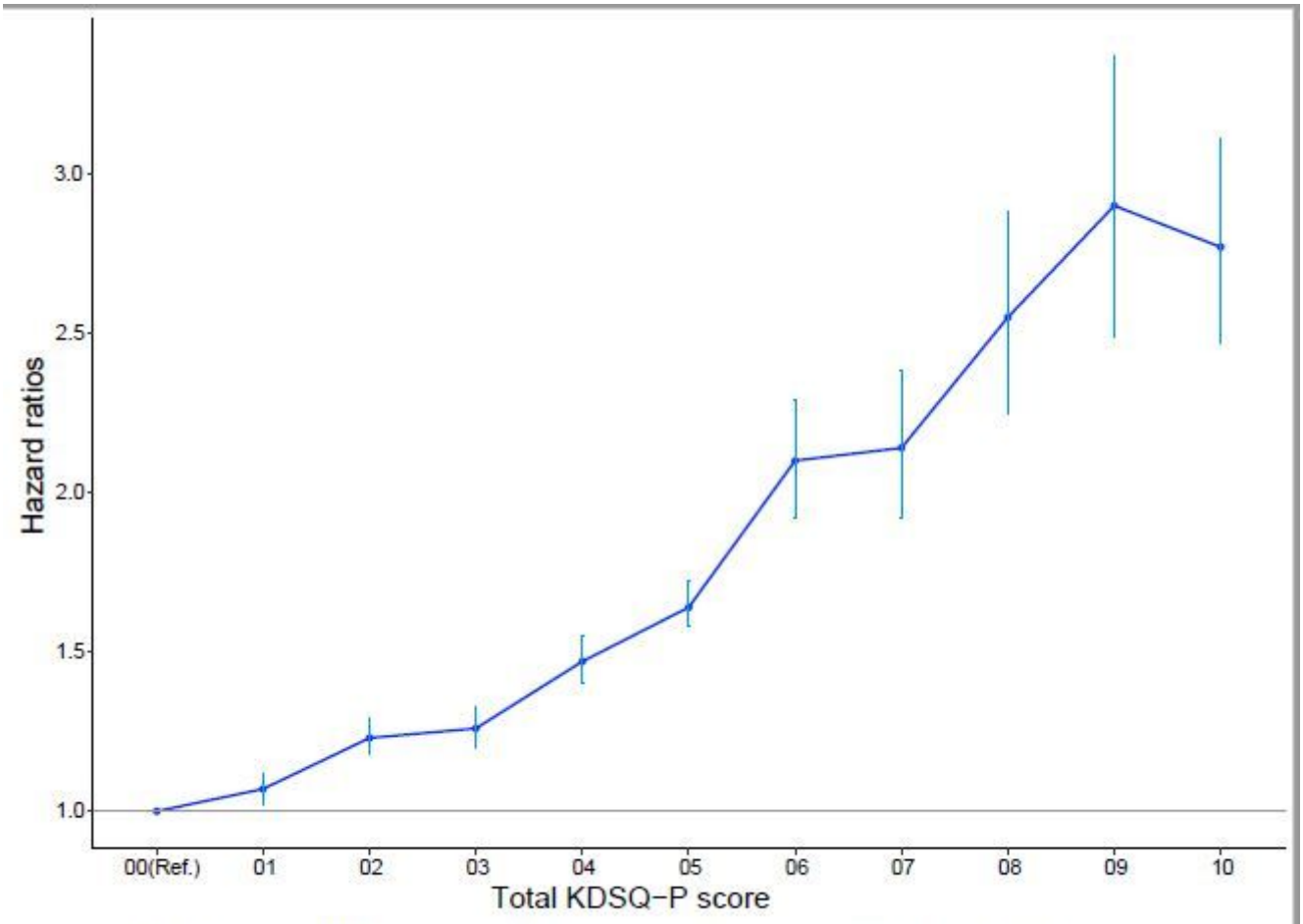


Figure 1

Kaplan–Meier estimates of the incidence of dementia.



KDSQ-P score	Without dementia	With dementia	aHR	95% CI, lower	95% CI, upper	P-value
0	288531	11085	(reference)	-	-	-
1	82386	3374	1.07	1.02	1.12	0.007
2	62484	3105	1.23	1.18	1.29	<0.0001
3	39212	2110	1.26	1.20	1.33	<0.0001
4	27944	1845	1.47	1.40	1.55	<0.0001
5	39252	3034	1.64	1.58	1.72	<0.0001
6	5403	577	2.10	1.92	2.29	<0.0001
7	3166	363	2.14	1.92	2.38	<0.0001
8	1989	280	2.55	2.25	2.88	<0.0001
9	1096	177	2.90	2.49	3.37	<0.0001
10	1980	317	2.77	2.47	3.11	<0.0001

Figure 2

Adjusted hazard ratios for dementia according to the Prescreening Korean Dementia Screening Questionnaire score. a Blue dots indicate the aHR and azure lines indicate the 95% confidence intervals. Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; KDSQ-P, Prescreening Korean Dementia Screening Questionnaire. aAdjusted for sex, income, lifestyle factors, healthcare visit frequency, past medical history, medication history, depression screening questionnaire score, laboratory findings, and physical examination findings.

