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Increased Risk of Dementia in Subjective Cognitive Decline if CT Brain Changes are Present

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Abstract.
Background: Subjective cognitive decline (SCD) has low predictive value for incident dementia.
Objective: We examined whether CT detectable brain changes add predictive value to SCD in a population sample with high scores on the Mini-Mental State Examination.
Methods: Subjective reports of memory and executive function were gathered in a non-demented population sample ≥70 years ($n = 921$). CT-brain was performed at baseline ($n = 626$). Brain atrophy, infarcts, and white matter lesions (WMLs) were classified using visual ratings. Dementia incidence was evaluated periodically during 12 years.
Results: The prevalence of SCD was 32.5% among individuals without dementia. During follow-up, 151 individuals (16.4%) developed dementia. The risk of dementia was increased in SCD, and increased further with WMLs and cortical atrophy present. However, the positive predictive values for incident dementia were low, 25% in SCD and 41% in SCD with WMLs and cortical atrophy.
Conclusions: Our observations add clinical value to the use of SCD and CT to select relevant populations for interventions against dementia, but more stringent screening methods are necessary to reach individuals at risk.

Keywords: Cognitive dysfunction, dementia, neuroimaging, subjective, white matter

INTRODUCTION

Subjective cognitive decline (SCD) often brings patients to clinical evaluation for suspected dementia. This was the reason why self-reported memory complaints were included in the original criteria for mild cognitive impairment (MCI) [1]. MCI classification was later revised to acknowledge both subjective memory and non-memory domains [2]. DSM-5 criteria for neurocognitive disorders also include "concern of the individual" regarding decline in any cognitive domain [3]. The prevalence of self-reported memory complaints, the most extensively investigated cognitive complaint, varies in population studies from 10 to 56% [4–7]. This variation mainly reflects differences between studies in assessments of memory complaints [8]. The risk of developing dementia is increased both in individuals with memory complaints [4, 6, 7] and with non-memory complaints [8, 9], especially regarding executive function and attention [8]. However, most population studies show

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that SCD has low sensitivity and low positive predictive value for the prediction of dementia [7, 10], providing a strong argument against using subjective complaints alone to detect those at risk of dementia.

Recent studies have shown that SCD is associated with neuroimaging changes, such as brain atrophy and vascular brain burden, including infarcts and white matter lesions (WMLs) [11–13]. Alzheimer's disease (AD) encephalopathy and cerebrovascular disease are often clinically silent during a long preclinical phase [9, 14]. In addition, it has been shown that individuals report less memory problems with accumulation of neurodegenerative changes and closer to dementia onset [15]. The inclusion of objective markers such as preclinical brain changes may increase the validity of subjective reports to detect individuals at risk of dementia. The correlation between SCD and brain changes, i.e., cortical atrophy and vascular brain burden, using brain CT has not been explored. Brain CT is the imaging technique of choice in primary care settings worldwide and has been used in dementia work-up beyond global cognitive tests (e.g., Mini-Mental State Examination (MMSE)) mostly to exclude other pathologies. Evidence that supports the validity of CT as a diagnostic tool in preclinical stages of dementia is scarce, but would be clinically meaningful.

The main question addressed by this study was if SCD in a non-demented population with high MMSE mean score is associated with structural brain changes as evidenced by CT (WMLs, infarcts, cortical atrophy) and if the clinical value of SCD to predict dementia increases by addition of information regarding brain changes. We hypothesized that the predictive validity of SCD in preclinical stages of dementia increases in the presence of cortical atrophy and vascular brain burden. Therefore, we examined self-reports of cognitive function and brain changes on CT (WMLs, infarcts, cortical atrophy) in a population aged 70 years and above, in relation to the development of dementia during 12-year follow-up.

PARTICIPANTS AND METHODS

Study sample

Data was derived from the 2000–2002 examination of the Prospective Population Study of Women (PPSW), which started in 1968 [16, 17], and the H70 study [18]. The studies included individuals living in private households and in residential care in Gothenburg, September 1, 2000, selected from the Revenue Office Register based on certain birth dates, without screening. From PPSW, we included 691 women (response rate 71.6%) born in 1908, 1914, 1918, 1922, and 1930 [19, 20]. From the H70-study, we included 327 70-year-olds (response rate 61.7%, 98 women and 229 men) born 1930 [19, 20]. Those with dementia diagnosed according to the comprehensive psychiatric examination at baseline ($n = 94$, 89 women, 5 men) were excluded. Three women were excluded due to missing data on cognitive self-reports. Thus, a total sample of 921 individuals (224 men and 697 women) was available. Re-examinations were performed in 2005 (688 participants) and 2009 (517 participants). The sample was also censored for dementia during 12 years (2001–2012) using the Swedish Hospital Discharge Register.

Participants and non-participants at baseline were similar regarding age and dementia diagnoses in the Swedish Hospital Discharge register [19]. Participants had higher 3-year survival rate, were more often women, and had less often psychiatric diagnoses and stroke in the Swedish Hospital Discharge register [19].

All 921 available participants were invited to CT-brain imaging at baseline, and 626 (68.0%) accepted.

Methods

The clinical assessments at baseline and follow-up comprised medical and psychiatric examinations, laboratory tests, and informant interviews administered by experienced psychiatric research nurses. Data on dementia and mental health were also collected from the Swedish Hospital Discharge register.

Participants (or their nearest relatives in cases with dementia) gave their informed consent for the study, which was approved by the Ethics Committee for Medical Research at the University of Gothenburg. The study complied with the guidelines of the Helsinki Declaration of 1975.

