



Review

Cerebrovascular damage in subjective cognitive decline: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:

Cognitive complaints
White matter signal abnormalities
MRI
Dementia risk

ABSTRACT

Background: Subjective cognitive decline (SCD) has been postulated as an early marker of Alzheimer's Disease (AD) but it can also be associated to other non-AD pathologies such as Vascular Dementia (VaD). Nevertheless, there is scarce data about SCD as a potential harbinger of cerebrovascular pathology. Thus, we conducted a systematic review and meta-analysis on the association between SCD and cerebrovascular damage measured by neuroimaging markers.

Method: This study was performed following the PRISMA guidelines. The search was conducted in 3 databases (PubMed, Scopus and Web of Science) from origin to December 8th, 2021. Primary studies including cognitively unimpaired adults with SCD and neuroimaging markers of cerebrovascular damage (i.e., white matter signal abnormalities, WMSA) were selected. Qualitative synthesis and meta-analysis of studies with a case-control design was performed.

Results: Of 241 articles identified, 21 research articles were selected. Eight case-control studies were included for the meta-analysis. A significant overall effect-size was observed for the mean WMSA burden in SCD relative to controls, where the WMSA burden was higher in SCD.

Conclusion: Our findings show the potential usefulness of SCD as a harbinger of cerebrovascular disease in cognitively healthy individuals. Further research is needed in order to elucidate the role of SCD as a preclinical marker of vascular cognitive impairment.

1. Introduction

Subjective cognitive decline (SCD) is defined by self-reported cognitive impairment that cannot be detected by an objective neuropsychological evaluation (Jessen et al., 2020). The conceptual framework for SCD published in 2014 by the SCD-Initiative (SCD-I) promoted the interest in the study of cognitive complaints since it postulates SCD as an early marker of Alzheimer's Disease (AD) (Jessen et al., 2014). Subsequently, most researchers in the field have focused on the progression from SCD to AD (Jessen et al., 2020); (Parfenov et al., 2020). Hence, SCD has mainly been studied in individuals from memory-clinic

cohorts (Slot et al., 2018) and mainly operationalized based on semantic memory complaints (Rabin et al., 2015). However, SCD may refer to other cognitive domains besides memory (Rabin et al., 2015) and research have shown that cognitive complaints can be associated also with non-AD pathologies, such as cerebrovascular disease (CVD) (Slot et al., 2018; Diaz-Galvan, Ferreira et al., 2021). In fact, longitudinal studies have demonstrated that the proportion of SCD individuals who progress to vascular dementia is almost as high as that of SCD individuals who progress to AD (Slot et al., 2018).

Cerebrovascular damage is frequently found in cognitively unimpaired older people, in the form of white matter signal abnormalities

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<https://doi.org/10.1016/j.arr.2022.101757>

Received 2 August 2022; Received in revised form 5 October 2022; Accepted 9 October 2022

Available online 12 October 2022

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(WMSA) assessed with Magnetic Resonance Imaging (MRI) (Cedres et al., 2021; Riphagen et al., 2018). The term WMSA refers to abnormal changes in the intensity of cerebral white matter observed on MRI, and it has been proposed as one of the neuroimaging markers for small vessel disease (SVD) (Wardlaw et al., 2013). WMSA have been associated with cerebrovascular damage that causes disruption in the axonal structure. WMSA can be measured as white matter hyperintensities or hypointensities depending on the MRI sequence. On T1 sequences, WMSA are observed as hypointensities, while on T2/FLAIR sequences, WMSA are observed as hyperintensities (Cedres et al., 2021; Riphagen et al., 2018). In the general population, both hyper- and hypointense WMSA have shown associations with other markers of CVD, and they are strongly correlated with each other (Cedres et al., 2021; Hilal et al., 2017; Maillard et al., 2012; Nordahl et al., 2006).

WMSA burden increases with age and is linked to cognitive dysfunction in clinical and population-based cohorts (Longstreth et al., 1996; Ferreira et al., 2018; Hilal et al., 2017; Radanovic et al., 2013). Furthermore, the presence of WMSA has been associated with an increased risk of future ischemic stroke, as well as higher mortality (Ghaznawi et al., 2021). These findings indicate that cerebrovascular pathology has clinically relevant consequences. Thus, WMSA is an important marker that might be useful when screening for individuals at risk for future cognitive impairment associated with CVD (Wardlaw et al., 2013). However, the question of whether SCD reflects underlying cerebrovascular damage and what impact it has on clinical progression remains unclear.

We conducted a systematic review of the current evidence on the association between SCD and WMSA as a marker of cerebrovascular damage. Furthermore, we evaluated whether WMSA were more severe in SCD compared to controls without SCD, using a meta-analytical approach. To further characterize the SCD individuals in the presence of underlying cerebrovascular damage, we also described the findings in the context of other important features in SCD, such as the origin of the sample (i.e., memory clinic vs. general population), type of complaints exhibited (i.e., memory vs. other cognitive domains), other biomarkers of disease (when available), sex, and age; as well as compared the SCD group with other clinical entities such as MCI, AD or Vascular Dementia (VaD).

2. Methods

2.1. Search strategy

The current study was performed in accordance with the PRISMA statement, which provides a detailed guideline for reporting systematic reviews and meta-analyses in health science (Moher et al., 2009). We consulted the electronic databases of PubMed, Scopus and Web of Science. The search strategy (Supplementary table S1) was performed in December 2021 and includes studies with no limit of time. The search strategy was built for each database using a combination of the medical subject headings (MeSH) and free terms for “subjective cognitive decline” and “white matter signal abnormalities” to be seen in the title and abstract.

2.2. Studies selection

Inclusion criteria for the current systematic review were original research articles that: (1) included cognitively unimpaired adults with subjective cognitive complaints who meet the criteria for SCD according to the SCD-I (Jessen et al., 2014); (2) evaluated the direct association between SCD and the WMSA burden, the association between SCD and WMSA burden over time, or compared WMSA burden between SCD individuals and a reference group (i.e. control group or clinical group), using neuroimaging techniques; and (3) were published in English or Spanish. The inclusion criteria for the meta-analysis were studies that: (1) included a control group without subjective cognitive complaints

and without objective cognitive impairment, neurological diseases or history of substance abuse; (2) provided the sample size, mean and standard deviation of a WMSA measure for the SCD and control groups. Study selection was performed by a single researcher (H.P.), including a second researcher (N.C.) when necessary. We excluded: (1) case-studies, reviews, and animal model studies; (2) studies including cognitively impaired participants, psychiatric disease, neurologic disease, or substance abuse among the SCD participants or with the absence of information about these aspects; (3) studies that did not investigate the direct association between SCD and WMSA (Fig. 1).

