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Subjective vs informant-reported cognitive complaints have differential clinical significance in covert cerebral small vessel disease

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ABSTRACT

Objective: Subjective cognitive complaints are common in patients with cerebral small vessel disease (cSVD), yet their relationship with informant evaluations, objective cognitive functions and severity of brain changes are poorly understood. We studied the associations of subjective and informant reports with findings from comprehensive neuropsychological assessment and brain MRI.

Method: In the Helsinki SVD Study, 152 older adults with varying degrees of white matter hyperintensities (WMH) but without stroke or dementia were classified as having normal cognition or mild cognitive impairment (MCI) based on neuropsychological criteria. The measures also included continuous domain scores for memory and executive functions. Cognitive complaints were evaluated with the subjective and informant versions of the Prospective and Retrospective Memory Questionnaire (PRMQ) and Dysexecutive Questionnaire (DEX); functional abilities with the Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL); and depressive symptoms with the Geriatric Depression Scale (GDS-15).

Results: Subjective cognitive complaints correlated significantly with informant reports (r=0.40–0.50, $p<0.001$). After controlling for demographics, subjective and informant DEX and PRMQ were not related to MCI, memory or executive functions. Instead, subjective DEX and PRMQ significantly associated with GDS-15 and informant DEX and PRMQ with WMH volume and A-IADL.

Conclusions: Neither subjective nor informant-reported cognitive complaints associated with objective cognitive performance. Informant-evaluations were related to functional impairment and more severe WMH, whereas subjective complaints only associated with mild depressive symptoms. These findings suggest that awareness of cognitive impairment may be limited in early-stage cSVD and highlight the value of informant assessments in the identification of patients with functional impairment.

Introduction

Subjective cognitive complaints increase with ageing [1]. They reflect an individual's own opinion of their cognitive abilities, whereas a test performance in a formal cognitive assessment is considered to represent objective functioning [2]. Awareness of cognitive impairment refers to the ability to evaluate one's own functioning in a realistic manner, and this awareness is commonly reduced in neurological conditions such as stroke and neurodegenerative diseases [3,4]. Awareness can be assessed by evaluating subjective cognitive complaints and by

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mirroring how well these relate to objective abilities [5].

Lack of awareness (anosognosia) may be a differentiating characteristic in the identification of those subjects with a higher likelihood of progressing from mild cognitive impairment (MCI, equivalent to mild neurocognitive disorder in DSM-V) to dementia. Patients with amnestic MCI have been found to underestimate their cognitive problems, and this discrepancy has been related to positive Alzheimer's disease CSF biomarkers and clinical decline [6]. However, the relationship between subjective symptoms and cognitive performance is complex and not always linear, as it can manifest in different ways through varying symptoms and aetiologies. A meta-analysis has shown that subjective cognitive complaints were related to a higher risk of converting to MCI or dementia over time [2]. In contrast, some studies with MCI and Alzheimer's disease patients have suggested that subjective cognitive complaints are not a reliable estimation of actual cognitive performance, and instead, informants' reports are more valuable in identifying potential cognitive decline [7–10].

Cerebral small vessel disease (cSVD) is a major contributor to progressive cognitive impairment in older individuals. White matter hyperintensities (WMH) of presumed vascular origin are one of the key characteristics of cSVD on brain imaging together with small subcortical infarcts, lacunes, cerebral microbleeds and perivascular spaces [11]. WMH are a strong determinant of cognitive and functional decline, a relationship that has been also observed in our studies [12–14]. The small number of studies investigating awareness of cognitive impairment in cSVD have produced mixed findings and frequently small sample sizes. In healthy late middle-aged to older adults, subjective cognitive complaints have been associated with WMH volume, Fazekas score and hippocampal atrophy [15]. Dey et al. [16] found that subjective cognitive complaints, but not objective cognitive functioning, differentiated subjects with and without cSVD, and suggested the use of questionnaires to distinguish the effects of subtle vascular pathology. Contrary to the aforementioned studies, a meta-analysis by Clancy et al. [17] found no significant associations between subjective cognitive complaints and WMH.