Head CT scans

Head CT scans without contrast enhancement were obtained using PICKER PQ6000 scanner with 8 mm thick, contiguous tomographic sections of the brain resulting in 12–14 transaxial non-overlapping sections depending on head size. The CT films ($n = 626$) were first examined by an experienced radiologist. Suspect parenchymal changes were deferred to consensus neuroradiologic diagnosis. CT-brain changes that were clinically silent were included in this study

(one calcified atheroma, one Paget disease of the skull, two meningiomas, two aneurysms, three craniotomies of which one was due to aneurysm, four intracranial artery calcifications, and five radiologically suspect normal pressure hydrocephalus without confirmed clinical symptoms). One individual with shunt due to normal pressure hydrocephalus was also included. Research neurologists re-examined the CTs for the presence of atrophy, infarcts, and WMLs (standardized visual evaluations). The degree of cortical atrophy in the frontal, temporal, parietal, and occipital lobes was rated and categorised using a four-point scale (normal, mild, moderate, and severe) according to the extent of sulcal widening [21]. After excluding baseline dementia, only individuals with normal and mild-to-moderate atrophy remained. We therefore used a dichotomous variable (normal versus mild-to-moderate atrophy) in the statistical analyses. Any cortical atrophy was defined as mild-to-moderate atrophy in at least one of the four regions considered. Vascular brain burden was represented by WMLs and infarcts. WMLs were defined as diffusely distributed low-density areas in periventricular or subcortical white matter rated on a four-point scale (normal, mild, moderate, severe) [22]. Infarcts were categorized as either small lacunar infarcts (round or oval shaped parenchymal lesion 2-15 mm typically located in subcortical territories supplied by small perforating arteries) or large territorial and watershed infarcts (cortical-subcortical parenchymal lesions larger than 15 mm that follow the territorial distribution of the anterior, middle or posterior cerebral artery or the junctions between their territories of supply; includes also the so-called "watershed infarcts" in the internal border zone adjacent to the lateral ventricles). The inter-rater reliabilities for CT measures have been found to be fair to good [23].

Cognitive assessments

Information about participants' subjective cognitive symptoms was based on ratings of self-reported memory, concentration, making decisions, and taking initiative from the semi-structured Comprehensive Psychopathological Rating Scale (CPRS) [24]. CPRS is sensitive to symptom changes and was adapted to include reports of symptoms during the last month or longer. The ratings were standardized according to a seven-step scale (0 – no symptoms and 1 to 6 – mild to moderate to severe impairment, allowing for intermediate steps) [24]. Participants were categorized as experiencing 'no decline' if no or occasional problems were reported (scores 0–2) and 'decline' if more persistent, troublesome symptoms were reported (scores $\geq$3). The data were further categorized into a memory domain, and an executive domain, comprising concentration, making decisions and taking initiative. Individuals were classified as having SCD if at least one item in one area of cognition, memory or executive function, reflected 'decline' (scores $\geq$3). No data were imputed, nor were participants excluded due to incomplete data.

Objective information about global cognitive function was also gathered during the interview using the MMSE [25] and the Clinical Dementia Rating (CDR) [26].

Other assessments

Affective symptoms were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) [27]. The MADRS score used in this study was based on 8 items (MADRS-8) after excluding concentration and taking initiative as these were used to define SCD.

Diagnosis of dementia

The diagnosis of dementia according to the diagnostic and statistical manual of mental disorders, IIIrd edition, revised (DMS-III-R) [28] was based on the comprehensive psychiatric interview and the informant interview, if available, both administered by experienced psychiatric nurses. The items pertaining to subjective cognitive decline were not used for the diagnosis of dementia. The individuals diagnosed with dementia were invited at each wave and were reassessed for dementia diagnosis and staging. Dementia diagnoses were also collected from the Swedish Hospital Discharge Register until December 31, 2012. The kappa agreement between dementia diagnoses from the Swedish Hospital Discharge Register and those based on study examinations was 28.2%.

Statistical analyses

The differences between SCD and 'No SCD', and between participants and non-participants in CT-brain examination, were analyzed using ANOVA with F-statistics for continuous variables (i.e., age, MMSE and MADRS-8 scores, and person years-at-risk), and Fisher's exact test for proportions (i.e., female sex, compulsory education, sensory

impairment, prevalent stroke and diabetes at baseline, APOE ε4 allele status, and dementia incidence). Baseline associations between SCD and CT-brain changes were tested using logistic regression models (LRM) adjusted for the effects of variables unevenly distributed between the groups according to univariate analyses (i.e., age, sex, MADRS-8 and MMSE scores). Other covariates, i.e., CDR sum-of-boxes, education, sensory impairment, diabetes mellitus, prevalent stroke, antihypertensives, anticholinergics, and APOE ε4 allele status, were disregarded since they were evenly distributed among the SCD and 'No SCD' groups. The risk of developing dementia was first estimated for SCD in the total sample and secondly for SCD and CT changes separately in the CT sample. We also computed the validity of each subjective cognitive symptom and objective brain changes to predict the development of dementia using *sensitivity* (percentage of 'true positives' at baseline among incident dementias), *specificity* (percentage of 'true negatives' at baseline among all non-demented during follow-up), *positive predictive value* (PPV - percentage of incident dementias among all 'test positives' at baseline), and *negative predictive value* (NPV - percentage of non-demented at follow-up among all 'test negatives' at baseline). Finally, the risk of developing dementia was compared between groups stratified by SCD with or without CT-brain changes using univariate and adjusted Cox proportional hazard models (backward stepwise with Wald statistics, variable removal at a probability level $p > 0.1$), adjustments being made for variables associated with SCD and dementia in univariate analyses: age, sex, and MADRS-8 score. Adding MMSE score as a covariate did not change the results. Therefore, only Cox models adjusted for age, sex, and MADRS-8 score are presented. The risk of dementia was estimated by hazard ratios (HR) and 95% confidence intervals (95% CI). Person years-at-risk was calculated from baseline to time-to-death, time-to-dementia onset or December 31, 2012, whichever occurred first. A two-tailed level of significance, $p < 0.05$, was used for all tests.

RESULTS

Baseline characteristics

In the total baseline sample ($n = 921$), 300 individuals (32.6 %) reported any SCD. Among these, 85 (28.3%) reported isolated memory decline, 127 (42.3%) isolated executive function decline (i.e., concentration, making decision or taking initiative, including overlapping symptoms), and 88 (29.3%) both memory and executive function decline. Approximately a third of the SCD group and a half of those without SCD remain stable in the same category during follow-up (Fig. 1).