A total of 240 articles were identified in the initial search. After removing duplicates ($n = 152$) and applying the inclusion/exclusion criteria (see Fig. 1), 21 research articles were selected. Of those, 8 case-control studies were selected for the meta-analysis. When an article did not contain the necessary information for the meta-analysis, means and standard deviation were calculated when possible, otherwise the authors were contacted with a request to provide the information.

2.3. Data extraction, risk of bias, and methodological quality

Data extraction was performed by a single researcher (H.P.). A

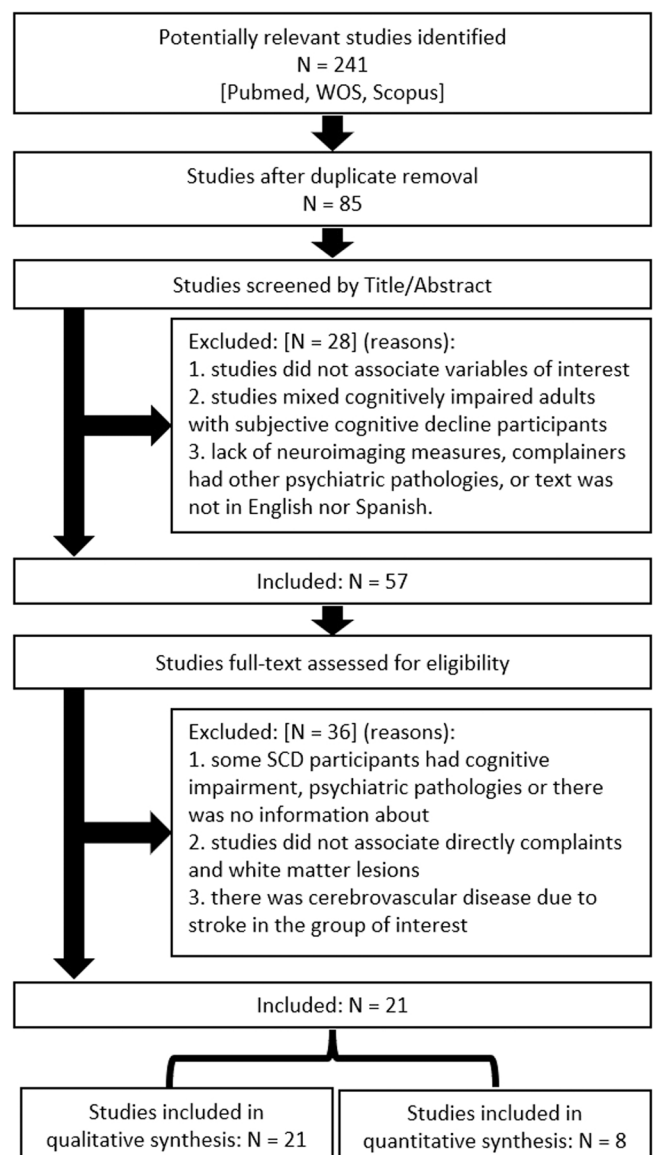


Fig. 1. PRISMA flow-chart diagram of the selection process for study inclusion.

second researcher (N.C.) verified these data with the original sources to guarantee the accuracy of the information extracted. A data extraction sheet was created covering the following aspects: authors' names and publication year, study design, type of subjective cognitive complaints reported (e.g. memory, attention, language, executive functions, etc.), type of WMSA measure (i.e. hyperintensities vs. hypointensities), neuroimaging modality (i.e. CT, T1-weighted MRI, T2-weighted MRI, FLAIR MRI), type of WMSA assessment (i.e. visual scale, automatic segmentation, manual, semi-automatic segmentation), origin of the study sample (i.e. clinic vs. community-based cohort), sample size, predominant sex (female vs. male) in SCD, average age of the SCD group, and mean and standard deviation (SD) of WMSA (i.e. including controls, SCD, and cognitively impaired participants, when available).

To assess the methodological quality of the studies included, we used

the FLC 3.0 tool (<http://www.lecturacritica.com/en/>), which allows for a qualitative estimation of the studies through a series of questions referring to different methodological aspects of each investigation.

2.4. Statistical analysis

A meta-analysis was conducted using Metafor package (Viechtbauer, 2010) for R version 2.4–0. A case-control meta-analysis was performed, including those studies which facilitated information about the mean and standard deviation of WMSA, as well as sample size, in an SCD group and controls ($n = 8$). For those studies that used the same cohort, we chose the study with the largest sample size. The random effects regression model was used to calculate the effect size of the differences between the groups (i.e., SCD vs. controls). Cochran Q was used to

Table 1a
Description of the selected studies.