Understanding the nature of awareness of cognitive difficulties in cSVD is important in order to gain a realistic understanding of the patient's condition. If awareness is impaired, informants may become a necessary part of the clinical assessment. Although a lack of awareness of cognitive symptoms is common in patients with vascular dementia [18], the level and clinical significance of awareness remains unclear in covert cSVD referring to the early stages of the disease, where brain imaging findings are evident, but overt neurological manifestations such as stroke, dementia or significant functional disability have not yet occurred [19]. We examined awareness of cognitive impairment in subjects with varying degrees of WMH but without clinical stroke or dementia. Specifically, we studied whether subjective and informant reports of cognitive functioning relate to 1) MCI classification, 2) memory or executive performance, 3) the presence of depressive symptoms, 4) instrumental activities of daily living (IADL) and 5) WMH volume.

Method

Subjects and design

In the Helsinki Small Vessel Disease Study, a total of 152 subjects were recruited from the Helsinki University Hospital imaging registry in Finland between 2016 and 2020 based on WMH finding of any degree. The subjects were recruited from patients who had recently had a brain scan at the hospital due to transient ischaemic attack (26%); dizziness (18%); headache/migraine (10%); subjective cognitive complaints (4%); visual symptoms (11%); fall (7%); syncope (3%); or other reasons (20%). A further study-specific magnetic resonance imaging (MRI) and comprehensive neuropsychological and neurological evaluations were completed in three visits within approximately 1 month. In-depth descriptions of the protocol can be found in earlier publications [12,14].

The study included subjects who a) were aged 65–75 years at enrolment; b) resided within the Helsinki and Uusimaa hospital district; c) had at most experienced minor, temporary and local neurological symptoms (onset within 3 to 12 months before the enrolment), or no apparent neurological symptoms; d) were functionally independent in basic daily activities (modified Rankin Scale score of 0–2; [20]); and e) were fluent in the Finnish language. The initial exclusion criteria were pre-existing significant neurological disorders (including clinical dementia), severe psychiatric disorders (including major depressive disorder), and sight or hearing disabilities that might impede neuropsychological testing or any factor that might exclude the use of MRI.

Additional MRI exclusion criteria were as follows: cortical infarct; subcortical infarct larger than 15 mm (20 mm on diffusion-weighted images); haemorrhage larger than microbleed (over 10 mm); brain tumour; and any type of brain injury (contusion, traumatic subarachnoid or intracranial haemorrhage, distinct diffuse axonal injury).

Close informants of the subjects were asked to complete questionnaires about the subject's cognitive (memory and executive functioning) abilities. A total of 134 informants filled in these questionnaires (16 unavailable or unwilling to participate, 2 refrained from returning the questionnaires). The informants were either the subject's spouses or life partners (n=88) children (n=36), grandchildren (n=3), close relatives (n=4) or friends (n=3).

Ethics approval

The Ethics Committee of the Helsinki University Hospital approved the study and the protocols from the Declaration of Helsinki were followed. Each subject agreed to take part in the study by informed written consent.

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Magnetic resonance imaging

MRI was conducted with a 3T MRI scanner with 32-channel head coil. In the standard protocol, the following sequences were included: a fast T1 gradient echo localizer in three orthogonal directions (0.9 Å~ 0.8 mm in-plane resolution, 8 mm slice thickness, TR 9 ms, TE 4 ms, FA 20 °), sagittal 3D FLAIR SPACE (1.1 Å~ 1.0 mm in-plane resolution, 1 mm slice thickness, 176 slices, TR 6000 ms, TE 389, ms, TI 2100 ms), sagittal 3D T2 SPACE

(1.0 Å~ 1.0 mm in-plane resolution, 1 mm slice thickness, 176 slices TR 3200 ms, TE 416 ms), and sagittal 3D T1 MPRAGE (1.1 Å~ 1.0 mm in-plane resolution, 1 mm slice thickness, 176 slices, TR 1900 ms, TE 2.47 ms, FA 9 °).

WMH of presumed vascular origin were determined on FLAIR sequences as hyperintense areas in the white matter (WM) without cavitation [21]. Deep and subcortical WMH were first visually assessed on a scale of 0 to 3 by a board certified neuroradiologist with the modified Fazekas scale [22]. Chronic small infarcts other than those specified in the exclusion criteria were evaluated by number and location.