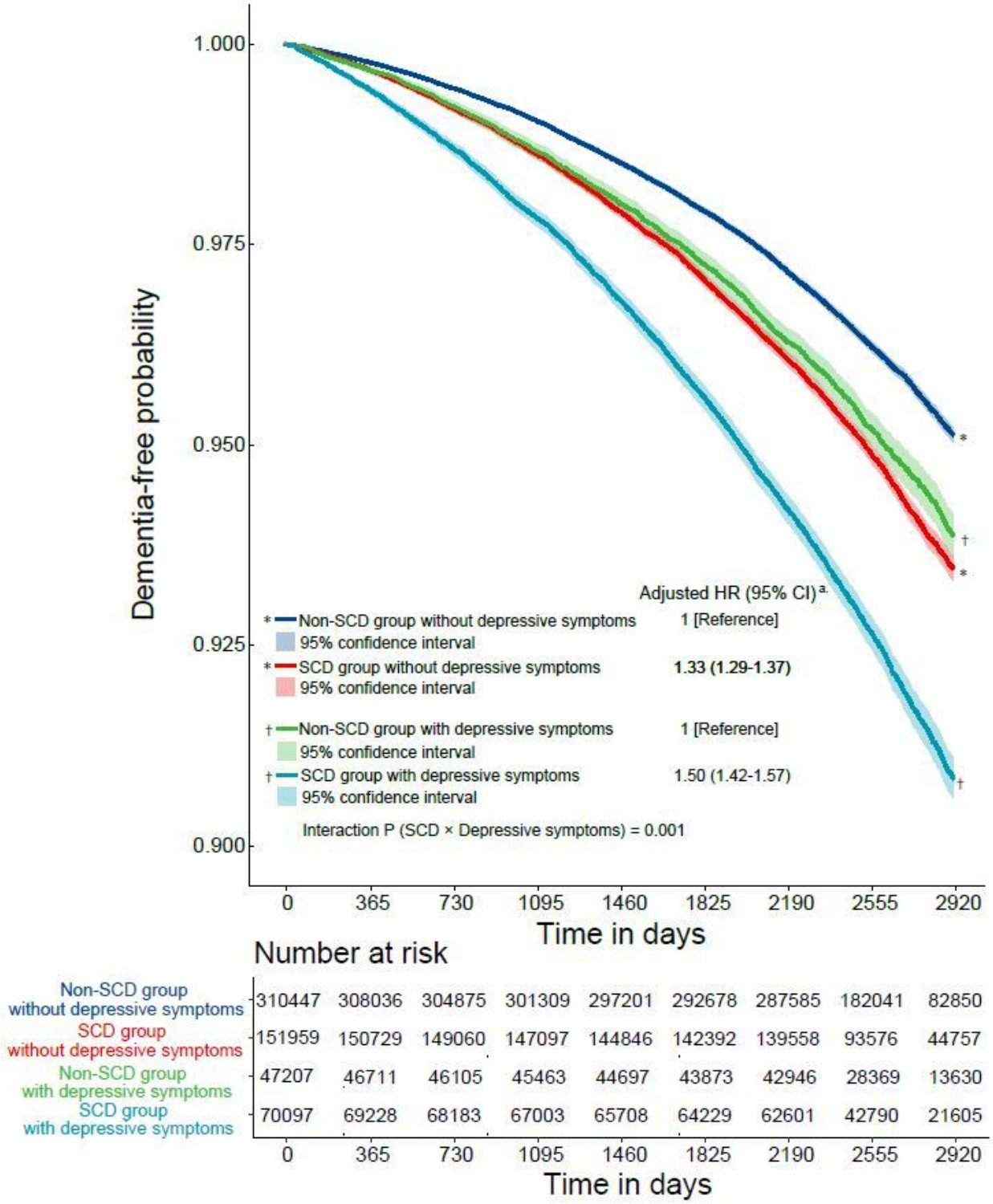


Figure 3

The interaction effect between subjective cognitive decline and depressive symptoms on subsequent dementia.

Supplementary Files

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