Ageing Research Reviews 82 (2022) 101772

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

# Do informant-reported subjective cognitive complaints predict progression to mild cognitive impairment and dementia better than self-reported complaints in old adults? A meta-analytical study

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ARTICLE INFO

*Keywords:*
Self-report
Informant-report
Subjective cognitive decline
Progression
Cognitive impairment
Meta-analysis

ABSTRACT

*Background:* Subjective cognitive complaints (SCCs) are considered a risk factor for objective cognitive decline and conversion to dementia. The aim of this study was to determine whether self-reported or informant-reported SCCs best predict progression to mild cognitive impairment (MCI) and/or dementia.
*Methods:* We reviewed prospective longitudinal studies of Cognitively Unimpaired (CU) older adults with self-reported and informant-reported SCCs at baseline, assessed by questions or questionnaires that considered the transition to MCI and/or dementia. A random-effects meta-analysis was performed to obtain pooled estimates and 95% CIs.
*Results:* Both self-reported and informant-reported SCCs are associated with an elevated risk of transition from CU to MCI and/or dementia. The association appears stronger and more robust for informant-reported data [1.38, with a 95% CI of 1.16 –1.64, $p < 0.001$] than for self-reported data [1.27 (95% CI 1.06 – 1.534, $p = 0.011$].
*Conclusions:* Our results suggest that corroborated information from one informant could provide important details for distinguishing between normal aging and clinical states.

## 1. Introduction

Subjective Cognitive Complaints (SCCs) have been defined as cognitive disturbances self-reported or reported by a third person, related to the feeling of persistent decline cognitive in comparison with a previously normal cognitive performance, in the absence of deficits on objective testing (Canevelli et al., 2013, p. 560; Jessen et al., 2020). Concern about a change in cognition is considered a risk factor for the development of objective cognitive impairment and/or dementia (Choe et al., 2018; Mendonça et al., 2016) and a core criterion for the diagnosis of mild cognitive impairment (MCI) (Albert et al., 2011). In recent years, SCCs have been proposed as an essential element of subjective cognitive decline (SCD), a pre-clinical stage of Alzheimer's disease, in which no effect is observed in objective cognitive performance tests (Jessen et al., 2014). According to the National Institute on Aging and Alzheimer's Association, this diagnostic entity would be included between the two first stages or traditional categories of the cognitive continuum, i.e. Cognitively Unimpaired (CU) and MCI (Jack et al., 2018). Some studies have shown that older adults with SCD have an increased risk of progressing to cognitive impairment and/or dementia (Buckley et al., 2016; Jessen et al., 2020; Pereiro et al., 2021). One meta-analytical study showed that of older adults expressing subjective memory complaints but with no objective decline, approximately 2.3% progressed to MCI and 6.6% progressed to dementia per year; after four years of follow-up, approximately 24.4% and 10.99% of the participants progressed to MCI and dementia respectively (Mitchell et al., 2014). Although a high percentage of older adults with SCCs progress to cognitive impairment during follow-up, the predictive value of SCCs for the future decline can

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https://doi.org/10.1016/j.arr.2022.101772
Received 3 November 2021; Received in revised form 5 October 2022; Accepted 27 October 2022
Available online 29 October 2022

be influenced by socio-demographic factors, mood and certain personality traits (Zullo et al., 2021). In this regard, research suggests that higher levels of SCCs are associated with old age, female sex, higher educational level (Crumley et al., 2014), increased symptoms of anxiety and depression (Lee et al., 2020; Liew, 2020), high scores on neuroticism and low scores on conscientiousness and openness to experience (Muñoz et al., 2020; Snitz et al., 2015).

The clinical significance and predictive value of self-reported and informant-reported change along the cognitive continuum are also important factors. Confirmation of SCCs by an observer is a core characteristic of SCD and is associated with an increased likelihood of future cognitive decline (Jessen et al., 2020). Other studies have questioned the validity of self-reported SCCs due to the strong influence of psychological factors (Jiménez-Huete et al., 2017; Yoon et al., 2017). However, the predictive validity of informant-reported data in the progression of cognitive decline relative to self-reported data is not yet clear. We are not aware of the existence of any meta-analytical study that has analyzed the predictive value of the different types of reports. The main objective of this study was to conduct a systematic review and subsequent meta-analysis to investigate whether self-reported or informant-reported SCCs better predict progression to MCI and/or dementia.

## 2. Methods

### 2.1. PICOTD evaluation

The research question was formed using the PICOTD framework (Kloda et al., 2020; Schardt et al., 2007), where P (Participants/Population) represents CU older adults who attend their general practitioners with subjective cognitive complaints (SCCs); I (Intervention) = no intervention/exposure, observational (cohort study); C (Comparison) = informants/relatives who subjectively perceive cognitive decline; O (Outcome) = risk of progression to MCI and/or dementia; T (Timing) = $\geq$ 6 months, and D (Design) = prospective longitudinal studies. Question review: Do informant-reported subjective cognitive complaints (SCCs) predict progression to MCI and dementia better than self-reported SCCs in old adults?