The prevalence of SCD at baseline in relation to demographic factors and brain structural changes is presented in Table 1. Due to sample characteristics, associations with age could only be examined in women, among whom the frequency of SCD increased with age. The mean MMSE score in the total sample at baseline was 27.8 (standard deviation (SD) 2.1). SCD was associated with lower MMSE score and higher CDR sum-of-boxes and MADRS-8 scores in univariate analyses (Table 1). SCD was also associated with WMLs at baseline (Table 1). The latter association remained significant after adjustment for age and sex (OR 1.5, 95% CI 1.04–2.1; adding MMSE and MADRS-8 scores as covariates did not change the result). There were no associations between SCD and infarcts or cortical atrophy at baseline (Table 1).

SCD validity to predict incident dementia in the total sample

During 12-year follow-up, 151 individuals (16.4%) developed dementia. Of these, 111 were diagnosed in participants at study examinations 2005 and 2009 ($n = 40$ also retrieved in the Swedish Hospital Discharge Register) and five were retrieved in participants without dementia at the examinations 2005 and 2009 using the Register during the follow-up 2010 to 2012. Thirty-five incident dementias were retrieved from the Register among those lost at follow-up (17 refusals, 18 deceased). SCD at baseline in relation to the risk of dementia during follow-up, and the sensitivity, specificity, PPV and NPV to predict dementia are presented in Table 2. SCD was associated with incident dementia in unadjusted and adjusted Cox regression models (adjusted for sex, age, and MADRS-8 score). The association was mainly driven by self-reported memory decline and concentration problems. However, the sensitivity and PPV were low, with highest sensitivity (29.1%) observed for memory decline (i.e., one of three individuals who developed dementia reported memory decline at baseline). Only one of four individuals who reported memory decline at baseline developed dementia, resulting in a PPV of 25.4% (specificity 83.2% and NPV 83.7%). Adding

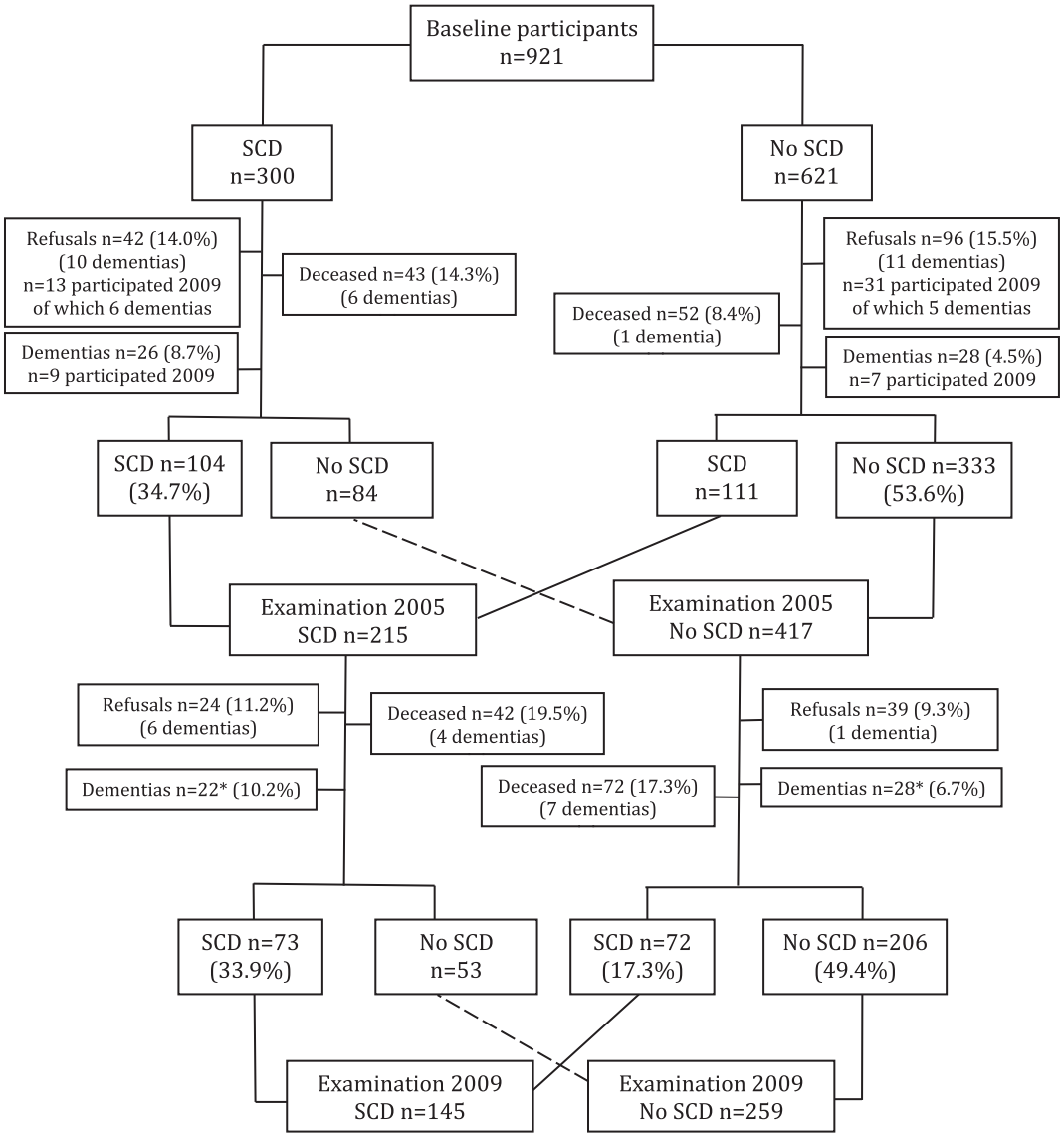

Fig. 1. SCD flow chart using the total sample followed during 2000–2012. Three participants at follow-up had no self-reported cognitive data at the examination 2005 (of these, one individual was diagnosed with dementia in 2006 and another in 2009). Dementia diagnosis in those lost to follow-up ($n = 35$ deceased and refusals) was based on the Swedish Hospital Discharge Register if not otherwise specified; all other dementias were diagnosed at the examinations 2005 and 2009 ($n = 111$) except for *five dementias in participants 2005–2009 retrieved from the Register during the follow-up 2010–2012 ($n = 2$ among SCD2005 & SCD2009 = 0 and $n = 3$ among SCD2005 = 0 of which only 1 developed SCD2009 = 1).

concentration problems to memory decline improved sensitivity from 29.1% to 34.4%, but specificity decreased from 83.2% to 79.2%. Highest sensitivity (46.4%) for incident dementia was obtained when all available subjective information on memory and executive function was combined, but specificity was lower (70.1%), and PPV and NPV were minimally improved compared to using only memory decline, or memory decline and concentration.

