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Subjective cognitive decline, brain imaging biomarkers, and cognitive functioning in patients with a history of vascular disease: the SMART-Medea study

Kim Blom [a], Huiberdina L. Koek [b], Maarten H.T. Zwartbol [a,c], Yolanda van der Graaf [a], Lara Kesseler [a], Geert Jan Biessels [d], Mirjam I. Geerlings [a,*], on behalf of the SMART Study Group

[a] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands
[b] Department of Geriatrics, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands
[c] Department of Radiology, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands
[d] Department of Neurology, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands

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ABSTRACT

We estimated associations of subjective cognitive decline (SCD) with neuroimaging markers of dementia and cognitive functioning in patients with a history of vascular disease without objective cognitive impairment. Within the Second Manifestations of ARTerial disease—Memory, depression and aging study, 599 patients (62 ± 9 years) had 1.5 T brain magnetic resonance imaging and cognitive testing at the baseline and after 8 years of follow-up. Using multiple regression analyses, we estimated cross-sectional and longitudinal associations of SCD according to research criteria with volumes of total brain, hippocampus, white matter hyperintensities, and presence of lacunes and with memory, executive functioning, information processing speed, and working memory. SCD was associated with increased risk of lacunes at the baseline (relative risk = 1.48, 95% confidence interval: 1.03; 2.12) but not during follow-up. No significant associations with volumes of white matter hyperintensities, total brain, or hippocampus were observed. SCD was cross-sectionally associated with poorer executive functioning and speed but not during follow-up. More prospective studies are needed to further elucidate the relationship between SCD, brain imaging markers, and cognitive decline and the role of SCD in the preclinical stage of Alzheimer's disease.

1. Introduction

Subjective cognitive decline (SCD) is common among older individuals (Burmester et al., 2016). Although SCD is often not indicative of underlying disease, it is also realized that those who express complaints of SCD are at increased risk of cognitive impairment and dementia (Burmester et al., 2016; Mendonça et al., 2015; Mitchell et al., 2014; Neto and Nitrini, 2016; Rabin et al., 2017). As such, SCD has been conceptualized as the earliest symptomatic prodromal state, or pre—mild cognitive impairment (pre-MCI) stage, of Alzheimer's disease (AD) (Jessen, 2014). Consequently, SCD is increasingly the focus of scientific research, and evidence exists that some patients with SCD may show early signs of brain changes related to MCI and AD (Garcia-Ptacek et al., 2014).

Most studies that investigated the etiology of SCD by examining brain magnetic resonance imaging (MRI) correlates investigated hippocampal volume and white matter hyperintensities (WMHs). These studies mainly found a decrease in hippocampal volume (Cherbuin et al., 2015; Hafkemeijer et al., 2013; Perrotin et al., 2015; Stewart et al., 2008, 2011; Striepens et al., 2010; van der Flier et al., 2004a, b) and an increase in WMH volume (de Groot et al., 2001; Minett, 2005; Stewart et al., 2008). These previous studies were mainly conducted in patients visiting memory clinics (Hafkemeijer et al., 2013; Minett, 2005; Perrotin et al., 2015; Striepens et al., 2010; van der Flier et al., 2004a, b) and in community-based populations (Cherbuin et al., 2015; de Groot et al., 2001; Stewart et al., 2011,

* Corresponding author at: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Stratenum 6.131, P.O. Box 85500, 3508 GA, Utrecht, The Netherlands. Tel.: +3188750670; fax: +31887568099.
E-mail address: m.geerlings@umcutrecht.nl (M.I. Geerlings).

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2008). It is likely that the factors associated with SCD depend on the setting in which it is examined. SCD in young adults, for example, likely has a different etiology (and prognosis) than in older persons attending a memory clinic. Furthermore, most studies focused on memory complaints rather than to include other cognitive complaints—such as attention deficits for example—as is now recommended by the Subjective Cognitive Decline—Initiative working group (Jessen et al., 2014).

Patients with vascular disease are at increased risk of cognitive decline and dementia (Kalaria et al., 2008; Mayeux and Stern, 2012; Reitz and Mayeux, 2014). Brain MRI markers of cerebral small vessel disease (cSVD), including WMH and lacunes of presumed vascular origin (lacunes), are also common in these patients (Geerlings et al., 2010). Yet, few studies have assessed the occurrence of SCD and associated abnormalities on brain MRI in these patients (Haley et al., 2009; Uiterwijk et al., 2014). In addition, it is unclear whether SCD is associated with increased risk of brain volume changes and cognitive decline over time in patients with vascular disease, as to our knowledge, only one study researched SCD and this association in patients with vascular disease (Haley et al., 2009).