### 2.2. Search strategy

The systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA 2020) (Page et al., 2021) and registered in the international prospective register of systematic reviews (PROSPERO, with registration number CRD42021227459) (National Institute for Health Research, 2021). The meta-analysis was also evaluated by MOOSE Checklist for Meta-analyses of Observational Studies (Stroup et al., 2000).

This is the first systematic review investigating the type of SCCs (self- or informant-reported) that best predict progression or conversion to MCI and/or dementia. We searched published articles between 1987 (the earliest found) and November 2020, and they were selected from PsycINFO, PubMed, Scopus, and Web of Science (WOS) databases of medical journals. The keywords used were: ("subjective decline" OR concern* OR complaint* OR SCD OR SMC OR SMD OR SCC) AND (risk OR association OR evolution OR progression OR conversion) AND (memory OR cogniti*) AND (dementia OR Alzheimer* OR MCI OR "mild cognitive impairment" OR "minor neurocognitive disorder" OR "major neurocognitive disorder") AND (informant* OR relative* OR partner OR "study partner") (eAppendix in the Supplement). The title was screened first, followed by abstracts and full article texts. References were compiled using Mendeley Desktop 1.19.4, and duplicates were removed using the same software.

### 2.3. Study selection

Two different researchers (L.P.-B. and A.F.) screened titles, abstracts and full-text articles. Rayyan QCRI (Ouzzani et al., 2016) was used for screening titles and abstracts. Consensus of 87% was reached between the reviewers. When any inconsistencies appeared, a final consensus was reached through discussion with a third reviewer (O.J.-R.), who finally eliminated two articles. The main reason for exclusion was the use of the instrument of SCCs to separate diagnostic groups, and not providing a total score on each report (self- and informant-). Results of the selection process are shown in Fig. 1.

Inclusion criteria were as follows: (1) studies focused on the association between SCCs and cognitive impairment or dementia throughout follow-ups; (2) prospective longitudinal studies including at least six months of follow-up; (3) studies including SCCs (identified by questions or questionnaires) reported by participants and informants; (4) studies reporting stability or progression of participants with SCCs to MCI and/or dementia; (5) the samples must include CU participants; (6) diagnosis of MCI and dementia following recognized criteria, such as those reported in Albert et al. (2011), Petersen et al., (1999, 2001), Petersen (2004), Winblad et al. (2004), DSM-IV (APA, 1994), DSM-5 (APA, 2013) and NINCDS-ADRDA (Dubois et al., 2007) and National Institute on Aging and Alzheimer's Association (NIA-AA) (Knopman et al., 2018). Exclusion criteria were as follows: (1) studies focused on the effect of interventions on SCCs; (2) studies that do not include CU participants; (3) studies that do not provide self- or informant-reported SCCs in CU participants; (4) studies that do not compare SCCs reported by participants and informants; (5) studies focused on (a) patients with prior diagnosis of depression and anxiety or other psychiatric disturbances following the DSM-IV-TR or DSM-5, (b) diagnosis of neurological disorder instilled or in the prodromal phase, including MCI, probable AD or other types of dementia following the DSM-IV-TR or DSM-5 or (c) previous brain damage or brain surgery; (6) systematic reviews and meta-analysis.

### 2.4. Data abstraction

A standardized Excel spreadsheet was compiled with the following variables: study information (i.e. first author, year), substantive characteristics (i.e. country, mean age, percentage of women in the sample, education level, personality traits, anxiety and depression symptoms, neurodegeneration biomarkers), methodological characteristics (i.e. months of follow-up, sample type, MCI/dementia criteria) and results, including parameters (self- and informant-reported) that predict progression or conversion to cognitive decline (i.e. OR and HR) and percentage of CU older adults with cognitive complaints who progress or do not progress to MCI and/or dementia during follow-up. One reviewer (L.P.-B.) abstracted data from each study included. The data extracted were discussed with the third reviewer (O.J.-R.) and with a fourth researcher (S.C.M.).

### 2.5. Quality scale

Study quality was assessed using the quality assessment tool for observational cohort and cross-sectional studies from the National Heart, Lung and Blood Institute (eTable2 in Supplementary material). The tool contains 14 criteria on which quality is determined. The criteria were rated as either yes, no or "other" (i.e. not applicable), and an overall rating for the study as "good," "fair," or "poor" was provided. Articles classified as "good" required 11 o more "yes" answers (11/14 means 78.5% positive answers), as "fair" when there were 10 or more "yes" answers (10/14 means 71% positive answers) and finally as "poor" when there were 9 or fewer "yes" answers to the items on the scale. The intersection point and classification of items 5 and 12 as "not applicable" were discussed, and disagreements were reconciled with the reviewers (O.J.-R. and S.C.M.).