CT sample

CT participants were more often men, had slightly higher MMSE scores, and lower CDR sum-of-boxes and MADRS-8 scores than those who declined CT participation (Table 3). CT participants were also younger than those who declined participation. However, prevalence of SCD at baseline and during follow-up and incidence of dementia, the

Table 1
Clinical and demographic characteristics of the total sample at baseline by subjective cognitive decline (SCD)

	No SCD $n=621$	SCD $n=300$	Unadjusted p-values
Age at psychiatric interview mean (SD)	**73.8 (5.2)**	**74.9 (5.7)**	**0.003**
Age mean in men (SD)	70.0 (0.2)	70.1 (0.2)	0.571
Age mean in women (SD)	**75.1 (5.5)**	**76.2 (5.7)**	**0.011**
MMSE mean (SD)[1]	**28.0 (1.9)**	**27.5 (2.2)**	**<0.001**
MADRS-8 items mean (SD)	**2.7 (3.2)**	**6.4 (6.8)**	**<0.001**
CDR sum-of-boxes mean (SD)[2]	**0.1 (0.4)**	**0.4 (1.0)**	**<0.001**
Women *n* (%)	461 (74.2)	236 (78.7)	0.163
Education >6 years *n* (%)[3]	235 (39.5)	104 (36.2)	0.376
Sensory impairment *n* (%)*	126 (20.3)	67 (22.3)	0.490
Diabetes mellitus *n* (%)[4]	108 (17.8)	52 (17.9)	1.000
Prevalent stroke *n* (%)	16 (2.6)	10 (3.3)	0.528
Antihypertensive medication *n* (%)[5]	148 (27.1)	82 (31.4)	0.211
Anticholinergic medication *n* (%)	8 (1.3)	3 (1.0)	1.000
APOE ε4 prevalence *n* (%)[6]	161 (27.9)	70 (25.4)	0.460
Dementia incidence *n* (%)	**81 (13.0)**	**70 (23.3)**	**<0.001**
Dementia incidence based on examinations *n* (%)	**61 (9.8)**	**50 (16.8)**	**0.003**
CT-brain changes	$n=426$	$n=200$	
Any cortical atrophy *n* (%)	245 (57.5)	127 (63.5)	0.163
Frontal atrophy *n* (%)	189 (44.4)	103 (51.5)	0.103
Temporal atrophy *n* (%)	171 (40.1)	91 (45.5)	0.224
Parietal atrophy *n* (%)	120 (28.2)	59 (29.5)	0.776
Occipital atrophy *n* (%)	73 (17.1)	33 (16.5)	0.909
Vascular brain burden *n* (%)	286 (67.1)	132 (66.0)	0.785
WMLs *n* (%)	**220 (51.6)**	**122 (61.0)**	**0.031**
Lacunar infarcts *n* (%)	202 (47.4)	86 (43.0)	0.304
Territorial & watershed infarcts *n* (%)	12 (2.8)	4 (2.0)	0.787

SD, standard deviation; MMSE, Mini-Mental Status Examination; WMLs, white matter lesions; MADRS, Montgomery-Åsberg Depression Rating Scale total score based on 8 items after excluding concentration and taking initiative to avoid overlap with SCD executive function items. *Vision and hearing impairment at a level that may have partially affected the psychiatric interview. Information missing in: [1]$n=1$; [2]$n=2$; [3]$n=39$; [4]$n=25$; [5]$n=113$; [6]$n=67$. Univariate Anova was used to test the differences in continuous parameters (i.e., age, MADRS-8 and MMSE score, and follow-up years) and Fisher's exact test for differences in proportions.

Table 2
Prediction of incident dementias ($n=151$) during 12-year follow-up by SCD in the total sample ($n=921$)

Self-reported cognitive function	*n* (%)	HR (95% CI) Unadjusted	HR (95% CI) Adjusted	Sens	Spec	PPV	NPV
SCD	300 (32.6)	**2.0 (1.5–2.8)**	**1.8 (1.3–2.5)**	46.4	70.1	23.3	87.0
Memory decline	173 (18.8)	**2.0 (1.4–2.8)**	**1.9 (1.3–2.7)**	29.1	83.2	25.4	85.7
Executive function decline[1]	215 (23.5)	**1.8 (1.3–2.6)**	**1.6 (1.2–2.3)**	33.6	78.5	23.3	85.9
Concentration	75 (8.2)	**2.0 (1.2–3.2)**	**1.9 (1.2–3.1)**	13.4	92.8	26.7	84.6
Making decisions	92 (10.1)	1.5 (0.9–2.3)	1.2 (0.7–1.9)	13.5	90.6	21.7	84.8
Taking initiative	143 (15.7)	**1.8 (1.2–2.6)**	1.3 (0.8–2.0)	22.1	85.6	23.1	84.9

SCD, subjective cognitive decline; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazard backward stepwise models with Wald statistics and stepwise removal at $p>0.100$ (covariates in the adjusted models: age, sex and MADRS-8 score). [1]Information missing in 6 women (2 incident dementias). Information was also missing in following items: Concentration one woman (no dementia), Making decisions and Taking initiative one woman (no dementia), and Taking initiative one woman (no dementia). These women were included in analyses of SCD without data imputation.

main outcomes of the study, were similar between participants and non-participants in CT scanning (Table 3).

SCD was not associated with MMSE score in the CT sample (28.0 ± 2.0 in 'No SCD' versus 27.8 ± 1.8 in SCD, $p=0.094$), but remained associated with scores of MADRS-8 (2.7 ± 3.3 in 'No SCD' versus 5.7 ± 6.1 in SCD, $p<0.001$) and CDR sum-of boxes (0.05 ± 0.2 in 'No SCD' versus 0.3 ± 0.9 in SCD, $p<0.001$).