An automated multi-stage segmentation method based on the Expectation-Maximization algorithm was used to segment total WMH volume on FLAIR images [23]. We used a three-step method: 1) classifying WM first from T1 image; 2) segmenting FLAIR into three classes (CSF, normal brain tissue, and hyperintense voxels); and 3) segmenting WM and subcortical regions from FLAIR image into two classes, using the class with higher intensities as the segmentation of WMH (described in detail by [24]). The total WMH volume (ml) was normalised according to intracranial volume and log transformed to obtain normal

distribution.

Subjective and informant reports of memory and executive functions

The Prospective and Retrospective Memory Questionnaire (PRMQ) is a validated questionnaire designed to identify subjective memory problems [25–27]. The questionnaire includes 16 questions and scoring ranges from 1 (never) to 5 (very often), with higher scores reflecting more severe memory complaints. We used both subjective and informant versions of the questionnaire.

The Dysexecutive Questionnaire (DEX) is used to examine subjective difficulties in executive functioning [28]. The DEX consists of 20 items related to four domains (emotional, motivational, behavioural and cognitive). Items are rated on a 5-point scale (0=never, 1=occasionally, 2=sometimes, 3=fairly often and 4=very often). The total score can range from 0 to 80, with higher scores indicating greater subjectively reported issues in executive functioning. We used both subjective and informant versions of the DEX.

Neuropsychological assessment

To assess cognitive functioning, we adopted a comprehensive neuropsychological assessment comprising both paper-and-pencil and computerised tests as described in detail in Jokinen et al. [14].

MCI was classified based on the Jak/Bondi comprehensive neuropsychological criteria [29,30]. Performance falling below one standard deviation from normative expectations in two or more test scores indicated impairment within a cognitive domain. Alternatively, a single impaired test score (>1 SD) across all domains was considered indicative of MCI. Details of the tests and normative data are provided in the Supplemental Table 1. The following five domains were evaluated (specific tests in brackets): a) processing speed (Wechsler Adult Intelligence Scale IV [WAIS-IV] Coding, Stroop colour-congruent part, and Flexible attention test [FAT] numbers); b) executive functions and working memory (phonemic word fluency, Stroop colour-incongruent, FAT number-letter, and Wechsler Memory Scale III [WMS-III] Digit span); c) memory and learning (WMS-III Word lists immediate and delayed recall, and delayed recall of Rey-Osterrieth complex figure); d) visuospatial functions (WAIS-IV Block design and copy of Rey-Osterrieth complex figure); and e) language (WAIS-IV Similarities and semantic word fluency).

In addition to categorical MCI diagnosis, we used continuous cognitive domain scores for memory and executive functions as measures of objective cognitive functioning to match the questionnaires assessing subjective functioning in those specific domains. The scores were calculated based on standardised z-scores as described in Jokinen et al. [14].

Depressive symptoms

We used the Geriatric Depression Scale-15, which contains 15 statements with yes or no responses, to assess depressive symptoms [31]. The scale is regarded as a screening tool with good diagnostic accuracy to detect depression in older individuals [32]. The scores 0–2 (no depressive symptoms) and >2 (depressive symptoms) were chosen as the binary measure of presence or absence of depressive symptoms.

Evaluation of functional abilities

Amsterdam Instrumental Activities of Daily Living questionnaire (A-IADL) is a validated and robust measure of informant-reported functional abilities [33,34]. The questionnaire includes 30 questions (short version) on the ability to perform complex activities (e.g. household, finances, computer-use). Score, which range from 0 (no difficulty) to 4 (unable to perform activity), evaluate current performance compared to past performance. The total score is calculated using item response theory and represents a score on the latent trait of daily functioning, with higher scores reflecting better functioning [35].

Statistical analyses

The bivariate associations between informant- and self-reported DEX and PRMQ scores were examined with Pearson's correlations. The associations of informant- and self-reported DEX and PRMQ scores with categorical variables MCI and depressive symptoms (present/absent) were studied with logistic regression analyses. The associations of DEX and PRMQ scores with continuous cognitive outcomes (executive functioning and memory), A-IADL and WMH were investigated with linear regression analyses. Due to a violation of the homoskedasticity assumption – that is, in the analyses of the A-IADL scores were not correctable with distribution transformations – we also analysed the data using heteroskedasticity-consistent standard error (HCSE) estimators [36]. All logistic and linear regression analyses where ran hierarchically, the first step with one independent variable (univariate models), and the second step by controlling for subjects' age, sex, and education. These control variables were selected based on their statistical associations and previously confirmed relationships with the variables of interest, and the hierarchical approach was adopted to reveal whether the relationships would change under the influence of demographic factors. Due to missing data, the number of cases included in each analysis varied (available-case analysis). Complete data for each subject (n=152) was available for WMH volume, MCI, and cognitive domain scores. GDS-15 was available for 151, PRMQ-subjective for 141, PRMQ-informant for 134, DEX-subjective for 140, DEX-informant for 134, and A-IADL for 132 subjects. The false discovery rate correction was used to correct for multiple analysis (accounting for the four independent variables in each analysis).