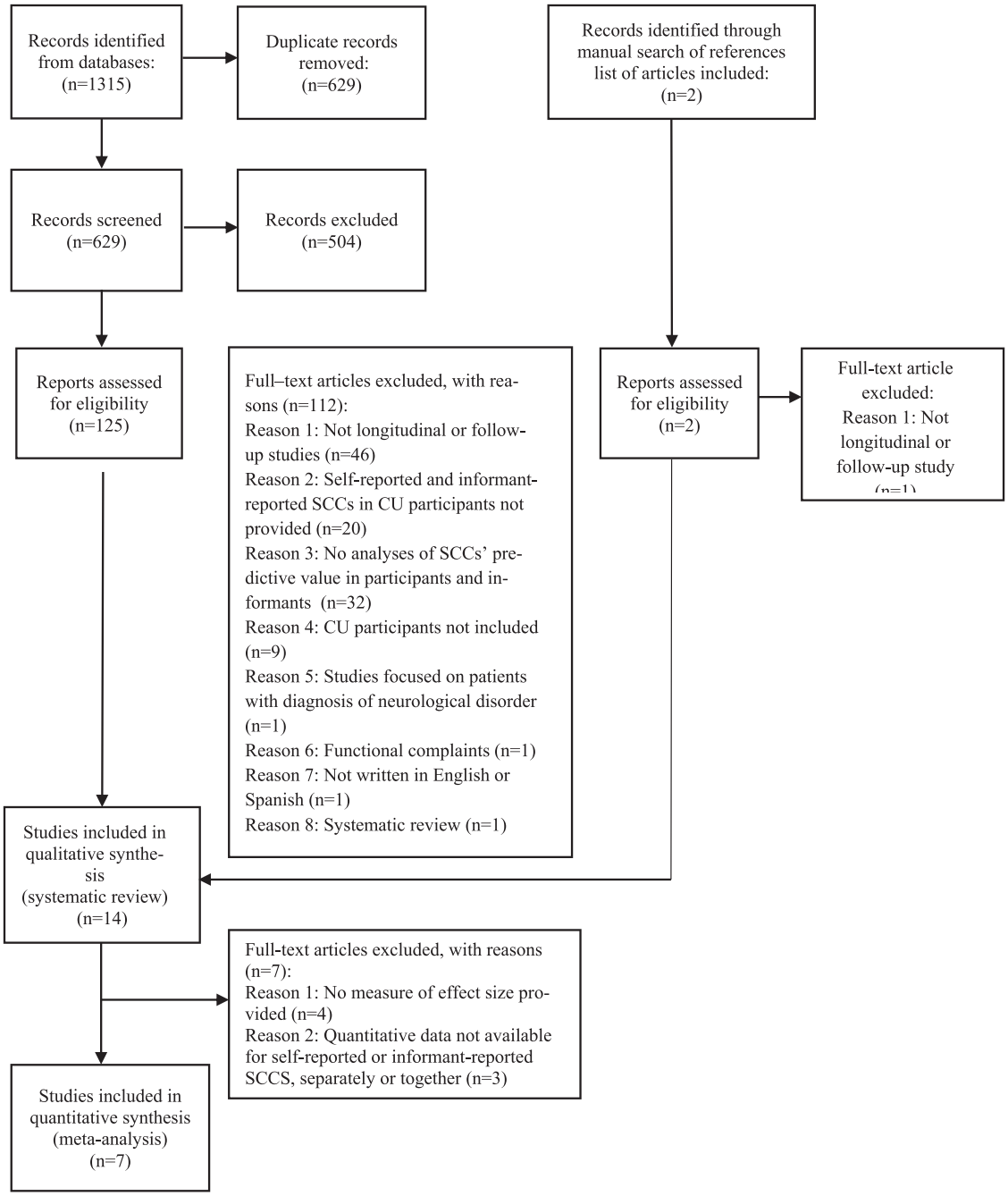


**Fig. 1.** Flowchart of the process of article selection and inclusion.

### 2.6. Meta-analysis

A meta-analysis was carried out to estimate the separate value of self-reported and of informant-reported SCCs for predicting progression to MCI and/or dementia in CU participants. The Odds Ratio (OR) or Hazard Ratio (HR) associated with the estimates were converted and interpreted as Relative Risk (RR), which was used as a measure of the effect size. The frequency of transition in the studies using OR ranged between 4% and 14%. Under the rare disease assumption (i.e. < 15%) pooling these estimates was considered reasonable. Only one of the studies reporting OR provided confidence intervals and the other two studies only provided p-values. In order to include these studies, we estimated their 95% confidence intervals from the reported p-values. Log-transformed ORs, RRs and HRs are preferred in meta-analysis because their sampling distribution is more symmetrical than that of the untransformed parameters. Therefore, in cases where only p-values were reported, we calculated the log OR as the natural logarithm of the reported OR and estimated the associated confidence limits using a test-based method. Assuming that the log OR values were normally distributed and that a two-tailed test was conducted, we first estimated the standard error of the log odds ratio by dividing the log odds ratio by the z-value associated with the reported p-value divided by two (reflecting the assumption of a two-tailed test). Next, the log OR plus or minus 1.96 times its standard error was used in the meta-analysis. After meta-analytic pooling, the log ORs and their associated confidence limits were back-transformed through exponentiation onto their original scale for inclusion in forest plots.