We aimed to examine whether SCD is associated with brain changes, particularly an increased WMH volume, presence of lacunes, decreased total brain volume, and decreased hippocampal volume, in a cohort of patients with a history of vascular disease without objective cognitive impairment. Furthermore, we aimed to examine if these patients with vascular disease and SCD showed more brain volume changes and cognitive decline over time than those without SCD. We hypothesized that SCD in this population would primarily be associated with vascular brain lesions rather than with loss of brain or hippocampal volume. We also hypothesized that SCD was associated with greater cognitive decline over time, in particular executive functioning and information processing speed, and that presence of cSVD markers became more apparent over time.

2. Methods

2.1. Study design

The Second Manifestations of ARTerial disease—Memory, depression and aging (SMART-Medea) study is an ongoing prospective cohort study aimed to investigate brain changes on MRI, late-life depression, and cognitive decline in patients with a history of vascular disease (Grool et al., 2011). The SMART-Medea study started in 2006 as an ancillary study to the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study, of which rationale and design have been described previously (Geerlings et al., 2010, 2009). In brief, from 2001 to 2005, 1309 middle-aged and older adult patients with coronary artery disease, cerebrovascular disease, peripheral arterial disease, or an aneurysm of the abdominal aorta were included in the SMART-MR study. Between January 2006 and May 2009, 754 patients had follow-up measurements for the SMART-MR cohort, and measurements were then added as part of the SMART-Medea study, including depression assessment, psychosocial risk factor questionnaires, saliva sampling for stress hormones, and a 3-dimensional T1-weighted MR image to assess hippocampal volumes. During a one-day visit to the hospital, patients underwent a physical examination, ultrasonography of the carotid arteries, sampling of blood and urine, neuropsychological and depression assessment, and a 1.5 tesla brain MRI scan. Questionnaires were used for assessing demographics, risk factors, and medical history, medication use, functioning, psychosocial vulnerability and stress factors, and depressive symptoms. From 2013 through 2017, a second follow-up (after a mean of 8 years) was performed in 329 participants including brain MRI and cognitive testing.

The SMART-MR and SMART-Medea study were approved by the ethics committee and written informed consent was obtained from all patients.

2.2. Subjective cognitive decline

SCD was assessed using self-report questions in line with the suggestions of the Subjective Cognitive Decline—Initiative working group (Jessen et al., 2014). They included questions on the memory domain and concentration (Jessen et al., 2014). The following questions were asked: (1) “Do you think your memory is worse than others of your age?,” (2) “Do you think your memory deteriorated compared to 5–10 years ago?,” (3) “Do you think your attention/concentration is worse than others of your age?,” and (4) “Do you think your attention/concentration deteriorated compared to 5–10 years ago?.” Scores were on a 5-point Likert scale. We defined patients as having SCD if they scored “a bit worse” or “a lot worse” on both memory questions or on both concentration questions.

2.3. Cognitive functioning

Objective cognitive functioning was assessed with a set of standard neuropsychological tests covering the domains memory, working memory, executive functioning, and information processing speed. Memory functioning was assessed with the 15 Word Learning Test (immediate recall based on 5 trials and delayed recall) (Brand and Jolles, 1985) and with the delayed recall of the Rey-Osterrieth Complex Figure test (Osterrieth, 1944). Working memory was assessed with the longest span scores of the Forward Digit Span and Backward Digit Span (Wechsler, 2008). Executive functioning was assessed by the Visual Elevator test (Robertson et al., 1996) (10 trials), the Brixton Spatial Anticipation test (Burgess and Shallice, 1996), and Verbal Fluency tests (letter “A” with a time span of 60 seconds and category “animal” with a time span of 120 seconds) (Wilkins et al., 1987). Information processing speed was assessed by the Digital Symbol Substitution Test (Lezak et al., 2004) (120 seconds).

Composite *z*-scores were calculated for four cognitive domains: memory, executive functioning, information processing speed, and working memory. Memory consisted of the immediate and delayed recall of the 15 Word Learning Test, and the delayed recall of the Rey-Osterrieth Complex Figure test. Executive functioning consisted of the Visual Elevator test, Brixton Anticipation test, and the Verbal Fluency tests. Information processing speed was a direct derivative from the *z*-score of the Digital Symbol Substitution Test and did not include other tests. Working memory consisted of the longest score and total scores of the Forward and Backward Digit Span. Composite scores of the cognitive domains were computed by converting all raw scores ([individual test score - mean test score]/standard deviation) to *z*-scores and averaging these for each domain before the final *z* transformation. Before creating the composite z-score, we performed a natural log transformation on the scores of the Visual Elevator test and then multiplied by minus 1, so that higher scores represented better performance. The Brixton Spatial Anticipation test scores were also multiplied by minus 1 so that higher scores represented better performance. At follow-up, composite z-scores of the cognitive domains were calculated by subtracting the respective mean test score at the baseline from the individual test score at follow-up divided by the standard deviation of the baseline test score of the study sample with follow-up cognitive scores available.