IBM SPSS Statistics version 28 was used for the analyses of the data and R version 4.0.5 and RStudio Version 1.2.5033 were used for making the figures.

Results

Subject characteristics

In total, 134 of 152 subjects had DEX and PRMQ questionnaires filled in by an informant. These subjects did not differ from those with missing informant data (n=18) in terms of age, sex, education, WMH volume or A-IADL score (all p-values>0.05). Demographic, MRI and clinical

Table 1
Subject characteristics.

Demographics	
Age, mean (SD)	70.6 (2.9)
Sex, female/male, n	95/57
Education, years, mean (SD)	13.0 (4.5)
WMH	
Fazekas score, none, mild, moderate, severe, n	14/76/42/20
WMH volume, ml*, mean (SD)	10.5 (13.8)
WMH volume, ml*, log transformed, mean (SD)	0.9 (0.4)
Clinical characteristics	
Hypertension, absent/present, n	47/105
Diabetes, absent/present, n	119/33
Hypercholesterolemia, absent/present, n	34/118
MoCA score, mean (SD)	23.5 (3.3)
MCI absent/present, n	85/67
Questionnaires	
GDS-15, no symptoms/symptoms, n	105/46
A-IADL, mean (SD)	66.7 (4.7)
DEX subjective, mean (SD)	12.7 (9.8)
DEX informant-reported mean (SD)	7.8 (7.2)
PRMQ subjective mean (SD)	30.8 (8.5)
PRMQ informant-reported mean (SD)	25.6 (8.0)

* Normalised for intracranial volume

characteristics as well as descriptive statistics for the DEX and PRMQ are shown in Table 1. Only a few subjects (n=11/134, 8%) had small chronic infarcts, and therefore these findings were considered in the subsequent analyses. Descriptive statistics on the cognitive tests can be found on the supplemental material published previously [37].

Amsterdam Instrumental Activities of Daily Living questionnaire (A-IADL); Montreal Cognitive Assessment (MoCA); white matter hyperintensities (WMH); Mild cognitive impairment (MCI); Geriatric Depression Scale 15 (GDS-15); Dysexecutive Questionnaire (DEX); Prospective and Retrospective Memory Questionnaire (PRMQ)

There were statistically significant positive correlations between subjective and informant DEX scores (r=0.40, p<0.001), and subjective and informant PRMQ scores (r=0.50, p<0.001).

Associations between subjective and informant reports and MCI

Subjective DEX scores had a significant bivariate association with MCI (OR 1.05, CI 95% 1.01–1.09, p=0.014). However, after controlling for the demographic factors, the association was no longer significant (OR 1.04, CI 95% 0.10–1.08, p=0.06) due to the effect of education (OR 0.85, CI 95% 0.77–0.94, p<0.002). Informant DEX scores were not significantly associated with MCI (p-value>0.23). Subjective or informant PRMQ scores had no statistically significant associations with MCI (p-values>0.33).

Associations between subjective and informant reports and cognitive domain scores

There were no significant associations between subjective cognitive complaints and the executive functions domain (p-values>0.32). The subjective DEX scores had a significant bivariate association with the memory domain score (standardised β=-0.19, p=0.027), yet the result was no longer significant (standardised β=-0.11, p=0.18) after controlling for education (standardised β=0.39, p<0.001), age and sex. The informant DEX scores were not significantly associated with memory nor executive functions domain scores (p-value>0.09). Informant PRMQ scores were not associated with memory (p-value>0.59), but they did have a bivariate association with executive functioning (standardised β=-0.17, p=0.044). The association was no longer significant (standardised β=-0.14, p=0.09 after controlling for the covariates due to the influence of education (standardised β=0.30, p<0.001).