The level of heterogeneity was indicated by the $I^2$ statistic (Higgins et al., 2003), and the interstudy variance, by $tau^2$. $I^2$ values higher than 75% represent high heterogeneity (Huedo-Medina et al., 2006). The

meta-analysis used a random effects model and was conducted using the "*metan*" command in Stata 16 (College Station, Tx) (Harris et al., 2008).

## 3. Results

### 3.1. Identification of studies

Overall, 1315 articles were identified, of which 686 were excluded as duplicates and 505 were excluded after screening the title and abstract. As a result, 126 full-text articles were assessed for eligibility according to inclusion and exclusion criteria. After full text screening, only 14 articles were included in the systematic review. Ten studies included a sample with CU older adults with SCCs who progressed to MCI and/or dementia (Amariglio et al., 2015; Caselli et al., 2014; Gerretsen et al., 2017; Gifford et al., 2014; Grutters et al., 2019; Nosheny et al., 2019; Numbers et al., 2020; Rabin et al., 2012; Slavin et al., 2015; Qi et al., 2018). The other five studies considered CU older adults with SCCs who underwent cognitive decline, taking into account the neuropsychological performance at follow-up (Gavett et al., 2011; Gifford et al., 2015a; Nicholas et al., 2017; Slavin et al., 2015; Vaskivuo et al., 2019). Of these 14 studies, only 7 studies were included in the meta-analyses (Caselli et al., 2014; Gifford et al., 2014; Grutters et al., 2019; Nosheny et al., 2019; Numbers et al., 2020; Rabin et al., 2012; Slavin et al., 2015). The main reasons for excluding articles from the meta-analyses were no quantitative information was provided for either type of report, and no size measures (i.e., OR, HR) were provided. A flowchart of the process of article selection and inclusion according to PRISMA is shown in Fig. 1.

### 3.2. Qualitative description of the studies reviewed

#### 3.2.1. Methodological and substantive characteristics of the studies

The characteristics of the studies included are summarised in Table 1. All studies were published between 2011 and 2020. Eight (57.1%) of the studies were conducted in the USA and two in Australia (14.3%), and one study was conducted each in the Netherlands, China, Finland and Canada. The duration of follow-up in these studies ranged from 24 to 81 months. Ten studies were population-based, and four were clinic-based. MCI was diagnosed using Petersen criteria and/or NIA-AA criteria, while dementia was diagnosed using DSM-IV and/or NINCDS/ADRDA. From the selected studies, nine only included CU individuals with SCCs at baseline, and five studies included CU individuals with SCCs and individuals diagnosed with MCI at baseline. All studies included information on SCCs reported by participants and by informants. The mean age of the CU participants was 72.46 years, and the proportion of females was 63.31%. The mean age of the MCI participants was 73.38 years, and the proportion of females was 50.04%. Eight studies indicated that most of the participants had completed university education (more than 13 years of education) and six studies reported that the participants had completed high school (between 9 and 13 years of education). Eight studies used specific questionnaires, three used memory questions and three studies used combinations of questions elaborated ad hoc from one or two specific questionnaires. Global cognitive status was evaluated at baseline in all except two studies, while objective memory was evaluated at baseline in all except one study. MMSE was the most commonly used objective measure of global cognition. Depressive symptomatology was assessed in ten studies, while anxiety was assessed in three studies. Personality traits (i.e. neuroticism, openness, conscientiousness) were evaluated in two studies. The APOE–4 positive neurodegeneration biomarker was obtained in six studies.

#### 3.2.2. Main outcomes

When taking into account the risk of transition to MCI and/or dementia in CU participants, only three studies found that self-reported SCCs predicted about twice the risk of progression after 36 months (Gifford et al., 2014; Nosheny et al., 2019) or 80 months (Caselli et al., 2014). One study showed that none of the indices of SCCs at baseline significantly increased the odds of being diagnosed with MCI at 48 months of follow-up (Slavin et al., 2015). Regarding informant reports, six studies identified that the information reported by one informant predicted an increase in the odds of transition in clinical states than self-reported information (Caselli et al., 2014; Gifford et al., 2014; Grutters et al., 2019; Nosheny et al., 2019; Numbers et al., 2020; Rabin et al., 2012). In particular, the informant-reported predicted the following: (a) around double and/or triple the risk of progression to MCI after 36 months (Gifford et al., 2014; Rabin et al., 2012; Nosheny et al., 2019) or quintuple the risk after 80.8 months (Caselli et al., 2014), and (b) almost 1 or 1.5 times more the risk of conversion to dementia at a follow-up range of 60–72 months (Grutters et al., 2019; Numbers et al., 2020).