At the baseline, objective cognitive impairment was defined as a score of 1.5 standard deviation below age-, sex-, and education-adjusted *z*-scores (composed from the cohort itself) of one or more cognitive domains. As we were interested in pre-MCI SCD, that is, cognitive complaints without objective cognitive impairment on formal cognitive testing (Jessen et al., 2014), we excluded persons with objective cognitive impairment (26%) from the study sample.

2.4. Magnetic resonance imaging protocol

At the baseline and follow-up, the MR images were obtained using a 1.5 tesla whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands). The protocol consisted of a transversal T1-weighted gradient-echo sequence (repetition time (TR)/echo time (TE): 235/2 ms; flip angle, 80°), a transversal T2-weighted turbo spin-echo sequence (TR/TE: 2200/11 ms and 2200/100 ms; turbo factor 12), a transversal T2-weighted fluid attenuating inversion recovery (FLAIR) sequence (TR/TE/inversion time (TI): 6000/100/2000 ms) and a transversal inversion recovery sequence (TR/TE/TI: 2900/22/410 ms) (field of view (FOV) 230 × 230 mm; matrix size, 180 × 256; slice thickness, 4.0 mm; slice gap, 0.0 mm; 38 slices) (Geerlings et al., 2009; Knoops et al., 2009). For hippocampus volumes, a T1-weighted 3D fast-field-echo sequences was acquired (TR/TE: 7.0/3.2 ms; flip angle, 8°; field of view 240 mm; matrix size, 240 × 256; slice thickness 1.0 mm; no gap; 170 slices) (Knoops et al., 2009).

2.5. Lacunes and other infarcts

Two trained investigators and a senior neuroradiologist visually inspected the whole brain for presence of lacunes and other infarcts, blinded to patient history and diagnosis. Rating discrepancies were re-evaluated in a consensus meeting. Lacunes were defined as cavitated lesions of 3–15 mm in diameter and located in the subcortical white matter, thalamus, or basal ganglia, according to STRIVE criteria(Wardlaw et al., 2013). Hyperintensities located in the white matter also had to be hypointense on T1-weighted and FLAIR images in order to distinguish them from WML. Dilated perivascular spaces were distinguished from lacunes based on their location (along perforating or medullary arteries, often symmetric bilaterally, usually in the lower third of the basal ganglia or in the centrum semiovale), shape (round/oval), and the absence of gliosis(Kloppenborg et al., 2012). We did not assess recent small subcortical infarcts, because we did not include a diffusion-weighted imaging (DWI) sequence in the MRI protocol.

2.6. Brain segmentation

The T1-weighted gradient-echo, inversion recovery sequence, and FLAIR sequence were used for brain segmentation according to the k-nearest neighbor classification, as has been described elsewhere (Anbeek et al., 2005, 2004). It distinguishes gray matter, white matter, sulcal and ventricular cerebrospinal fluid, and brain lesions (WMHs, lacunes, and other infarcts). All segmentations were visually checked by an investigator to check if lacunes and other infarcts were correctly segmented and adjusted if necessary. In addition, all WMH segmentations were visually checked by an investigator using an image processing framework (MeVisLab 2.7.1., MeVis Medical Solutions AG, Bremen, Germany) to ensure that brain infarcts (including lacunes) were correctly removed from the WMH segmentations. Incorrectly segmented voxels were added to the correct segmentation volumes using the image processing framework. Total brain volume was calculated by summing the volumes of gray and white matter and, if present, the volumes of WMH, lacunes, and other infarcts. All volumes superior to the foramen magnum were included. As a result, the total brain volume included the cerebrum, brainstem, and cerebellum. Total intracranial volume was calculated by summing up total brain and CSF volumes.

Manual segmentation of hippocampal volumes has been described in detail elsewhere (Knoops et al., 2012). Briefly, the sagittal T1-weighted images were tilted to the coronal plane and orientated perpendicular to the long axis of the left hippocampus. The hippocampus was manually outlined by two trained investigators, blinded to all clinical information, on an average of 40 slices and included the hippocampus proper, subiculum, fimbria, alveus, and dentate gyrus.

For the present study, segmentations of total brain volume, CSF, WMH volume, and lacunes were available at the baseline and follow-up. Manual segmentations of hippocampal volume were available for the baseline but not for the follow-up.

2.7. Other variables

Age, sex, and highest level of education were assessed with questionnaires. Education was recalculated into 3 categories from the Dutch educational system which ranged from no education/primary school to University education. Low level of education included no education or primary school only (comparable to up to 6 years of education), high-level education included higher professional education and (pre-) university education (comparable to ≥15 years of education), and all other educational levels were defined as an intermediate level of education (comparable to around 7–14 years of education).

Depressive symptoms were assessed with the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001). The PHQ-9 assesses the presence of 9 symptoms for major depression according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition in the past two weeks using a Likert scale and has a score range of 0–27.