Table 3
Baseline clinical and demographic characteristics in non-demented individuals by participation in CT scanning

Characteristics	Declined CT scanning $n = 295$	Participated in CT scanning $n = 626$	p-values
Age at psychiatric interview mean (SD)	**75.7 (5.6)**	**73.5 (5.1)**	**<0.001**
Age mean in men (SD)	70.0 (0.0)	70.0 (0.2)	0.156
Age mean in women (SD)	**76.7 (5.5)**	**74.8 (5.5)**	**<0.001**
MMSE score mean (SD)[1]	**27.6 (2.2)**	**27.9 (1.9)**	**0.010**
MADRS-8 items mean (SD)	**4.5 (5.7)**	**3.7 (4.6)**	**0.016**
CDR sum-of-boxes mean (SD)[2]	**0.3 (0.9)**	**0.1 (0.5)**	**<0.001**
Women *n* (%)	**251 (85.1)**	**446 (71.2)**	**<0.001**
Education >6 years *n* (%)[3]	96 (35.8)	243 (39.6)	0.328
Sensory impairment *n* (%)*	73 (24.7)	120 (19.2)	0.056
Diabetes mellitus *n* (%)[4]	47 (17.2)	113 (18.1)	0.777
Prevalent stroke *n* (%)	5 (1.7)	21 (3.4)	0.202
Antihypertensive medication *n* (%)[5]	56 (24.8)	174 (29.9)	0.165
Anticholinergic medication *n* (%)	2 (0.7)	9 (1.4)	0.518
APOE ε4 prevalence *n* (%)[6]	57 (22.8)	174 (28.8)	0.076
Dementia incidence *n* (%)	43 (14.6)	108 (17.3)	0.341
Dementia incidence based on examinations *n* (%)	28 (9.5)	83 (13.3)	0.128
Self-reported cognitive function at baseline			
SCD *n* (%)	100 (33.9)	200 (31.9)	0.598
Memory decline *n* (%)	56 (19.0)	117 (18.7)	0.928
Executive function decline *n* (%)	74 (25.3)	141 (22.6)	0.403
Concentration *n* (%)	30 (10.3)	45 (7.2)	0.121
Making decisions *n* (%)	28 (9.6)	64 (10.3)	0.814
Taking initiative *n* (%)	52 (17.9)	91 (14.6)	0.241
Self-reported cognitive function at follow-up			
SCD 2005 *n* (%)	56 (19.0)	159 (25.4)	0.777
SCD 2009 *n* (%)	42 (14.2)	117 (18.7)	0.740

*Vision and hearing impairment at a level that may have partially affected the psychiatric interview. SD, standard deviation; MMSE, Mini-Mental Status Examination; SCD, subjective cognitive decline. Information missing in: [1]$n = 1$ non-participant; [2]$n = 1$ non-participant; [3]$n = 39$ (12 participants and 27 non-participants); [4]$n = 25$ (3 participants and 22 non-participants); [5]$n = 113$ (44 participants and 69 non-participants); [6]$n = 67$ (22 participants and 45 non-participants). ANOVA was used to test the differences in continuous parameters (i.e., age, MMSE score and follow-up years) and Fisher's exact test for differences in proportions.

Validity of SCD and CT brain changes to predict incident dementia

SCD was associated with incident dementia also in the CT sample. The sensitivity, specificity, PPV, and NPV of SCD to predict incident dementias ($n = 108$) did not differ substantially between the CT subsample and the total sample (Table 4).

WMLs were associated with incident dementia in Cox regression models (unadjusted and adjusted for age, sex, and MADRS-8 score) (Table 4). Although any cortical atrophy and regional cortical atrophy were not associated with incident dementia, the sensitivity for incident dementia had approximately the same magnitude for any cortical atrophy (74.1%) and WMLs (71.3%) (Table 4).

SCD and WMLs were independently associated with dementia in Cox regression models adjusted for any cortical atrophy, age, sex, and MADRS-8 (HR 1.8, 95% CI 1.2–2.6 and HR 1.6, 95% CI 1.02–2.4, respectively).

Risk of dementia in individuals presenting both SCD and CT brain changes

The CT sample was stratified by the presence of SCD, with or without WMLs. The group with no SCD and no WMLs was used as control ($n = 206$). The association with dementia remained significant only in individuals with SCD who also had WMLs on CT ($n = 122$) compared with controls (HR 2.6, 95% CI 1.5 to 4.5). There were no associations with incident dementia in those with SCD without WMLs ($n = 78$, HR 1.1, 95% CI 0.5 to 2.4) or in those with WMLs but no SCD ($n = 220$, HR 1.2, 95% CI 0.7 to 2.1) (Fig. 2).

When we added information related to brain atrophy, the risk of developing dementia remained in individuals with SCD who had both WMLs and any

Table 4
Prediction of incident dementias ($n = 108$) during 12-year follow-up by SCD and CT-brain structural changes in the CT sample ($n = 626$)