Reference (year)	Design	Sample origin	Cohort	Sample size in SCD	Mean age (years) in SCD	% Women in SCD	Education (years) mean in SCD
Rhodijs-Meester et al. (2017)	Cohorts, longitudinal	Alzheimer clinic	Memory clinic	906	62 ± 9	45 %	5 ± 1
Pařzková et al. (2017)	Cross-sectional	Memory clinic	Memory clinic	46	69.09 ± 6.44	57 %	15.22 ± 3.25
Lamar et al. (2011)	Cohorts, longitudinal	Memory clinic	Derwert memory clinic	12	60.06 ± 8.9	41.6 %	–
Caillaud et al. (2020)	Cross-sectional	Memory clinic and community-based	CIMA-Q ^a	67	72.3 ± 5.1	62.6 %	15.2 ± 3.2
Nobili et al. (2008)	Cross-sectional	Cognitive disorders centre	DESCRIPA ^b	15	67.2 ± 6.4	43.5 %	10.3 ± 4.1
Van Rooden et al. (2018)	Cross-sectional	Memory clinic and community-based	Detroit, MI, United States and Leiden, Netherlands	25	68 ± 9.1 (45–84)	72 %	3
Kramberger et al. (2017)	Cross-sectional	Memory clinic	Karolinska University Hospital, Huddinge, Estocolmo, Suecia	194	58 (40–82)	62 %	–
Auning et al. (2015)	Cross-sectional	Memory clinic	–	22	58.5 ± 6.5 (45–68)	59.1 %	–
Claus et al. (2016)	Cross-sectional	Memory clinic	Terggoi Hospital, Blaricum, Netherlands	333	71.8 ± 10.2	56 %	4.7 ± 1.4
Niemantsverdriet et al. (2018)	Cohorts, longitudinal	Memory clinic	BeDeCo ^c	102	68.6 ± 9.8	54 %	–
Sacuiu et al. (2018)	Cohorts, longitudinal	Community-based	PPSW ^d and H70 study ^e	300	74.9 ± 5.7	78.7 %	> 6 education years (36.2 %)
Hong et al. (2019)	Cross-sectional	Dementia clinic	–	31	73.00 ± 4.66 (A+SCD) and 67.83 ± 6.92 (A-SCD)	73.9 % (A-SCD) and 62.5% (A+SCD)	9.85 ± 5.43 (A-SCD) and 8.25 ± 2.66 (A+SCD)
Cedres et al. (2019)	Cross-sectional	Community-based	GENIC ^f	223	58.5 ± 11.5	54.3 %	Education level ^h (0/1/2/3/4), % = 1.2/11.8/34.9/22.7/29.4
Scarapicchia et al. (2019)	Cross-sectional	Cognitive disorders investigation centre	ADNI-2 ^g	19	72.2 ± 5.2	52 %	16.3 ± 3.16
Chau et al. (2020)	Cross-sectional	Memory clinic	–	8	69.5 ± 7.5	75 %	–
Benedictus et al. (2015)	Cohorts, longitudinal	Memory clinic	Amsterdam Dementia Cohort	334	62 ± 10	47 %	–
Diaz-Galvan, Ferreira et al., 2021	Cross-sectional	Community-based	GENIC ^f	399	60.50	62.5 %	–
Kang et al. (2021)	Cross-sectional	Memory clinic	Samsung Medical Center in Seoul, Korea	294	69.9 ± 8.4	34.01 %	11.3 ± 4.9
Hong et al. (2022)	Cross-sectional	Dementia clinic	–	31	73.78 ± 4.52 (A+SCD) and 68.27 ± 6.92 (A-SCD)	55.6 % (A+SCD) and 68.2 % (A-SCD)	7.33 ± 2.18 (A+SCD) and 9.80 ± 5.20 (A-SCD)
Smith et al. (2021)	Cross-sectional	Memory clinic	COMPASS-ND ⁱ	35	69.4 ± 6.2	74.3 %	–
Diaz-Galvan, Cedres et al., 2021	Cross-sectional	Community-based	GENIC ^f	123	56.9 ± 11	55 %	Education level ^h (0/1/2/3/4), % = 4/42/26/29

Note: SCD, subjective cognitive decline; TD, typical deviation; ^aCIMA-Q: Quebec Consortium for the Early Identification of Alzheimer's disease; ^bDESCRIPA: Development of screening guidelines and criteria for predementia Alzheimer's disease; ^cBeDeCo: Belgian Dementia Council; ^dPPSW: Prospective Population Study of Women; ^eH70 study: community-based study of normative aging in people over 70 years of age; ^fGENIC: community-based study from Canary Islands, Spain; ^gADNI-2: Alzheimer's Disease Neuroimaging Initiative; ^hEducation level: illiterate (0), acquired Reading and/or writing skills (1), primary level (2), secondary level (3), university level (4) ⁱCOMPASS-ND: Comprehensive Assessment of Neurodegeneration and Dementia.

measure the heterogeneity between studies. Additionally, the I^2 statistic was used to describe the percentage of the heterogeneity across studies. An $I^2 < 40\%$ was considered indicative of low heterogeneity; an I^2 between 40% and 60% was considered indicative of moderate heterogeneity; and an $I^2 > 60\%$ was considered indicative of high heterogeneity. To determine publication bias, visual inspection of the funnel plot and regression analysis were carried out including the standard error of the effect sizes as a predictor. All results were interpreted at a 95% confidence interval (CI). Table 1a.

3. Results

3.1. Main characteristics of the studies and methodological quality

A total of 21 research articles were included in this systematic review (table 1). Among the 21 studies, 15 included participants from memory clinics; four studies included community-based participants; and two studies included both memory clinic and community-based cohorts (Fig. 2A). The sample sizes of the SCD group ranged from 8 to 906 participants across the studies. The age of the SCD individuals ranged from 40 to 84 years, and the majority of participants were women (Fig. 2A). Regarding the assessment of SCD, all studies were based on self-reported cognitive complaints. Ten studies evaluated cognitive complaints in multiple domains (i.e., memory, language, orientation, attention, and/or executive functions; activities of daily living); six studies evaluated memory complaints exclusively; and five studies did not report the specific domain of the cognitive complaint (see Table 1b, column “type of complaints”; Fig. 2A). Two studies included biomarker data about cerebral amyloid deposition using Positron Emission Tomography (PET) and further classified the SCD individuals into amyloid-positive SCDs and amyloid-negative SCDs.

Regarding other populations included in the studies apart from SCD, 10 studies included a group of healthy individuals without subjective cognitive complaints as a control group (Table 1b, column “comparison groups”). Likewise, 12 studies compared SCD individuals with cognitively impaired patients who had a clinical diagnosis of AD ($n = 4$), MCI (amnesic or non-amnesic) ($n = 9$), VaD ($n = 2$), or had other comorbid pathology ($n = 3$) (Auning et al., 2015; Caillaud et al., 2020; Chau et al., 2020; Claus et al., 2016; Hong et al., 2019; Kramberger et al., 2017; Lamar et al., 2011; Niemantsverdriet et al., 2018; Nobili et al., 2008; Paízková et al., 2017; Rhodius-Meester et al., 2017; Smith et al., 2021).