Regarding adults with MCI, two studies have demonstrated the ability of self-reported SSCs to predict subsequent dementia (Nosheny et al., 2019; Slavin et al., 2015). This studies indicated that after a 36-month follow-up, the self-reported predicted the risk of cognitive worsening increased by 1 OR. Regarding informant-reported SCCs, four studies showed that the information from one observer predicted a significantly greater increase in the risk of transition to dementia than self-reported SCCs (Gerretsen et al., 2017; Gifford et al., 2014; Nosheny et al., 2019; Slavin et al., 2015). After a 36-month follow-up, it was found that the informant-reported doubled (Gerretsen et al., 2017; Gifford et al., 2014) or tripled (Nosheny et al., 2019) the risk of clinical conversion to dementia.

Some studies provided additional information on the predictive capacity of SCCs based on the neuropsychological assessment, which can be summarized as follows: (a) only informant-reported data predicted cognitive decline at a follow-up ranging from 36 to 48 months (Gavett et al., 2011; Nicholas et al., 2017; Slavin et al., 2015); (b) both self-reported and informant-reported SCCs predicted cognitive decline after 24 months (Gifford et al., 2015) and 72 months follow-up (Numbers et al., 2020); and (c) only self-reported SCCs provided a significantly better prediction of the cognitive decline across 24 months at follow-up (Vaskivuo et al., 2019).

#### 3.2.3. Quality assessment

Ten studies (71.42%) were qualified as of good quality, while three studies (21,42%) were valued as of poor quality. One study (7.14%) had an overall rating of fair quality (eTable1 in Supplementary material). Methodological flaws were found in item seven (*"Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?")* (2/14), item nine ("*Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants*? (3/14), item eleven ("*Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants*?" (3/14) and item thirteen ("*Was loss to follow-up after baseline 20% or less?")* (1/14). Answers to item five ("*Was a sample size justification, power description, or variance and effect estimates provided?*") and item twelve ("*Were the outcome assessors blinded to the exposure status of participants")* were not reported.

### 3.3. Quantitative analysis of the studies

#### 3.3.1. Risk of transition to MCI/dementia from self-reported SCCs in CU older adults

A forest plot for self-report is shown in Fig. 2. In this analysis, the $I^2$ value was 77.5% and $tau^2$ value, 0.0318. The pooled relative risk was 1.27 (95% CI 1.06 – 1.534) and was statistically significant ($z = 2.53$, $p = 0.011$).