	n (%)	HR (95% CI) Unadjusted	HR (95% CI) Adjusted	Sens	Spec	PPV	NPV
SCD	200 (31.9)	**2.0 (1.4–2.9)**	**1.8 (1.3–2.7)**	46.3	71.0	25.0	86.4
Memory decline	117 (18.7)	**1.9 (1.2–2.9)**	**1.9 (1.3–3.0)**	28.7	83.4	26.5	84.9
Executive function decline	141 (22.6)	**1.9 (1.2–2.8)**	**1.6 (1.1–2.4)**	32.7	79.5	24.8	85.1
Concentration	45 (7.2)	**2.1 (1.1–3.7)**	1.7 (0.97–3.1)	12.1	93.8	28.9	83.7
Making decisions	64 (10.3)	1.5 (0.9–2.6)	1.3 (0.7–2.2)	14.2	90.5	23.4	83.7
Taking initiative	91 (14.6)	**1.6 (1.02–2.7)**	1.3 (0.8–2.2)	19.6	86.4	23.1	83.8
CT-brain changes							
Any cortical atrophy	372 (59.4)	**2.1 (1.4–3.3)**	1.3 (0.9–2.1)	74.1	43.6	21.5	89.0
Frontal atrophy	292 (46.6)	**1.6 (1.1–2.3)**	1.0 (0.7–1.5)	56.5	55.4	20.9	85.9
Temporal atrophy	262 (41.9)	**2.3 (1.6–3.4)**	1.4 (0.9–2.1)	59.3	61.8	24.4	87.9
Parietal atrophy	179 (28.6)	**2.1 (1.5–3.1)**	1.2 (0.8–1.8)	43.5	74.5	26.3	86.4
Occipital atrophy	106 (16.9)	**2.0 (1.3–3.1)**	1.0 (0.6–1.6)	26.9	85.1	27.4	84.8
Vascular brain burden	418 (66.8)	**2.1 (1.3–3.4)**	1.5 (0.9–2.4)	79.6	35.9	20.6	89.4
WMLs	342 (54.6)	**2.3 (1.5–3.5)**	**1.6 (1.03–2.5)**	71.3	48.8	22.5	89.1
Lacunar infarcts	288 (46.0)	**1.7 (1.1–2.4)**	1.2 (0.8–1.8)	56.5	56.2	21.2	86.1
Territorial & watershed infarcts	16 (2.6)	0.4 (0.1–2.6)	0.2 (0.03–1.6)	0.9	97.1	6.3	82.5

SCD, subjective cognitive decline; WMLs, white matter lesions; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value. Univariate and backward stepwise covariate adjusted Cox proportional hazard models with Wald statistics were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). Adjustments were made in the covariate models for age, sex, and MADRS-8 score.

cortical atrophy ($n = 83$) compared to those with no SCD and no brain changes (control group $n = 109$) (HR 3.1, 95% CI 1.4–6.7). No association with dementia was found in other groups: SCD with WMLs or any cortical atrophy, but not both ($n = 83$, HR 1.5, 95% CI 0.6–3.5), WMLs or any cortical atrophy in the absence of SCD ($n = 148$, HR 1.2, 95% CI 0.5–2.7), WML without any cortical atrophy and SCD ($n = 72$, HR 1.4, 95%CI 0.6–3.5), any cortical atrophy without WMLs and SCD ($n = 97$, HR 1.1, 95% CI 0.4–2.6), and SCD without CT brain changes ($n = 34$, HR 0.6, 95% CI 0.1–2.9) (Fig. 3).

Of 83 individuals with SCD, WMLs and any cortical atrophy, 34 developed dementia (PPV 41.0%). The sensitivity for incident dementia in those with SCD, WMLs and any cortical atrophy was 31.5%, specificity 90.5% and NPV 86.4%.

The association with incident dementia remained in individuals with isolated memory and isolated executive function decline and CT-brain changes, except in those with isolated executive decline and any cortical atrophy (Table 5).

DISCUSSION

In a representative sample of older adults without dementia and high mean MMSE score, we found that approximately one third reported SCD at baseline. SCD was associated with WMLs on brain CT. SCD and WMLs were both associated with dementia during 12-year follow-up and the risk of developing dementia during follow-up in those with SCD increased in the presence of WMLs. Any cortical atrophy further increased the risk of dementia in those with SCD and WMLs.

SCD frequency in population and its associations

The frequency of SCD (32.6%) in this representative sample of 70-year-olds and older was lower than previously reported, e.g., 72.0% in a community sample with a mean age of 72 years (using a 15-item questionnaire regarding cognitive failures) [11] and 76.9% in another representative community study with a mean age of 67 years (using a 5-axis scale of cognitive functions) [10]. Clinical samples report an even higher prevalence of SCD up to 91% [13]. In SCD based on memory decline only, the prevalence is between 20 to 50% in clinical and community samples [4] which is closer to our findings. Methodological factors related to setting (e.g., clinical or community sample), demographic characteristics, and assessment methods partly explain the large variations in SCD prevalence [8].

Our study use methods very close to the newly proposed framework for research of SCD [29]. MMSE and CDR were the only objective cognitive assessments available at baseline, which may have limited our ability to identify subtle cognitive impairments. Although the total sample presented a high mean MMSE score, we cannot fully exclude the possibility that some of the SCD may also have MCI since