Regarding the type of WMSA measure used (see Table 1b), 5 studies included measures based only on WM hypointensities (Cedres et al., 2019; Claus et al., 2016; Diaz-Galvan, Ferreira et al., 2021; Sacuiu et al., 2018; Smith et al., 2021), 10 studies used WM hyperintensities (Auning et al., 2015; Caillaud et al., 2020; Hong et al., 2019, 2022; Kang et al., 2021; Kramberger et al., 2017; Lamar et al., 2011; Nobili et al., 2008; Paízková et al., 2017; Scarapicchia et al., 2019) and six combined both types of measures (Benedictus et al., 2015; Cedres et al., 2019; Chau et al., 2020; Niemantsverdriet et al., 2018; Rhodius-Meester et al., 2017; Scarapicchia et al., 2019) (see Fig. 2B). Regarding WMSA assessment, 13 studies used only visual rating scales such as the Fazekas scale (Fazekas et al., 1987) ($n = 6$), the Leukoaraiosis Scale of Junque (Junque et al., 1990) ($n = 1$), the Age-Related White Matter Changes (ARWMC) scale (Wahlund et al., 2001) ($n = 2$) and other in-house visual rating scales ($n = 4$). Five studies used automatic segmentation tools for volume such as FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>) ($n = 3$), MSmetrix-cross (Steenwijk et al., 2017) ($n = 1$), and Brain Software Library ($n = 1$); and 3 studies combined automatic segmentation tools for volumes and visual scales: FreeSurfer and Fazekas visual rating scale ($n = 1$), volBrain pipeline (Manjón and Coupé, 2016) and Hachinski scale (Hachinski et al., 1974) ($n = 1$), and an in-house automatic

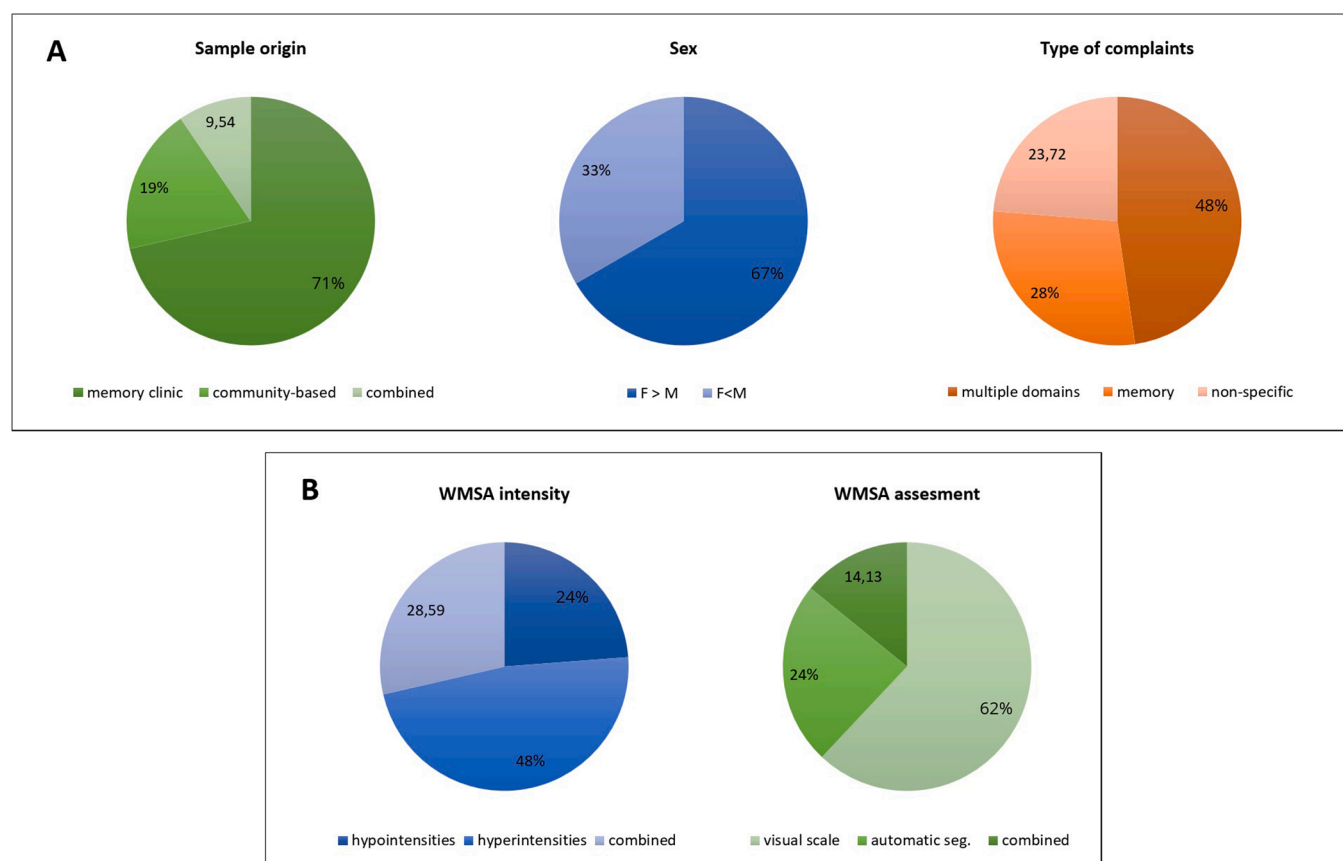


Fig. 2. Main characteristics of the included studies. Panel (a) Sample origin, sex distribution and cognitive complaints characteristics. Panel (b) Type of WMSA intensity and assessment. M: male; F: female; WMSA: white matter signal abnormalities.

Table 1b
Description of the selected studies (continuation).