#### 3.3.2. Risk of transition to MCI/dementia from informant-reported in CU older adults

In the analysis of informant report, the $I^2$ value was 83.8% and the

**Table 1**
Summary of studies included.

| Author, year | Substantive characteristics | Sample type | Method of assessing SCCs (questionnaire/answer) | Follow-up (months) | Method of diagnosis (MCI/dementia) | Main significant outcomes |
|---|---|---|---|---|---|---|
| Amariglio et al. (2015) | **CU** n = 468<br>–79.9 years;<br>59.61% female<br>–University education | Community | –Self: CFI (14-item)<br>–Informant: CFI (14-item) | 48 | Petersen (2004); DSM-IV | –Mutual complaint: OR= 1.01 [1.01–1.02] |
| Caselli et al. (2014) | **CU** n = 447<br>–61.3 years;<br>68.90% female<br>–University education | Community | –Self: MANS (87-item)<br>–Informant: MANS (87-item) | 80.8 | Petersen et al. (2001); NINCDS/ADRDA DSM-IV | –Self-reported SCCs: OR= 2.78, p = 0.004<br>–Informant-reported SCCs: OR= 4.58, p = 0.004 |
| Gavett et al. (2011) | **CU** n = 384<br>–70.37 years;<br>100% female<br>–University education | Community | –Self: IQCODE (16-item)<br>–Informant: IQCODE (16-item) | 36 | Petersen et al. (1999) | –Cognitive decline predicted by informant-reported SCCs (β = –0.175) |
| Gerretsen et al. (2017) | **CU** n = 372<br>–74.6 years;<br>53.5% female<br>–University education<br>**MCI** n = 499<br>–72.95 years;<br>43.28% female<br>–University education | Clinical | –Self: Ecog–scale (12-item)<br>–Informant: Ecog–scale (12-item) | 60 | NINCDS/ADRDA | **From MCI to dementia**<br>–Informant-reported SCCs: OR= 1.64 [1.12–2.40] |
| Gifford et al. (2015a) | **CU** n = 6133<br>–72.5 years; 68% female<br>–University education<br>**MCI** n = 3010<br>–74.5 years; 55% female<br>–University education | Clinical | –Self: CDR Assessment: *"Do you have problems with your memory or thinking?"*<br>–Informant: CDR Assessment: *"Do you have problems with your memory or thinking?"* | 24 | Petersen et al. (2004); NIA-AA | –Cognitive decline predicted by both self-report (β = –0.19) and informant-report (β = –0.25) SCCs for CU participants.<br>–Cognitive decline predicted by both self-reported (β = –0.35) and informant-reported (β = –0.45) SCCs for MCI participants. |
| Gifford et al. (2014) | **CU** n = 4414<br>–72.7 years; 69% female<br>–University education<br>**MCI** n = 1843<br>–74.5 years; 52% female<br>–University education | Community | –Self: CDR Assessment: *"Do you have problems with your memory or thinking?"* –Informant: CDR Assessment: *"Do you have problems with your memory or thinking?"* | 36 | Petersen et al. (2004); NIA-AA; NINCDS/ADRDA; DSM-IV | **From CU to MCI:**<br>–Self-reported SCCs: OR= 2.1 [1.5–2.9]<br>–Informant-reported SCCs: OR= 2.2 [1.2–3.9]<br>–Mutual complaints: OR= 4.2 [2.9–6.0]<br>**From MCI to dementia:**<br>–Informant-reported SCCs: OR= 2.2 [1.2–4.3]<br>–Mutual complaint: OR= 2.9 [1.8–4.8] |
| Grutters et al. (2019) | **CU** n = 168<br>–71.7 years;<br>38.76% female<br>–High school | Community | –Self: SCF (4-item)<br>–Informant: DECO (19-item) | 60 | NIA-AA; DSM-IV | –Informant-reported SCCs: HR= 1.76 [1.12–2.78]<br>–Mutual complaint: HR= 1.73 [1.09–2.76] |
| Author, year | Substantive characteristics | Sample type | Method of assessing SCCs (questionnaire/answer) | Follow-up (months) | Method of diagnosis (MCI/dementia) | Main significant outcomes |
| Nicholas et al. (2017) | **CU** n = 1261<br>–58.68 years;<br>70.20% female<br>–University education | Clinical/ Research | –Self: MFQ (18-item of the Frequency of Forgetting)<br>–Informant: IQCODE (16-item) | 48 | Changes in memory performance (RAVLT) | –Cognitive decline predicted by informant-reported SCCs (β = −0.015). |
| Nosheny et al. (2019) | **CU** n = 420<br>–73.8 years;<br>52.4% female<br>–University education<br>**MCI** n = 482<br>–72.4 years;<br>40.9% female<br>–University education | Clinical | –Self: Ecog-scale (39-item)<br>–Informant: Ecog-scale (39-item) | 36 | Petersen et al. (1999); NINCDS/ADRDA | **From CU to MCI**<br>–Self-reported SCCs: HR= 3.10 [1.57–7.80]<br>–Informant-reported SCCs: HR= 3.21 [1.83–6.83]<br>**From MCI to dementia**<br>–Self-reported SCCs: HR= 0.97 [0.76–1.34]<br>–Informant-reported SCCs: HR= 3.11 [2.23–4.69] |
| | **CU** n = 873<br>–78.65 years; | Community | –Self: questions ad-hoc (18-item) and MAC–Q (6-item) | 72 | Petersen et al. (2004); Winblad et al. (2004) | –Informant-reported SCCs: HR= 1.20 [1.12–1.28] |

(*continued on next page*)