During the visit to the hospital, blood pressure was measured three times in supine position and the average was calculated. Hypertension was defined as mean systolic blood pressure ≥140 mmHg, mean diastolic blood pressure ≥90 mmHg, or use of antihypertensive drugs. Hyperlipidemia was defined as use of lipid-lowering drugs, or a cholesterol ratio ≥5.0 which was calculated by using fasting levels of cholesterol and the formula: total cholesterol/high-density lipoprotein cholesterol. Body mass index was calculated as weight (kg)/height $(m)^2$ after measuring height and weight without shoes or heavy clothing. Diabetes mellitus (DM) was defined as either a referral diagnosis of DM, self-reported DM, use of glucose-lowering agents or insulin, a known history of DM, nonfasting plasma glucose ≥11.1 mmol/L, or fasting plasma glucose ≥7.0 mmol/L. Pack years of smoking were calculated by use of a questionnaire on smoking habits. Alcohol use was determined with a questionnaire and expressed in units per week.

2.8. Study sample

Of the 754 patients of the SMART-Medea study, 121 patients had cognitive impairment and 32 had missing data on cognitive impairment, and these 153 persons were excluded from the present study sample. Of the remaining 601 persons, 2 persons did not have data on subjective decline available, leaving 599 persons with SCD data and cognition data. Of these 599 persons, 22 did not have an MRI, 10 had artifacts, and 1 had a segmentation failure, leaving 566 persons with brain volume data. Because the scan protocol for hippocampus measurements was implemented later in the study (April 2006 instead of January 2006), segmentations of the

hippocampus were available in 509 persons. At the follow-up, 267 persons of the 599 had cognitive test scores available, and 250 of the 566 had brain volume data, including WMH volume and lacunes. Follow-up data on hippocampal volume were not available for this study.

2.9. Data analysis

First, baseline characteristics were calculated for the participants with and without SCD. Next, we used linear regression analysis to estimate the associations between SCD and volume of WMH, total brain volume and hippocampal volume, respectively. WMH volume was naturally log-transformed because of non-normal distribution, and after analyses transformed back to mL via exponentiation. We used a modified Poisson-regression with log-link function and robust standard errors to estimate the relative risks (RRs) of SCD with presence of lacunes. We estimated RR as these are recommended instead of odds ratios when an outcome is frequent (>10%) to prevent overestimation of the true risk (Knol et al., 2012). Analyses were adjusted for age, sex, educational level, intracranial volume, and depression (model 1). In model 2, we additionally adjusted for smoking, alcohol use, body mass index, hypertension, hypercholesterolemia, and DM.

For the prospective associations between SCD and change in brain volume, WMH volume and presence of lacunes, linear regression and modified Poisson-regression with log-link function and robust standard errors were again used, where the respective MRI marker at follow-up was used as the dependent variable (total brain volume, WMH volume, presence of lacunes) and adjustments were made for the corresponding baseline MRI marker. Other covariates were the same as models 1 and 2 from the cross-sectional analyses.

Similarly, we used linear regression analysis and analysis of covariance to estimate the cross-sectional and prospective associations between SCD and cognitive performance per cognitive domain. In model 1, we adjusted the analysis for age, sex, educational level and depressive symptoms, and for the prospective analysis with follow-up, where cognitive performance was the dependent variable; we also adjusted for the baseline *z*-score of the corresponding cognitive domain. In model 2, we additionally adjusted for cardiovascular risk factors.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0.

3. Results

Table 1 shows the baseline characteristics of the study sample for participants with and without SCD. Of the 599 participants, 143 (23.9%) had SCD. Participants without SCD were on average older (62 [SD 9] years of age) than those with SCD (60 [SD 9] years of age). Results of neuropsychological tests and depression questionnaires for participants with and without SCD are presented in Supplementary Table 1. The score on the Mini–Mental State Examination was 28.8 (SD 1.2) for participants without SCD and 28.7 (SD 1.4) for participants with SCD. Of the participants without SCD, 10% had a score of 6 or higher on the PHQ-9, and of the participants with SCD, this was 31%.