Reference (year)	Lesión measure (scale/software)	Sequence	Type of complaints	Comparison groups
Rhodijs-Meester et al. (2017)	Visual scale (Fazekas)	3D-T1 and FLAIR	Memory, language, attention and executive functions	MCI and AD
Pařzková et al. (2017)	Visual scale (Fazekas)	FLAIR	Memory	Control and aMCI
Lamar et al. (2011)	Visual scale (Leukoaraiosis Scale of Junque)	T2	Memory	Control and aMCI
Caillaud et al. (2020)	Automatic segmentation (volBrain pipeline) and visual scale (Hachinski scale)	FLAIR	Memory	Control and MCI
Nobili et al. (2008)	Visual scale (ARWMC)	FLAIR	Memory and other domains	Control, aMCI and naMCI
Van Rooden et al. (2018)	Automatic segmentation (Hafkemeijer, A., 2014) and visual scale (Fazekas)	T1, T2 and FLAIR	Memory	Control
Kramberger et al. (2017)	Visual scale (Fazekas)	FLAIR	Non-specific	MCI and AD
Auning et al. (2015)	Automatic segmentation (FreeSurfer) and visual scale (Fazekas)	FLAIR	Non-specific	MCI
Claus et al. (2016)	Visual scale (Fazekas)	CT	Memory	MCI, AD, VaD, other dementias, other pathologies
Niemantsverdriet et al. (2018)	Automatic segmentation (MSmetrix-cross)	3D-T1 and FLAIR (optional)	Non-specific	Control, MCI and AD
Sacuiu et al. (2018)	4-point visual rating scale	CT	Memory or executive functions	Control
Hong et al. (2019)	3-point visual rating scale	FLAIR	Activities of daily living, attention, language, visuospatial function, memory and executive functions	A+SCD and A-SCD
Cedres et al. (2019)	Automatic segmentation (FreeSurfer)	3D-T1, T2 and FLAIR	Orientation, memory, language, attention and visoperceptive functions	–
Scarapicchia et al. (2019)	Automatic segmentation (Brain Software Library)	T2 and FLAIR	Memory	Control
Chau et al. (2020)	Visual scale (Fazekas)	3D-T1 and 3D-FLAIR	No information	Control, type II diabetes, VaD and AD
Benedictus et al. (2015)	Visual scale (Fazekas)	T1, T2 and FLAIR	Memory, language, attention, executive functions general cognition	–
Diaz-Galvan, Ferreira et al., 2021	Automatic segmentation (FreeSurfer)	3D-T1	Memory, orientation, executive functions, face recognition, language production, language comprehension, word-finding, reading and writing	Control
Kang et al. (2021)	Visual scale (WMH visual rating scale)	FLAIR	Attention, language and related function, visuospatial function, memory, frontal/executive function.	MCI and dementia
Hong et al. (2022)	3-point visual rating scale	FLAIR	Activities of daily living, attention, language, visuospatial function, memory and executive functions	A+SCD and A-SCD
Smith et al. (2021)	Visual scale (ARWMC)	CT	Non-specific	AD, V-MCI, MCI and PD/LBD
Diaz-Galvan, Cedres et al., 2021	Automatic segmentation (FreeSurfer)	3D-T1	Memory, orientation, executive functions, language and visuoperception	–

Note: 3D-T1, 3D-T1-weighted; T1, T1-weighted; T2, T2-weighted; FLAIR, fluid attenuated inversion recovery; DTI, diffusion tensor imaging; ARWMC, Age-Related White Matter Changes scale; Periventricular/Deep WMH, Periventricular/Deep White Matter Hyperintensities (i.e., periventricular/deep white matter hyperintensities); MCI, mild cognitive impairment; aMCI, amnesic mild cognitive impairment; naMCI, non-amnesic mild cognitive impairment; AD, Alzheimer disease; VaD, vascular dementia; A+SCD, amyloid-positive SCD; A-SCD, amyloid-negative SCD; V-MCI, vascular mild cognitive impairment; PD/LBD, Parkinson's disease/Lewy body dementias.

segmentation tool and Fazekas visual rating scale ($n = 1$) (see Fig. 2B). All the studies used MRI as the neuroimaging method, except for three studies that used CT. Among the MRI sequences, a FLAIR ($n = 8$) was the most frequently used sequence, followed by 3D-T1-weighted ($n = 2$), and T2-weighted ($n = 1$) sequences. Some studies based their assessment of WMSA on more than one MRI sequence: three combined 3D-T1 and FLAIR, two combined T1, T2 and FLAIR, one combined T2 and FLAIR.

3.2. Quantitative analysis of the association of SCD with WMSA

Eight studies were eligible for the extraction of quantitative data (i.e., presented values for sample size, and mean and standard deviation of WMSA assessment in SCD and control individuals). The studies comprised a total of 2637 SCD individuals. Our analyses showed low-to-moderate heterogeneity across studies ($Q_7 = 14.20$; $p = 0.048$; $I^2 = 42.5\%$) (i.e. I^2 between 25 % and 50% (Huedo-Medina et al., 2006)). The estimated average standardized mean difference based on the

random-effects model was equal to -0.40 [CI 95% $-6.62, -0.19$] showing a moderate global effect size (Fig. 3). Thus, SCD participants had a higher WMSA burden compared to controls (i.e. the SCD group showed an increased cerebrovascular damage compared to individuals without cognitive complaints). The standardized mean difference for each study ranged between -1.07 and 0.37 , showing moderate to high differences between SCD and control individuals in four of the eight studies included (Fig. 3) (Caillaud et al., 2020; Cedres et al., 2019; Niemantsverdriet et al., 2018; Nobili et al., 2008).

Regarding publication bias, a mixed-effect meta-regression model was carried out for distribution testing and a funnel plot was generated. Visual inspection of the funnel plot (Fig. 4) showed that only one study produced estimates of effect size outside of the established confidence intervals. Furthermore, the regression model showed that the distribution of studies was not significantly asymmetric ($z = 0.885$; $p = 0.38$), which suggests a low risk of publication bias across all studies.