Associations between subjective and informant reports and depressive symptoms

After controlling for age, sex and education, subjective DEX (OR 1.10, CI 95% 1.05–1.16, p<0.001) and PRMQ scores (OR 1.06, CI 95% 1.01–1.11, p=0.014) were significantly associated with presence of depressive symptoms (as a binary measure: no depressive symptoms vs depressive symptoms) measured with the GDS-15. There were no significant associations between informant DEX or PRMQ scores and depressive symptoms (p-values>0.12).

Associations between subjective and informant reports and A-IADL

Subjective DEX and PRMQ scores were not significantly associated with A-IADL (p-values>0.09). However, there was a significant association between informant DEX (standardised β=-0.50, p<0.001) and A-IADL, with higher levels of DEX relating to lower A-IADL scores (Fig. 1). The association between informant PRMQ and A-IADL was also significant (standardised β=-0.41, p<0.001, Fig. 1), with higher levels of PRMQ relating to lower A-IADL scores. Here, the assumption of homoskedasticity was not fulfilled; therefore, the analyses were repeated with HSCE estimators and the results remained unchanged (DEX standardised β=-0.33, p=0.001, f^2=0.30; PRMQ standardised β=-0.24, p=0.011, f^2=0.19).

Associations between subjective and informant reports and WMH

Subjective DEX (standardised β=0.09, p>0.31) and PRMQ (standardised β=0.11, p>0.18) were not significantly associated with WMH. After controlling for age, sex and education, there were weak but statistically significant associations between WMH and informant DEX (standardised β=0.26, p=0.002, f^2=0.08) and WMH and informant PRMQ (standardised β=0.24, p=0.007, f^2=0.06), with higher informant-reported scores relating to higher WMH volume (Fig. 2).

Further details of the results from linear and logistic regression analyses (Sections 3.2–3.6) are given in Supplemental Tables 2–6.

Discussion

We explored awareness of cognitive impairment in covert cSVD by studying the associations between subjective and informant-reported cognitive complaints and brain imaging findings (WMH volume), objective indicators of cognitive performance (MCI, executive and memory functioning), depressive symptoms and instrumental activities

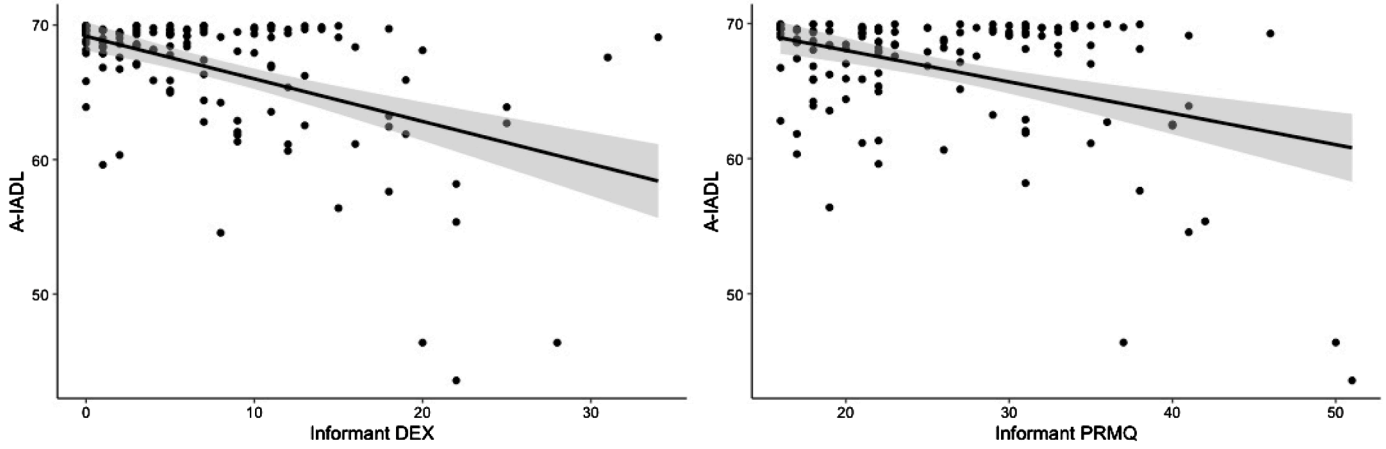

Fig. 1. Associations of informant-reported Dysexecutive Questionnaire (DEX) and Prospective and Retrospective Memory Questionnaire (PRMQ) scores with Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL) total score in linear regression analyses adjusted for age, sex and education. Grey areas represent 95% confidence intervals. The associations were significant also in analyses repeated with heteroskedasticity-consistent standard error estimators and after false discovery rate correction.