**Table 1** (*continued*)

| Author, year | Substantive characteristics | Sample type | Method of assessing SCCs (questionnaire/answer) | Follow-up (months) | Method of diagnosis (MCI/dementia) | Main significant outcomes |
|---|---|---|---|---|---|---|
| Numbers et al. (2020) | 56.1% female<br>–High school | | –Informant: questions ad-hoc (3-item), IQCODE (13-item), and CFCOG (3-item) | | | –Cognitive decline predicted by both self-reported (β = –0.009) and informant-reported SCCs (β = –0.013). |
| Rabin et al. (2012) | **CU** n = 627<br>–80.05 years;<br>59.96% female<br>–High school | Community | –Self: CERAD (15-item), Albert Einstein Health Self-Assessment (5-item), and GDS (1-item)<br>–Informant: CERAD (25-item) | 36 | Petersen et al. (2004); NIA-AA; DSM-IV | –Informant-reported SCCs: HR= 1.33 [1.02–1.74] |
| Slavin et al. (2015) | **Non demented** n = 398<br>–78.0 years;<br>54.7% female<br>–High school | Community | –Self: questions ad-hoc (18-item) and MAC–Q (6-item)<br>–Informant: questions ad-hoc (3-item), IQCODE (13-item), CFCOG (3-item) | 48 | DSM-IV | **From CU to MCI:**<br>–Self-reported SCCs: OR= 1.049, p = 0.317<br>–Informant-reported SCCs: OR= 1.093, p = 0.66<br>**From MCI to dementia:**<br>–Self-reported SCCs: OR= 1.202; p < 0.001<br>–Informant-reported SCCs: OR= 1.244: p < 0.001<br>–Cognitive decline predicted by informant-reported SCCs (β = –0.074) |
| Vaskivuo et al. (2019) | **CU** n = 303<br>–70.0 years;<br>51.2% female<br>–High school | Community | –Self: PRMQ (16-item)<br>–Informant: PRMQ (16-item) | 24 | Changes in memory, executive domain, and processing-speed (modified NTB) | –Cognitive decline predicted by self-reported SCCs (β = –0.0005) |
| Qi et al. (2018) | **CU** n = 1713<br>–73.6 years;<br>69.70% female<br>–High school | Community | –Self: *Do you think that you have any problems with your memory?*<br>–Informant: *Do you believe the subject has any problems with memory?* | 60 | NIA-AA | –Mutual complaint: OR= 1.60 [1.04–2.48] |

Note: SCCs: subjective cognitive complaints; MCI: mild cognitive impairment; CU: cognitively unimpaired; University education (more than 13 years of education); High school (between 9 and 13 years of education); CFI: Cognition Function Instrument; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition; MANS: Multidimensional Assessment of Neurodegenerative Symptoms; NINCDS/ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; Ecog-scale: Everyday Cognition Scale; ADNI group: Alzheimer's Disease Neuroimaging Initiative group; NIA-AA: National Institute on Aging and Alzheimer's Association; CDR Assessment: Clinical Dementia Rating Assessment Protocol; SCF: Subjective Cognitive Functioning; DECO: Cognitive Deterioration Observed; CDS: Cognitive Difficulties Scale; RAVLT: Rey Auditory Verbal Learning Test; MFQ: Memory Functioning Questionnaire; MAC–Q: Memory Complaints Questionnaire; CFCOG: General Practitioner Assessment of Cognition; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; GDS: Geriatric Depression Scale; PRMQ: The Prospective and Retrospective Memory Questionnaire; NTB: Neuropsychological Test Battery (NTB). Main significant outcomes: all values are significant at $p < 0.05$

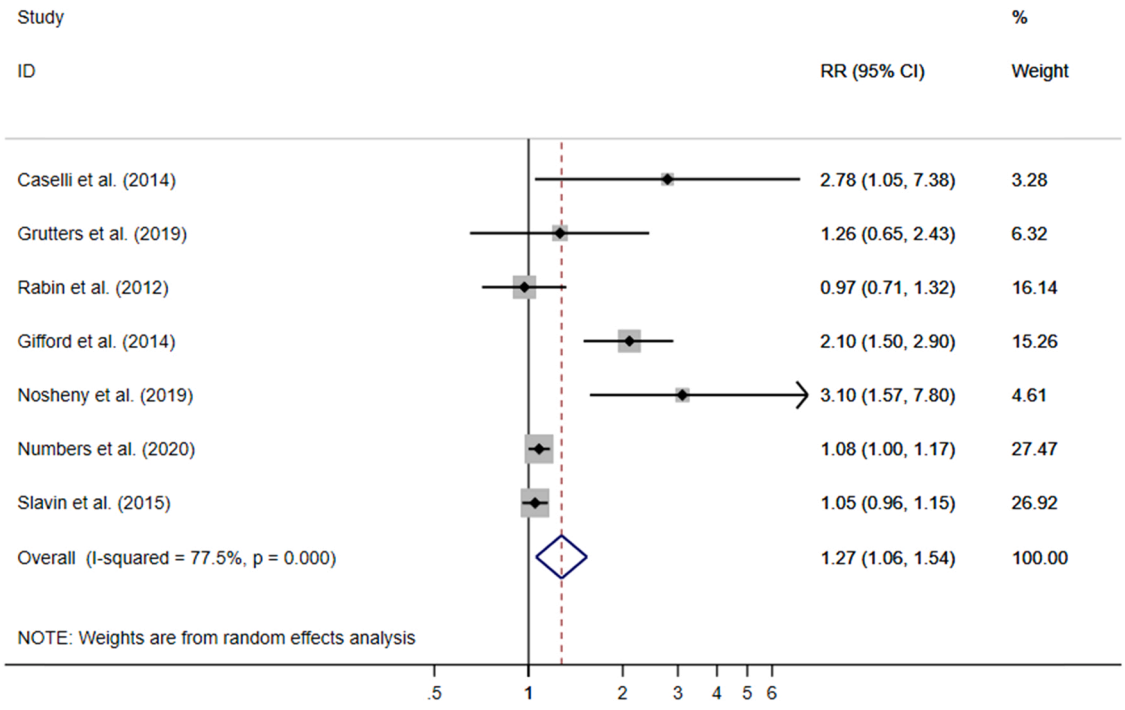


**Fig. 2.** Forest plot displaying a random-effects meta-analysis of relative risk of transition to MCI/dementia associated with self-reported SCCs.