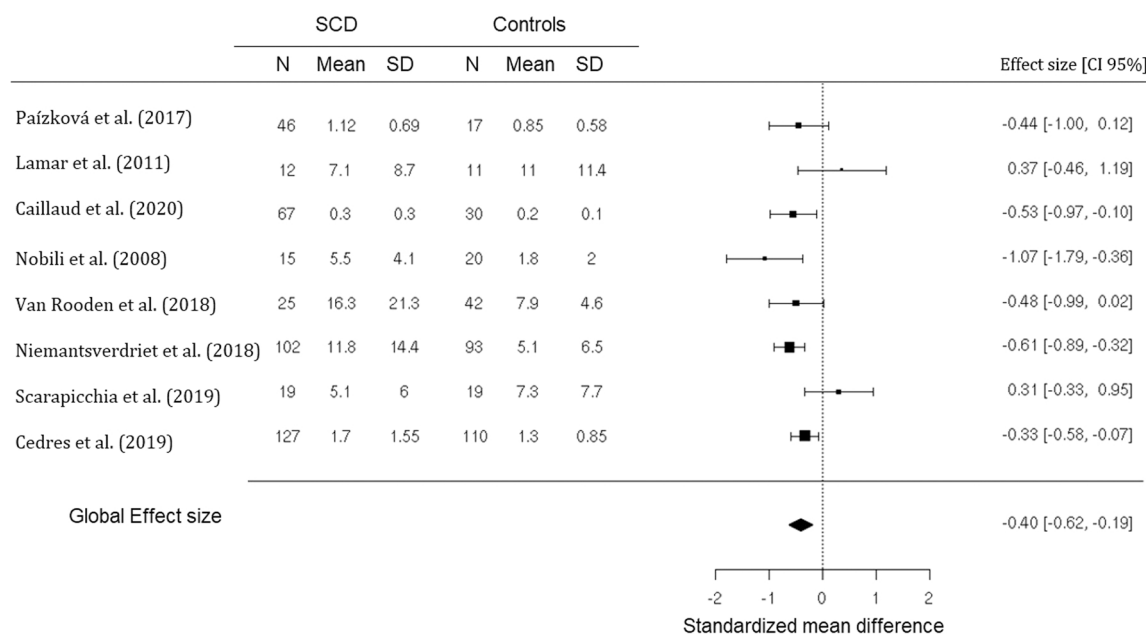


Fig. 3. Effect sizes of the case-control meta-analysis for standardized mean differences in WMSA burden between SCD and control individuals. Global effect size of the meta-analysis is represented as a diamond at the bottom. Error bars represent 95% confidence intervals for standardized mean differences from each study. SCD: Subjective cognitive decline; SD: standard deviation; WMSA: white matter signal abnormalities.

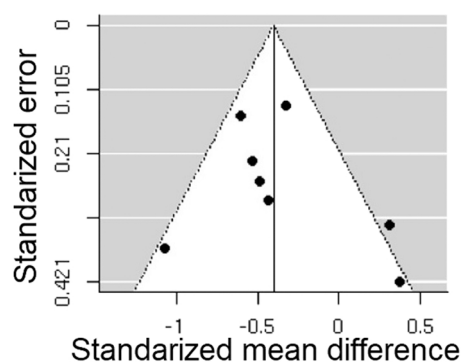


Fig. 4. Funnel plot for the visual inspection of publication bias. Each dot represents a case-control study included in the meta-analysis. The y-axis represents study precision as measured by the standard error; the x-axis shows standardized mean difference between SCD and controls for WMSA volume in each study. SCD: Subjective cognitive decline; WMSA: white matter signal abnormalities.

3.3. Qualitative report of WMSA in SCD

Four studies out of 21 included community-based participants (Cedres et al., 2019; Diaz-Galvan, Cedres et al., 2021; Diaz-Galvan, Ferreira et al., 2021; Sacuiu et al., 2018). Cedres et al. (2019) used an automatic segmentation measure of WMSA volumes and reported a significant association between the number of cognitive complaints and the volume of WMSA, indicating that more complaints were associated with greater WMSA volumes (Cedres et al., 2019). In the same cohort (i.e., GENIC-Database), (Diaz-Galvan, Cedres et al., 2021) also used an automatic segmentation of WMSA volumes and confirmed that more complaints were associated with greater WMSA volumes in a smaller sample. In addition, WMSA were associated with concurrent worse white matter integrity assessed on Diffusion Tensor Imaging (DTI) from MRI. Sacuiu et al. (2018) used a visual scale to assess WMSA burden and found an association between the presence of WMSA and cognitive complaints, also indicating increased WMSA burden in the SCD group. Further, Sacuiu et al. (2018) reported an increased risk of future

cognitive impairment in these individuals (12-year follow-up). Finally, using the GENIC-Database, Diaz-Galvan et al. (2021) found that individuals reporting amnesic+multiple domains SCD (amSCD; i.e., individuals reporting amnesic complaints together with complaints regarding other cognitive domains) showed increased WMSA burden compared to controls. Additionally, we found a study from ADNI (Scarapicchia et al., 2019) that showed no significant differences in WMSA volume between the SCD group and the control group using an automatic segmentation measure for hyperintensities. In brief, we found that regardless of the type of WMSA measure (i.e., hyper-/hypointensities) studies using community-based samples show associations between cognitive complaints and WMSA burden, as well as risk of future cognitive decline in SCD individuals with high WMSA burden.

Regarding clinical settings, 15 of 21 studies included samples from hospitals and memory clinics. Twelve of them used visual scales for the assessment of WMSA (Benedictus et al., 2015; Chau et al., 2020; Claus et al., 2016; Hong et al., 2019, 2022; Kang et al., 2021; Kramberger et al., 2017; Lamar et al., 2011; Nobili et al., 2008; Paízková et al., 2017; Rhodius-Meester et al., 2017; Smith et al., 2021). Most of these studies found an association between SCD and greater WMSA burden: 6 studies included a group of healthy controls (Caillaud et al., 2020; Niemantsverdriet et al., 2018; Nobili et al., 2008; Paízková et al., 2017; Scarapicchia et al., 2019; van Rooden et al., 2018) and 9 studies compared SCD individuals with patients who had a clinical diagnosis (i.e., AD, MCI, or other neurodegenerative disorders) (Auning et al., 2015; Benedictus et al., 2015; Claus et al., 2016; Hong et al., 2019, 2022; Kang et al., 2021; Kramberger et al., 2017; Rhodius-Meester et al., 2017; Wardlaw et al., 2013). In contrast, two studies using visual scales (i.e., Leukoaraiosis Scale of Junque or Fazekas) for WMSA in the form of hyperintensities (Lamar et al., 2011) and hyper-hypointensities (Chau et al., 2020), did not observe any significant differences in the degree of WMSA burden between the control group and the SCD group. In studies with clinical samples, where SCD is compared to groups with neurodegenerative pathologies, cross-sectional studies such as Kramberger et al. (2017) found that SCD group and clinical groups (i.e., MCI and AD) had a similar WMSA burden. Similarly, Claus et al. (2016), observed that 11.4 % of SCD participants had a score of 2 on the Fazekas scale (i.e., presence of diffuse lesions that comprise entire regions). Smith et al.