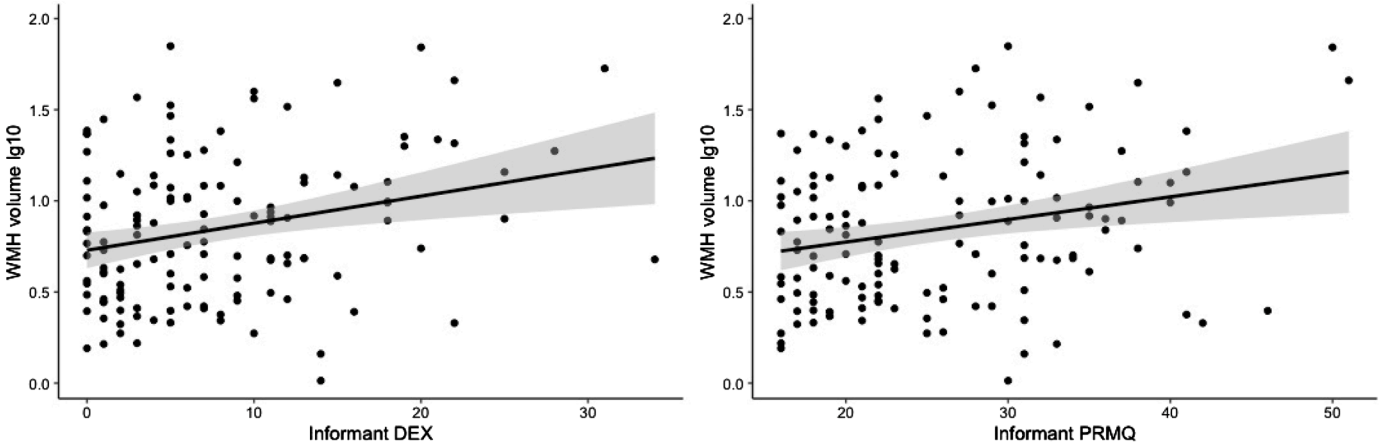

Fig. 2. Associations of informant-reported Dysexecutive Questionnaire (DEX) and Prospective and Retrospective Memory Questionnaire (PRMQ) scores with the log transformed white matter hyperintensity (WMH) volume in linear regression analyses adjusted for age, sex and education. Grey areas represent 95% confidence intervals. Associations were significant after false discovery rate correction.

of daily living. We have previously shown in this same sample that WMH have strong associations with objective cognitive performance and functional abilities [12,14]. In the current study, we found no significant associations between subjective or informant-reported cognitive complaints and objective cognitive outcomes. Interestingly, while subjective cognitive complaints were only significantly associated with depressive symptoms, informant reports were related to WMH volume and functional abilities.

In our sample of subjects with varying degrees of WMH, neither MCI nor the domain scores of executive functions and memory were associated with subjective or informant reports. This finding is not completely in line with the results of a meta-analysis that examined this topic in older adults [1]. Burmester et al. [1] found a small but significant association between objective cognitive functioning and subjective cognitive complaints, especially in studies that used a more comprehensive methods for evaluating subjective cognitive complaints in comparison to those that only adopted a binary yes or no response. However, the authors reported large heterogeneity between studies as well as evidence of publication bias. In our study, the weak relationships between cognitive measures and subjective cognitive complaints were no longer significant after controlling for age, sex, and years of education.

Depressive symptoms have been found to associate with subjective cognitive complaints in community-dwelling adults in some previous studies [38,39]. The meta-analysis by Burmester et al. [1] also found strong associations between depressive symptoms and subjective cognitive complaints in ageing. In our study, associations were found between depressive symptoms and subjective cognitive complaints, with even mild depressive symptoms relating to a higher number of subjective cognitive complaints. These results support previous studies showing depressive mood can affect subjective reports and should therefore always be considered in subjective assessments.