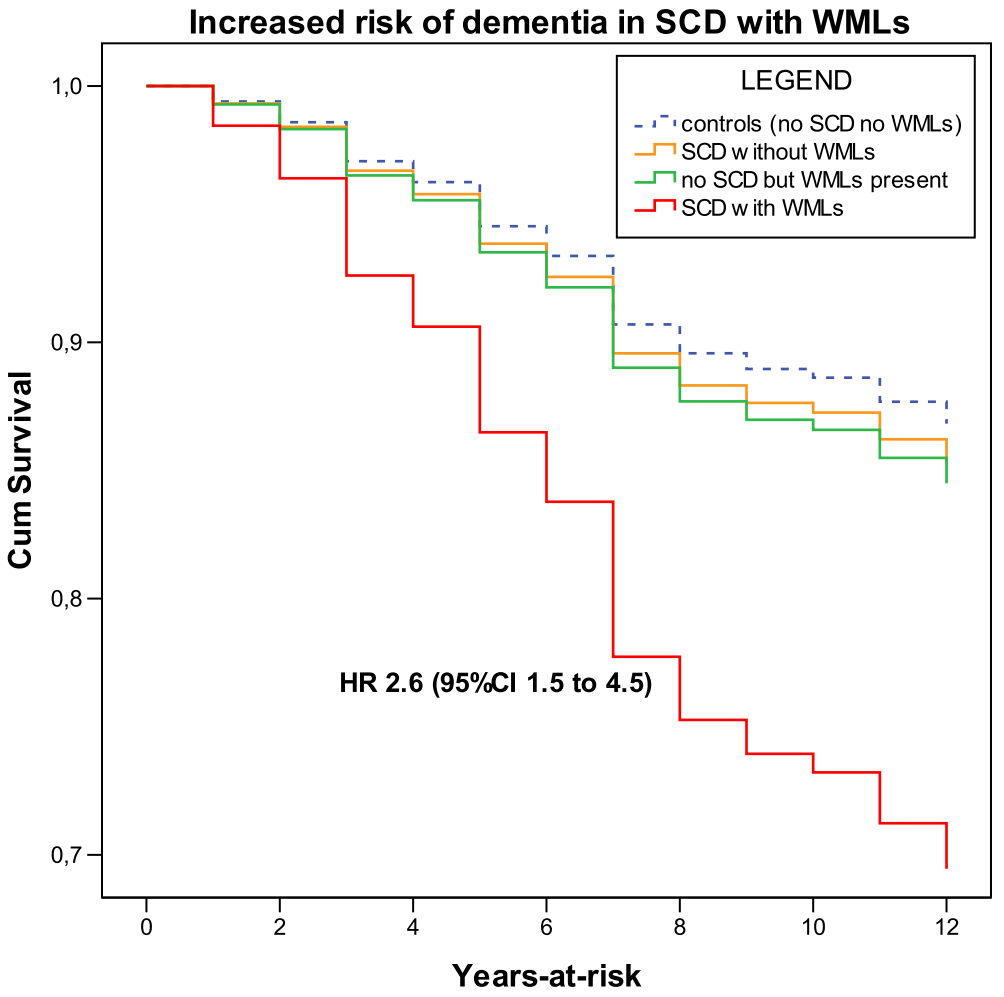

Fig. 2. Increased risk of dementia in SCD with WMLs on brain CT. Cox regression models adjusted for age, sex and MADRS-8 score. Note: The order of legend labels follow the hierarchic order of survival curves (colour version available online).

SCD at baseline had lower MMSE scores than those with no SCD [30]. However, the mean CDR sum-of-boxes at baseline in the CT sample was 0.1 (SD 0.5), which indicates that the majority of the individuals had normal cognitive performance rather than MCI. Moreover, mean MMSE score in the CT sample was higher than in those who did not participate in CT, and there were no differences in MMSE scores between the SCD and no SCD groups in the CT sample.

SCD was associated with WMLs at baseline, but not with brain infarcts and cortical atrophy. The lack of association with cortical atrophy is in contrast to reports from MRI studies [12, 31]. This discrepancy is most likely due to rather crude visual ratings of atrophy based on axial CT slices used in this study, which made it difficult to rigorously differentiate hippocampus and medial temporal lobe, regions usually associated with cortical neurodegeneration in AD [32]. Moreover, cortical atrophy at baseline was mild-to-moderate in our sample after exclusion of dementia, with the majority of cases showing mild atrophy. Mild brain atrophy including medial temporal lobe atrophy may be related to physiologic brain aging [33, 34]. Although cross-sectional correlations cannot elucidate cause-effect relationships, there is an underlying assumption that brain changes may result in cognitive decline. We found that WMLs were associated with SCD, in line with previous findings [35]. Others have shown that WMLs are associated with depressive symptoms [36] which may in turn be associated with SCD [5]. SCD was associated with higher MADRS-8 score in our sample, but MADRS-8 score did not affect the association between SCD and WMLs, further supporting the direct association

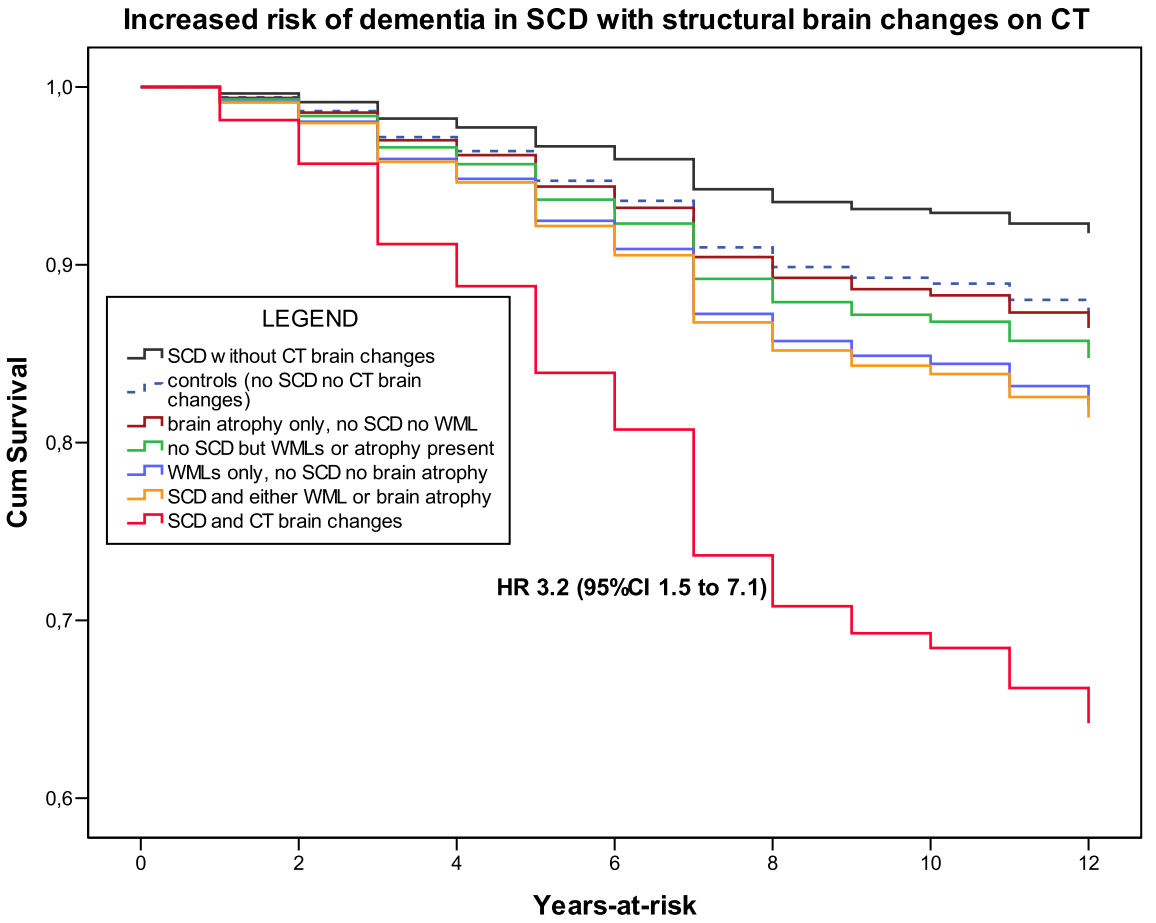

Fig. 3. Increased risk of dementia in SCD with structural brain changes on CT represented by WMLs and cortical atrophy. Cox regression models adjusted for age, sex and MADRS-8 score. Note: The order of legend labels follow the hierarchic order of survival curves (colour version available online).

between WMLs and SCD, at least in the absence of severe depressive symptoms (MADRS <20).