(2021) found that scores 1 (focal lesions) and scores 2 (confluent lesions) were the most frequent in the SCD group according to the ARWMC visual rating scale. A longitudinal study (Benedictus et al., 2015) found that the association between complaints and WMSA increased the risk of clinical progression towards objective cognitive impairment. In their study, Benedictus et al. (2015) showed that 16 % of SCD participants progressed to MCI or dementia. Therefore, SCD participants showed greater cerebrovascular damage compared to cognitively unimpaired individuals without complaints, showing a WMSA burden similar to the groups with cognitive impairment (i.e., dementia or MCI) in clinical samples.

Other factors have also been studied in clinical samples. For instance, Hong et al. (2019) showed that SCD participants with abnormal levels of amyloid pathology had a more severe WMSA burden than those without amyloid pathology. Later, in 2021, Hong et al. found in the same cohort that the older amyloid-positive SCD participants showed more periventricular WMSA ($p = 0.009$) compared with amyloid-negative SCD participants. Kang et al. (2021) studied which factors were associated with amyloid pathology after controlling for WMSA and vice versa. They found that amyloid positivity decreased in all groups (including SCD) as the severity of WMSA increased. Within the SCD group, 29.9 % had a moderate WMSA burden and 12% had a severe WMSA burden. Among the studies from clinical settings, only one used automatic segmentation of WMSA exclusively (Niemantsverdriet et al., 2018). Even though Niemantsverdriet et al. (2018) found that there was no global significant effect when including the clinical groups in the model (i.e., controls, SCD, MCI, and AD), our meta-analysis showed a significant effect size in the WMSA volumes mean difference between SCD and control groups. Other three studies using clinical settings based their WMSA assessments on the combination of automatic segmentation of WMSA volumes and visual rating scales (Auning et al., 2015; Caillaud et al., 2020; van Rooden et al., 2018). van Rooden et al. (2018) found higher WMSA volumes in people with complaints, and that SCD participants were more likely to have higher scores on Fazekas scale, indicating more severe damage than participants without complaints. In addition, Auning et al. (2015) found that SCD had a higher average score on Fazekas scale compared to the MCI group. Caillaud et al. (2020) did not find significant differences when comparing WMSA burden in SCD and healthy controls. However, they found negative correlations between WMSA and performance in executive functions in SCD individuals. Larger volumes of WMSA were also associated with lower verbal fluency scores and with lower scores on the Hayling test (used to assess inhibition).

4. Discussion

This systematic review and meta-analysis investigated the association between cerebrovascular damage, based on neuroimaging markers, and SCD. Our main aim was to synthesize and analyze the current evidence on the association between SCD and WMSA to determine the role of SCD as a harbinger of CVD. We showed that SCD was significantly associated with a higher WMSA burden. This association was found significant in most of the studies, including both clinical settings and community-based samples and across a wide range of ages (i.e., between 40 and 84 years old; see Fig. 3).

Our findings highlight that SCD individuals show more severe cerebrovascular damage compared to cognitively unimpaired people without SCD, and seem to have a WMSA burden similar to that cognitively impaired groups (i.e., dementia or MCI) regardless of the type of WMSA measure (i.e., hyper/hypointensities) and origin of the sample (i.e., community-based samples vs. clinical settings). Nevertheless, two of the studies including SCD from a clinical setting and a research-oriented cohort showed no significant differences between WMSA volumes in SCD and the control group (Chau et al., 2020; Lamar et al., 2011). This may be due to factors such as low statistical power (i.e., $N = 12$ and $N = 8$ SCD individuals respectively) or the type of complaints registered (i.e., complaints only referring to semantic memory). It has been

demonstrated that anomic and amnesic subjective cognitive complaints in SCD are differently associated with MRI pathological markers (Diaz-Galvan, Ferreira et al., 2021). While amnesic SCD is associated with AD-like brain atrophy patterns, complaints regarding multiple domains and/or naming are associated with higher WMSA burden. Thus, by restricting the assessment of SCD to the amnesic domain, it may be difficult to demonstrate a significant association with a CVD marker.

The longitudinal studies included confirm that SCD individuals are at risk of developing future cognitive impairment (Benedictus et al., 2015; Rhodius-Meester et al., 2017; Sacuiu et al., 2018). This observation highlights the importance of an early detection of pathologies contributing to neurodegeneration in SCD, such as CVD, as well as interventions based on vascular risk factors to prevent future cognitive decline. Nevertheless, there is an increased risk of comorbidity in clinical samples since the presentation of other pathologies (e.g., amyloid or tau) is much more frequent than in the general population (Slot et al., 2018). In fact, Hong et al. (2019); (2021) showed that SCD individuals with abnormal levels of amyloid burden had a higher burden of WMSA compared to SCD without amyloid burden, in a clinical setting. These findings emphasized that special attention is needed to SCD individuals from clinical settings, since they may present additional risks for future objective cognitive impairment.

The present systematic review showed that WMSA burden increases with age (Cedres et al., 2019; Claus et al., 2016; Hong et al., 2019, 2022; Rhodius-Meester et al., 2017). It is however important to consider the co-occurrence of cognitive complaints and aging, since these SCD individuals show greater vascular damage than what is expected based on their age. The presence of depressive symptoms has also been associated with SCD (Cedres et al., 2019; van Rooden et al., 2018). Nonetheless, it was recently demonstrated that SCD was associated with higher WMSA burden, older age, and increased depressive symptomatology, but the depressive symptomatology was independent of WMSA volumes (Cedres et al., 2019).