Table 2 presents the cross-sectional associations between the presence of SCD and WMH volume, lacunes, total brain volume, and hippocampal volume. Participants with SCD had larger WMH volume compared with those without SCD, but this was not statistically significant (log-transformed WMH volume: B = 0.18, 95% confidence interval [CI]: −0.04; 0.41. Back-transformed WMH volume: B = 1.20 mL, 95% CI: 0.91; 1.49. $p = 0.115$ model 1), and which remained similar after adjustment for cardiovascular risk factors. Participants with SCD had an increased risk of lacunes (RR = 1.47, 95% CI: 1.00; 2.16, $p = 0.052$ model 1) compared with those without SCD, which remained increased after adjustment for cardiovascular

Table 1
Baseline characteristics of the study sample (n = 599)

Characteristics	No SCD n = 456	SCD n = 143	*p*-value
Age (y)	62.3 ± 9.4	59.7 ± 9.3	0.005
Mean age of all patients ± SD			
Sex			
Male	83%	80%	0.422
Female	17%	20%	
Education			
Low level of education	8%	10%	0.602
Intermediate level of education	66%	66%	
High level of education	26%	24%	
Hypertension	74%	71%	0.493
Hyperlipidemia	81%	87%	0.070
Diabetes mellitus	20%	22%	0.515
Body mass index (kg/m^2), mean ± SD	27.3 ± 3.4	27.3 ± 4.1	0.955
Smoking (pack years), mean ± SD	21.1 ± 18.6	24.7 ± 19.6	0.050
Alcohol use			
Less than 1 unit per week	27%	34%	0.284
1 till 10 units per week	41%	41%	
11 till 20 units per week	21%	16%	
More than 20 units per week	11%	9%	
History of cerebrovascular disease	19%	34%	<0.0001
Depressive symptoms (max. score 27), mean ± SD	2.1 ± 2.8	4.2 ± 3.9	<0.0001
Depression (PHQ score ≥6)	10%	31%	<0.0001
White matter lesions volume (mL), median (10th percentile − 90th percentile)	1.14 (0.22–7.08)	1.10 (0.27–8.36)	0.814[a]
Lacunes	19%	24%	0.177
Total hippocampal volume (mL), mean ± SD	5.99 ± 0.72	5.98 ± 0.71	0.934
Brain volume (mL), mean ± SD	1150 ± 102	1137 ± 106	0.195
Large (sub)cortical infarction present	10%	15%	0.120
Intracranial volume (mL), mean ± SD	1466 ± 124	1445 ± 130	0.085

p-value based on the Pearson chi-square test or independent *t*-test.
Key: PHQ, Patient Health Questionnaire; SCD, subjective cognitive decline.
[a] Difference between the group tested on natural log-transformed value using independent *t*-test.

Table 2
Cross-sectional association of subjective cognitive decline (yes/no) with brain MRI parameters

Model	White matter hyperintensity volume (mL)[a]		Lacunes (yes/no)	
	Unstandardized B (95% CI)	*p*-value	Relative risk (95% CI)	*p*-value
1	1.20 (0.91; 1.49)	0.115	1.47 (1.00; 2.16)	0.052
2	1.20 (0.90; 1.49)	0.124	1.48 (1.03; 2.12)	0.034
Model	Brain volume (mL) Unstandardized B (95% CI)	*p*-value	Hippocampal volume (mL) Unstandardized B (95% CI)	*p*-value
1	−5.54 (−11.95; 0.86)	0.090	−0.002 (−0.14; 0.14)	0.982
2	−5.35 (−11.53; 0.84)	0.090	−0.005 (−0.15; 0.14)	0.942

Complete case analyses with all covariates were available for n = 547 in analyses with white matter hyperintensity and brain volume, n = 541 with lacunes, and n = 494 for hippocampal volume (no SCD n = 378, SCD n = 116).
Model 1: Adjusted for age, sex, intracranial volume, educational level, and depressive symptoms.
Model 2: Model 1 + hypertension, hypercholesterolemia, diabetes mellitus, body mass index, smoking, and alcohol use.
Key: CI, confidence interval; MRI, magnetic resonance imaging.
[a] Unstandardized B and 95% confidence intervals presented are back-transformed volumes from natural log-transformed values that were used for the analyses.

risk factors (RR = 1.48, 95% CI: 1.03; 2.12, $p = 0.034$ model 2). To explore if the relation between SCD and lacunes reflected more common occurrence of cognitive concerns in those who had a history of stroke, rather than a relation between the lacunar lesion itself and SCD, we ran an additional analysis with a history of stroke as covariate. Adding a clinical history of stroke to model 1 with lacunes attenuated the relationship (RR = 1.24; 95% CI: 0.88; 1.75, $p = 0.230$).

Compared with participants without SCD, those with SCD had smaller total brain volumes, but this did not reach statistical significance (B = −5.54 mL, 95% CI: −11.95; 0.86, $p = 0.090$ model 1) and remained similar in model 2. No association between SCD and hippocampal volume was observed (B = −0.002 mL, 95% CI: −0.14; 0.14, $p = 0.982$ model 1). In addition, when we used hippocampal volume based on FreeSurfer (version 5.3.0) segmentation, we did not find a relationship between SCD and hippocampal volume (B = 0.07; 95% CI: −0.09; 0.23, $p = 0.411$, model 1). To explore whether age might modify the relationship between SCD and total brain or hippocampal volume, we performed post hoc analyses stratified for age. For total brain volume, the estimates were similar and the interaction between age (as a continuous variable) and SCD was not statistically significant ($p = 0.448$) (<60 years [n = 245] B = −5.86; 95% CI: −14.87; 3.15, $p = 0.201$, model 1; 60 years or older [n = 354] B = −2.88; 95% CI: −11.70; 5.95, $p = 0.522$, model 1). For hippocampal volume, the estimates were also fairly similar and the interaction between age and SCD was not statistically significant ($p = 0.540$) (<60 years B = −0.03; 95% CI: −0.24; 0.17, $p = 0.739$, model 1; 60 years or older B = 0.07; 95% CI: −0.13; 0.26, $p = 0.502$, model 1).