To our knowledge, the relationships between subjective cognitive complaints, informant reports and activities of daily living have not been previously studied in cSVD. Informant reported cognitive difficulties have been shown to better predict cognitive and functional decline than subjective cognitive complaints over a 4-year follow-up in a study of non-demented older individuals from a memory clinic sample [40]. We found that informant reports on cognitive functioning had consistent associations with complex activities of daily living, which may have direct clinical implications for the need of informant input when evaluating a patient in an assessment setting. The results suggest that there may be an advantage of informant involvement in early-stage cSVD assessment to aid the recognition of those in need of more support. Short informant-reported questionnaires on cognitive functioning are also useful for identifying patients who may experience more difficulties in complex activities of daily living.

The lack of an association between WMH and subjective cognitive complaints is contrary to some smaller-scale studies that reported WMH to be significantly related to subjective cognitive complaints [15,16]. These contrary findings might be explained by differences in inclusion criteria (community-dwelling adults vs patient populations) and sample sizes. However, our finding is in line with a recent meta-analysis that found no significant relationship between subjective memory complaints and WMH severity [17]. To our knowledge, no studies have investigated the relationship between WMH and informant reported cognitive difficulties in cSVD. In Alzheimer's disease research, informant reports have been found to relate to disease biomarkers and, in comparison to subjective reports, be more consistently associated with objective measures of the disease [41]. A recent meta-analysis has also shown informant reports to have a stronger ability to predict the risk to progress to dementia than subjective cognitive complaints in Alzheimer's disease [42].

A strength of our study includes the extensive set of subjective and informant questionnaires that measured memory and executive function complaints in detail. Another strength is the comprehensive neuropsychological assessment, which was the base for the MCI classification and considered several important cognitive domains (as opposed to short cognitive screening). In addition to categorical MCI, we also analysed more sensitive continuous cognitive domain scores, which comprised several cognitive test measures and corresponded to the cognitive domains covered in the subjective and informant reports. The age range of this study (65–75 years) was chosen to represent the so called young-old individuals, in whom SVD brain changes and MCI may be present, but the likelihood of coexisting neurodegenerative disorders is still relatively low. The results shed light to patients with covert cSVD findings often seen in clinical settings but may not fully represent older age groups or more severe stages of cognitive decline.

A limitation of our study is the cross-sectional study design, which precludes making inferences on a possible predictive value of subjective and informant reports for longitudinal cognitive decline. Classification of normal vs impaired cognitive test performance for MCI diagnosis was based on different normative data samples instead of a unitary large reference dataset, as such data for the Finnish population are not available. Although comprehensive neuropsychological assessment is the closest measure available for objective cognitive functioning, the question of validity remains, especially when cognitive performance is compared to a normative mean. For instance, in highly educated people the self-reported cognitive decline might be accurate but would not necessarily show as an impairment in the neuropsychological testing.

The present analyses were controlled for age, sex, and years of education of the subjects. However, demographics of the informants were not considered since complete informant data was unavailable. Another limitation might be the somewhat heterogenous and relatively small sample, which might make comparisons to other populations challenging. Ideally, future research should use multiple sources rather than a sole informant to gain information about a person's daily functioning. Future studies with longitudinal designs are needed to gain more knowledge on the progression of cSVD from covert to overt presentations and to also examine how awareness of symptoms might change across the different stages of the disease.

In summary, the results suggest that awareness of cognitive decline may be limited in covert cSVD. Neither subjective nor informant reports were associated with objective cognitive outcomes. Informant-reported cognitive complaints were related to WMH volume and functional abilities, whereas subjective cognitive complaints were only associated with depressive symptoms. These results highlight the importance of informant-provided information on a patient's functioning already at the covert stages of cSVD when adverse clinical outcomes such as stroke or dementia are not yet evident. The results also indicate a need to assess a patient's depressive symptoms, which could be related to potential subjective cognitive complaints.

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Declaration of Competing Interest

MA has received a personal fee for educational event from Merck KGaA. AK has received payment for expert testimony from the Finnish National Insurance Centre, for a neuroradiologist expert testimony on a court of justice, support for travel from Helsinki University Hospital and is the board member of the Finnish Radiological Society. JK and JL are shareholders at Combinostics Ltd. TP is a board member at the Finnish Brain Council, the Finnish Neuropsychological Society, and the Finnish Alzheimer's Disease Research Society. The other authors report no competing of interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2023.100182.

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