Regarding performance in neuropsychological tasks, we observed that SCD individuals with WMSA showed worse performance in several cognitive domains (e.g., memory, attention, executive functions, learning, or global cognition), albeit on a subclinical level (Benedictus et al., 2015; Caillaud et al., 2020; Cedres et al., 2019; Lamar et al., 2011; Niemantsverdriet et al., 2018). From a longitudinal perspective, SCD individuals have shown an increased risk to develop vascular-related cognitive impairment over time (Slot et al., 2018). In fact, according to the study by Slot et al. (2018), VaD is the second type of dementia with the highest incidence in SCD, especially in community-based samples. The results of the longitudinal studies in this review are in line with the findings from Slot et al. (2018), confirming that SCD individuals with high WMSA burden are at increased risk of developing vascular cognitive impairment (Benedictus et al., 2015; Rhodius-Meester et al., 2017; Sacuiu et al., 2018). The evidence thus supports the idea of SCD as a preclinical state, not only of AD, but also of VaD. Future research studying the relationship between vascular risk factors and cerebrovascular damage may facilitate the design of effective intervention programs to reduce WMSA burden in SCD. A preventive intervention through changes in lifestyle, exercise, diet, smoking cessation, cognitive stimulation or pharmacotherapy for the treatment of vascular risk factors, may be key to minimizing cognitive decline.

This systematic review has some limitations. Although most of the included studies revealed an association between SCD and underlying cerebrovascular damage, the meta-analysis data showed low-to-moderate heterogeneity and this should be considered when interpreting the results. Yet, this was expected given the relatively small number of studies included in the meta-analysis ($n = 8$) and the vulnerability of the Q-statistic and I^2 index to overestimate the heterogeneity in small meta-analyses (Huedo-Medina et al., 2006). The comparison of effect sizes that come from different types of WMSA measures (i.e., from visual scales to automatic segmentation methods) may have also contributed to the heterogeneity across studies. Nevertheless, using a broader number

of studies ($n = 21$) we described into detail the heterogeneity across all the selected studies in terms of several contributors to variability of WMSA in SCD. The systematic review and qualitative synthesis of all 21 studies showed that the association between SCD and WMSA was found independently of the WMSA measure used. Future meta-analysis including a larger number of studies should focus on potential moderating effects that factors such as age, sex or cerebrovascular risk factors may play in the variability of the association between WMSA and SCD. Although all the methods aim to capture the same pathology and have been shown to be comparable (Cedres et al., 2021), they are not identical. Another limitation is the risk assessment using *FLC 3.0*, which, although widely accepted as a method for evaluating the quality of studies, involves subjective interpretations. Even though some of the studies had moderate quality levels, none were excluded. The variability in SCD assessment across studies is another source of heterogeneity. Some studies operationalized SCD using one cognitive domain whereas others used several domains. Furthermore, in some cases the cognitive domain to which the complaints refer was not specified. In addition, the number of community-based cohort studies was lower than those from clinical settings. Hence, future studies focusing on the role of cerebrovascular damage in SCD from community-based samples are needed, as well as using multiple-domain cognitive assessments.

5. Conclusions

Our findings show the potential usefulness of SCD when screening for individuals at risk for future cognitive impairment associated with CVD. The evidence suggests that studies with an emphasis on improving the characterization of SCD individuals in the general population with a special focus on cerebrovascular risk factors are needed. We summarized some of the main characteristics of SCD individuals with cerebrovascular damage or underlying CVD. However, further characterization is necessary to quickly and effectively identify SCD individuals susceptible to developing objective cognitive impairment of vascular origin. It remains necessary to further investigate whether the general population with SCD is more likely to progress to VaD compared to SCD patients from memory clinics. It is also important to elucidate the impact of other comorbid underlying pathologies, such as amyloid and tau, in addition to cerebrovascular damage in SCD. The findings of the current systematic review and meta-analysis support the notion of SCD as a preclinical marker of future vascular cognitive impairment. In persons with SCD, changes in lifestyle, exercise, diet, smoking cessation, cognitive stimulation, or pharmacotherapy for the treatment of vascular risk factors, may be key to minimizing the risk for future cognitive decline.

Funding

This research was funded by the Estrategia de Especialización Inteligente de Canarias RIS3 de la Consejería de Economía, Industria, Comercio y Conocimiento del Gobierno de Canarias, co-funded by the Programa Operativo FEDER Canarias 2014–2020 (ProID2020010063); the Fundación Canaria Dr. Manuel Morales; Olle Engkvist Byggmästare; Center for Innovative Medicine, the regional agreement on medical training and clinical research between Stockholm County Council and Karolinska Institutet, Hjärfonden, Alzheimersfonden, Demensfonden, Neurofonden, Gun och Bertil Stohnes Stiftelse, and Stiftelsen För Gamla Tjänarinnor. The funders of the study had no role in the study design nor the collection, analysis, and interpretation of data, writing of the report, or decision to submit the manuscript for publication.

CRediT authorship contribution statement

Helda Pitti, Conducted the literature search; Prepared the data base; Analyzed and interpreted the data, and drafted the manuscript for intellectual content, Patricia Díaz-Galván, Design and conceptualized study; Interpreted the data; and revised the manuscript for intellectual

content., José Barroso, Funding acquisition; Design and conceptualized study; Interpreted the data; and revised the manuscript for intellectual content., Atef Badji, Interpreted the data; and revised the manuscript for intellectual content., Jonas Olofsson, Interpreted the data; and revised the manuscript for intellectual content., Eric Westman, Interpreted the data; and revised the manuscript for intellectual content., Daniel Ferreira, Design and conceptualized study; Interpreted the data; and revised the manuscript for intellectual content., Nira Cedres, Funding acquisition; Design and conceptualized study; Supervision of the literature search; supervision of the data base preparation; Interpreted the data; revised the article critically; and contributed to draft the manuscript for intellectual content.

Data Availability

Data will be made available on request.

Acknowledgements

The authors thank Dr. Juan Andrés Hernández Cabrera for the development of the ULLRtoolbox (<https://sites.google.com/site/ullr-toolboxeng>) and R scripts used for the meta-analysis in the current study, and his methodological advice.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.arr.2022.101757](https://doi.org/10.1016/j.arr.2022.101757).

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