Table 3 shows the longitudinal associations between SCD and brain MRI markers at the follow-up. We found no significant associations between the presence of SCD and an increase in WMH volume (back-transformed B = 0.97; 95% CI: 0.82; 1.12, $p = 0.683$, model 1), nor with presence of lacunes (RR = 1.10; 95% CI: 0.63; 1.92, $p = 0.740$, model 1), or a decrease in brain volume (B = 3.82; 95% CI: −2.87; 10.51, $p = 0.262$, model 1).

Table 4 and Fig. 1 present the cross-sectional associations between SCD and performance on the cognitive domains. Compared with patients without SCD, those with SCD performed worse on executive functioning (B = −0.27; 95% CI: −0.44; −0.11, $p = 0.001$, model 1) and speed (B = −0.18; 95% CI: −032; −0.03, $p = 0.020$, model 1), and also on memory, but this did not reach statistical significance. No association with working memory was observed.

Table 5 and Fig. 2 show the results of the longitudinal associations between SCD and cognitive performance. Although all patients declined in their cognitive performance (Fig. 2), no significant differences were observed between patients with and without SCD, except for information processing speed where patients with SCD showed less decline compared with patients without SCD (Table 5).

4. Discussion

In this study among patients with a history of vascular disease without objective cognitive impairment, SCD was associated with an increased risk of lacunes, independent of age, sex, education,

Table 3
Longitudinal association of subjective cognitive decline (yes/no) with brain MRI parameters at follow-up

Model	White matter hyperintensity volume[a]		Lacunes	
	Unstandardized B (95% CI)	*p*-value	Relative risk (95% CI)	*p*-value
1	0.97 (0.82; 1.12)	0.683	1.10 (0.63; 1.92)	0.740
2	0.98 (0.83; 1.14)	0.838	1.17 (0.62; 2.19)	0.624
Model	Brain volume Unstandardized B (95% CI)	*p*-value		
1	3.82 (−2.87; 10.51)	0.262		
2	3.04 (−3.73; 9.81)	0.376		

Complete case analyses with all covariates were available for n = 237 in analyses with white matter hyperintensity and brain volume, and n = 235 with lacunes.
Model 1: Adjusted for baseline value of corresponding MRI marker, age, sex, intracranial volume, educational level, and depressive symptoms.
Model 2: Model 1 + hypertension, hypercholesterolemia, diabetes mellitus, body mass index, smoking, and alcohol use.
Key: CI, confidence interval; MRI, magnetic resonance imaging.
[a] Unstandardized B and 95% confidence intervals presented are back-transformed volumes from natural log-transformed values that were used for the analyses.

Table 4
Cross-sectional associations of the presence of subjective cognitive decline (yes/no) with performance on cognitive domains (z-scores)

Model	Memory		Executive functioning	
	Unstandardized B (95% CI)	*p*-value	Unstandardized B (95% CI)	*p*-value
1	−0.16 (−0.33; 0.01)	0.068	−0.27 (−0.44; −0.11)	0.001
2	−0.14 (−0.31; 0.03)	0.104	−0.26 (−0.43; −0.09)	0.003
Model	Speed		Working memory	
	Unstandardized B (95% CI)	*p*-value	Unstandardized B (95% CI)	*p*-value
1	−0.18 (−0.32; −0.03)	0.020	−0.05 (−0.23; 0.14)	0.617
2	−0.17 (−0.32; −0.02)	0.023	−0.06 (−0.24; 0.12)	0.522

Complete case analyses with all covariates were available for n = 577 in models 1 and 2.
Model 1: adjusted for age, sex, educational level, and depressive symptoms.
Model 2: Model 1 + hypertension, hypercholesterolemia, diabetes mellitus, body mass index, smoking, and alcohol use.
The unstandardized B's represent the difference in z-score of the respective cognitive domain at the baseline between persons with and without SCD.
Key: CI, confidence interval; SCD, subjective cognitive decline.