Those who reported memory decline and concentration problems had increased risk for incident dementia, but the sensitivity was low. Sensitivity and PPV increased when multiple domains were affected which is in line with previous findings [9]. Adding information on brain changes further improved PPV for incident dementia, but sensitivity decreased.

Increased risk of dementia in those with SCD and CT-brain changes

Any cortical atrophy was not associated with the development of dementia during the 12-year follow-up in the absence of WMLs and SCD. This finding reveals a considerable window of opportunity for preventive intervention against cerebrovascular risk factors in those who present with SCD and have mild to moderate cortical atrophy on brain CT. Although the lack of association between cortical atrophy on brain CT and incident dementia seems surprising and in contrast to findings from MRI and earlier CT findings [37, 38], it has to be pointed out that the majority of brain imaging studies have focused on medial temporal lobe and its subregions. As we only used axial CT sections, we could not examine medial temporal areas. Almost 60% of this representative population showed mild-to-moderate brain atrophy after excluding dementias at baseline, reflecting crude dichotomization of the data (no atrophy versus mild-to moderate atrophy) and the use of any cortical atrophy rather than regional atrophy. However, estimation of global cortical atrophy has become a widespread parameter in the work-up of individuals with cognitive impairment and is thus highly relevant in population studies [39].

Table 5
Prediction of incident dementias ($n = 108$) during 12-year follow-up by SCD domain and CT brain structural changes in the CT sample ($n = 626$)

CT-brain changes	SCD by domain	Total *n* (%)	Dementias *n* (%)	HR (95% CI) Unadjusted	HR (95% CI) Adjusted
No brain CT-changes	No cognitive decline	181 (28.9)	20 (11.0)	1.0	1.0
Any cortical atrophy	Isolated memory decline	38 (6.1)	12 (31.6)	**3.2 (1.6–6.6)**	**2.1 (1.03–4.5)**
	Isolated executive function decline	51 (8.1)	15 (29.4)	**3.3 (1.7–6.5)**	1.6 (0.8–3.3)
	Both memory and executive decline	38 (6.1)	15 (39.5)	**4.6 (2.4–9.0)**	**2.8 (1.4–5.7)**
No brain CT-changes	No cognitive decline	206 (32.9)	21 (10.2)	1.0	1.0
WMLs	Isolated memory decline	38 (6.1)	12 (31.6)	**3.7 (1.8–7.5)**	**3.0 (1.5–6.1)**
	Isolated executive function decline	54 (8.6)	17 (31.5)	**3.8 (2.0–7.3)**	**2.1 (1.1–4.1)**
	Both memory and executive decline	30 (4.8)	11 (36.7)	**4.5 (2.2–9.4)**	**3.0 (1.4–6.2)**
No brain CT-changes	No cognitive decline	109 (17.4)	9 (8.3)	1.0	1.0
Any cortical atrophy and WMLs	Isolated memory decline	26 (4.2)	9 (34.6)	**5.1 (2.0–12.9)**	**3.2 (1.2–8.1)**
	Isolated executive function decline	35 (5.6)	14 (40.0)	**6.6 (2.8–15.2)**	**2.7 (1.1–6.5)**
	Both memory and executive decline	22 (3.5)	11 (50.0)	**8.6 (3.6–20.9)**	**4.3 (1.7–10.5)**

SCD, subjective cognitive decline; WMLs, white matter lesions. Univariate and backward stepwise covariate adjusted Cox proportional hazard models with Wald statistics were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). Adjustments were made for age, sex, and MADRS.

Strengths and limitations

The strength of our study resides in the inclusion of a large, representative population of older adults from the community, without screening, who underwent the same comprehensive examinations conducted by trained research psychiatric nurses during a long follow-up. We have also used medical records register to detect dementia in deceased and refusals 2005–2009 and during the follow-up 2010–2012. Although medical records have low sensitivity for dementia, this approach increases the chance to include most incident dementias in the population. The results remained the same when we only used incident dementias diagnosed at study examinations ($n = 111$). Furthermore, the approach of this study mimics the clinical work-up of patients seeking help for cognitive decline, considering that MMSE and CT-brain scans are largely used in primary care worldwide and complex, standardized psychometric testing by trained professionals is not readily available in this setting. The limitations of the study should also be addressed. First, two-thirds of the sample consented to CT scanning. However, the prevalence of SCD and incidence of dementia did not vary by participation in CT scanning and thus could not have affected the results. Although the response rate was relatively high, the participants in CT examinations had higher MMSE score than non-participants. This may, however, contributed to homogenization in the CT-subsample since no differences in MMSE remained among participants in CT-scanning, regardless SCD. Further, we used rather crude measures of brain atrophy on axial CT-brain, which may have contributed to the lack of association between SCD and cortical atrophy, or between cortical atrophy and incident dementia. Another limitation was that standardized cognitive testing, except MMSE, was not available for this study. However, newly proposed research criteria for SCD do not require confirmation by cognitive testing, but MCI or prodromal AD must be excluded [29].

In conclusion, our observations underline the importance of using SCD and WMLs for initiation of interventions against dementia in older adults. These findings may have implications for the clinical work-up at primary care level in the preclinical stage of dementia and in the selection of participants for preventive trials in individuals 70 years and older with high cognitive reserve. However, due to low PPV and sensitivity, more stringent screening procedures, e.g., functional assessment of complex daily activities or psychometric tests with higher ecological validity for the individual, should be in place in specialized facilities to detect older adults with high cognitive reserve at risk to develop dementia.

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