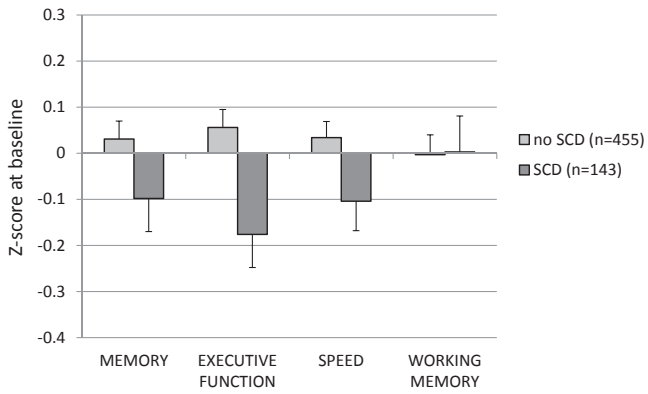

Fig. 1. Mean differences between subjective cognitive decline (SCD) (yes/no) and cognitive functioning per cognitive domain at the baseline. Adjusted for age, sex, education, and depressive symptoms (model 1).

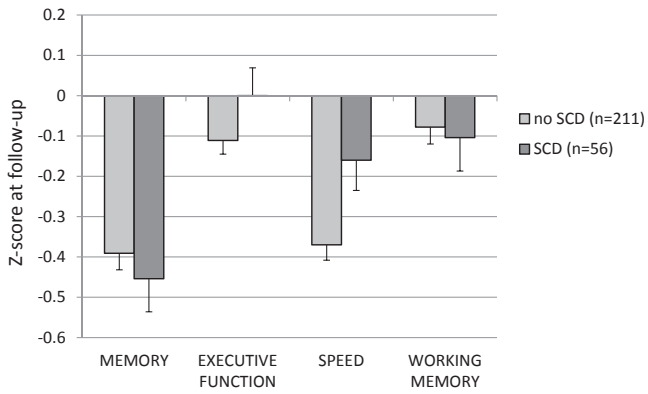

Fig. 2. Mean differences between subjective cognitive decline (SCD) (yes/no) and cognitive functioning per cognitive domain at the follow-up. Adjusted for age, sex, education, depressive symptoms, and baseline z-score per cognitive domain (model 1).

depressive symptoms, and cardiovascular risk factors. SCD was also associated with smaller total brain volume and larger volume of WMHs, although this relationship did not reach statistical significance. No association with hippocampal volume was observed. Furthermore, SCD was associated with poorer executive functioning and information processing speed, but not with memory or working memory. During on average 8 years of follow-up, SCD was not associated with a decrease in total brain volume or an increase in WMH volume or lacunes. In addition, SCD was not associated with a decline in cognitive performance.

To our knowledge, no other study examined the association between SCD and presence of lacunes. The question is if the presence of lacunes by itself relates to SCD or whether the notion of having experienced a stroke—which also relates to lacune presence—is a key determinant of SCD. In our analyses, the relationship between SCD and lacunes was partly explained by a history of stroke. It is possible that co-occurring large vessel disease, if the participant was aware of this, led to complaints of cognitive decline.

We found that SCD was associated with a larger WMH volume, although this relationship did not reach statistical significance. During follow-up, SCD was not associated with an increase in WMH volume. Results from previous studies that examined the association between SCD and WMH in different populations were inconsistent. In community-dwelling older adults, one study found no association between SCD and severity of WMH (Bartley et al., 2012), whereas others found more severe WMH to be associated with SCD (de Groot et al., 2001; Stewart et al., 2011, 2008). One of these studies also found an association between an increase in WMH and the presence of SCD after 4 years of follow-up (Stewart et al., 2011). A study in patients with hypertension did not find an association between SCD and WMH (Uiterwijk et al., 2014), whereas another study in patients with cardiovascular disease did find SCD to be associated with an increase in WMH (Haley et al., 2009). In memory-clinic patients, one study found that the severity of WMH was associated with SCD (Minett, 2005).

In our study within patients with vascular disease, SCD was associated with slightly smaller total brain volume, but this did not reach statistical significance. No association with hippocampal volume was observed. Previous cross-sectional studies that were conducted in patients from a memory clinic also found no significant associations between SCD and global brain volume (Striepens et al., 2010) or between SCD and total gray matter volume (Scheef et al., 2012). Studies examining the association between SCD and hippocampal volume found various results across different settings. Some studies observed smaller hippocampal volumes in persons with SCD in memory clinics (Hafkemeijer et al., 2013; Perrotin et al., 2015; van der Flier et al., 2004a, b), whereas others did not (Hong et al., 2015; Ryu et al., 2017; Tepest et al., 2008). In community-dwelling older adults, one study found an association between SCD and a smaller hippocampal volume (Cantero et al., 2016), and others found that people with a smaller hippocampal volume more often had SCD (Stewart et al., 2008, 2011). One of the latter studies was a longitudinal study and also reported an association between loss of total gray matter volume and an increase in reported SCD at the follow-up (Stewart et al., 2011), which is in contrast with our study as we did not find an association between SCD and a decrease in brain volume over time. Another longitudinal study found an association between smaller hippocampal volume and SCD only at follow-up but not at the baseline (Cherbuin et al., 2015). It is possible that loss of brain or hippocampal volume contributes to SCD, whereas having SCD is not per se associated with a smaller brain or hippocampal volume, as is the case in our population of patients with a history of vascular disease.

In this study, we found that the presence of SCD was associated with poorer performance on executive functioning and information processing speed, and with memory, although the latter did not reach statistical significance. It should be noted that we excluded patients with objective cognitive impairment based on age-, sex-, and education-adjusted z-scores of one or more cognitive domains. Still, differences—particularly in the executive functioning and

Table 5
Longitudinal associations of the presence of subjective cognitive decline (yes/no) and performance on cognitive domains (z-scores) at the follow-up

Model	Memory		Executive functioning	
	Unstandardized B (95% CI)	*p*-value	Unstandardized B (95% CI)	*p*-value
1	−0.06 (−0.25; 0.13)	0.513	0.11 (−0.05; 0.27)	0.169
2	−0.08 (−0.28; 0.11)	0.416	0.10 (−0.07; 0.26)	0.241
Model	Speed		Working memory	
	Unstandardized B (95% CI)	*p*-value	Unstandardized B (95% CI)	*p*-value
1	0.22 (0.05; 0.40)	0.012	0.00 (−0.19; 0.19)	0.996
2	0.24 (0.07; 0.41)	0.007	0.00 (−0.19; 0.20)	0.982

Complete case analyses with all covariates were available for n = 256 in analyses with memory, n = 257 with executive functioning, n = 255 with speed, and n = 254 with working memory.
Model 1: Adjusted for z-score at the baseline per cognitive domain, age, sex, educational level, and depressive symptoms.
Model 2: Model 1 + hypertension, hypercholesterolemia, diabetes mellitus, body mass index, smoking, and alcohol use.
The unstandardized B's represent the difference between persons with and without SCD in absolute change in z-score of the respective cognitive domain between the baseline and follow-up.
Key: CI, confidence interval; SCD, subjective cognitive decline.

speed domain—could be observed between patients with and without SCD. During follow-up, however, we did not find statistically significantly decreases in cognitive performance associated with SCD. Unexpectedly, we observed a smaller decline in speed in patients with SCD compared with those without, a finding for which we do not have a clear explanation. In addition, previous studies mainly focused on the associations between SCD and objective cognitive performance (Burmester, Mitchell) or on progression of SCD complaints to MCI and dementia (Mendonça et al., 2015; Mitchell et al., 2014; Neto and Nitrini, 2016; Rabin et al., 2017), and our findings are therefore difficult to compare. In addition, previous studies did not exclude patients with objective cognitive impairment at the baseline, which make these studies and our study not fully comparable.

A strength of this study is that we examined different neuroimaging markers, including neurodegenerative and cSVD markers in contrast to many previous studies that examined one or two markers, and that we examined objective performance across different cognitive domains. In addition, SCD was defined according to recently proposed research criteria, such as the inclusion of other cognitive domains apart from memory (Jessen et al., 2014). Previous studies used various methods of reporting cognitive complaints, mainly focusing on memory complaints, which limits comparability. In addition, we were able to examine brain MRI markers and cognitive functioning at the baseline and after 8 years of follow-up. Finally, we adjusted our analyses for cardiovascular risk factors and depressive symptoms. Adjustment for depressive symptoms is lacking in some other studies (Cantero et al., 2016; Hafkemeijer et al., 2013; Hong et al., 2015; Perrotin et al., 2015; Rogne et al., 2016; Ryu et al., 2017; W M; van der Flier et al., 2004a, b).

A limitation of this study is the relatively large number of patients who were lost to follow-up, either because they died or because they were unwilling or unable to participate. As a result, power to detect associations was reduced, and more importantly, the most resilient and healthy patients likely participated at the follow-up. Yet, patients with and without SCD at the baseline were fairly similarly likely to be lost to follow-up (59% lost to follow-up in patients with versus 53% without SCD). Another limitation is that we did not have hippocampal volume available at the follow-up. A last limitation could be that we did not assess recent small subcortical infarctions. However, this should not impact the assessment of lacunes because lacunes are cavitated by definition, whereas recent small subcortical infarctions are not. Hypothetically, recent subcortical infarctions could be misclassified as WMHs.

In conclusion, in this cohort of patients with a history of vascular disease without objective cognitive impairment, SCD was associated with an increased risk of lacunes, and with poorer executive functioning and information processing speed at the baseline, but not during 8 years of follow-up. More prospective studies are needed to further elucidate the relationship between SCD, brain imaging markers, and cognitive decline and the role of SCD in the preclinical stage of Alzheimer's disease.

Disclosure

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.07.011.

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