$tau^2$ value, 0.025. The forest plot is presented in Fig. 2. The pooled estimate of effect was 1.38 (95% CI of 1.16 −1.64). This association was highly significant (z = 3.69, p < 0.001).(Fig. 3).

## 4. Discussion

To our knowledge, this is the first meta-analysis aimed at determining whether self-reported or informant-reported SCCs better predict progression to MCI and/or dementia. The systematic review revealed a small number of prospective longitudinal studies analyzing the predictive ability of both types of reports in relation to the risk of further decline in cognition, demonstrating the limited scientific literature on the subject.

When considering CU individuals, the findings of this meta-analysis suggest that both self-reported and informant-reported SCCs are associated with an elevated risk of transition to MCI or dementia, thought surprisingly the association was stronger and more robust for informant-reported data [1.38, with a 95% CI of 1.16 –1.64, p < 0.001] than for self-reported data [1.27 (95% CI 1.06 – 1.534, p = 0.011]. Cross-sectional studies has pointed out that self-reported SCCs may be at least as useful as informant-reported SCCs in predicting objective cognitive impairment in people without objective cognitive deficits or with very slight impairment (Buckley et al., 2015; Rueda et al., 2015). Greenop and colleagues (2011) explained that this may be because CU older adults and people with early MCI are aware of their memory problems and can efficiently apply compensatory strategies (i.e. using calendars, diaries, notes). Thus, the informant-reported SCCs is limited to reporting the "*concern*" the person verbalizes frequently on a daily basis, or when there is a severe change relative to a previously higher cognitive state (Greenop et al., 2011; Mendonça et al., 2016). While it is true that in our meta-analysis both self- and informant-reported SCCs predicted clinical transition, it is worth noting that most studies establish a stronger association between the transition to cognitive decline with the informant's report (Caselli et al., 2014; Grutters et al., 2019; Gifford et al., 2014; Rabin et al., 2012; Nosheny et al., 2019). Rabin and colleagues (Rabin et al., 2017) suggested that self-reported SCCs may be more significant at pre-clinical stages, while informant-reported data may be more accurate at the advanced stage between MCI and AD dementia (Rabin et al., 2017). Our meta-analytical findings support the possibility that both self-reported and informant-reported SCCs may be an early sign of global cognitive impairment in CU adults (Burmester et al., 2016; Mitchell et al., 2014), but that the information corroborated by an informant indicates a stronger association.

Regarding adults with MCI, we were unable to carry out a meta-analysis because we only found four studies on this type of impairment (Gerretsen et al., 2017; Gifford et al., 2014; Nosheny et al., 2019; Slavin et al., 2015). Of these studies, one did not provide any size measures for self-reported data (Gerretsen et al., 2017), and the others reported a higher transition rate (>15%) thus making it impossible to convert and interpret the data as Relative Risk (RR). Our systematic review provides evidence that the confirmation of cognitive impairment by a family member or close observer is required at clinical stages (Rabin et al., 2021). Indeed, Edmonds et al. (2014) confirmed that disagreement between self-reported and informant reported information may indicate the degree of underestimation of cognitive impairment in older individuals at risk for developing Alzheimer's disease/dementia. On the other hand, Gifford et al., (2015b) demonstrated that a single self-reported or informant-reported complaint would not be enough to predict Alzheimer's disease in elderly people with MCI, but reports from both sources would be sufficient. In this respect, our findings indicate that a mutual complaint would be more closely related to diagnostic conversion than a single complaint, not only in people with MCI (Gifford et al., 2014), but also in CU individuals (Amariglio et al., 2015; Gifford et al., 2014; Grutters et al., 2019; Qi et al., 2018). Therefore, both self-reporting and informant-reporting of concerns represent complementary approaches to predicting the progression to MCI and/or dementia (Rabin et al., 2017).

Finally, regarding studies analyzing cognitive decline in terms of neuropsychological performance, only two studies found that self-reported SSCs were more closely, although weakly, related to the future risk of developing cognitive impairment than informant-reported SCCs after a 24-month follow-up period (Gifford et al., 2015a; Vaskivuo et al., 2019). By contrast, as the follow-up time increased, the informant-reported SCCs appeared to be more significant in CU individuals or with MCI even after controlling socio-demographic and mood variables (Gavett et al., 2011; Nicholas et al., 2017; Numbers

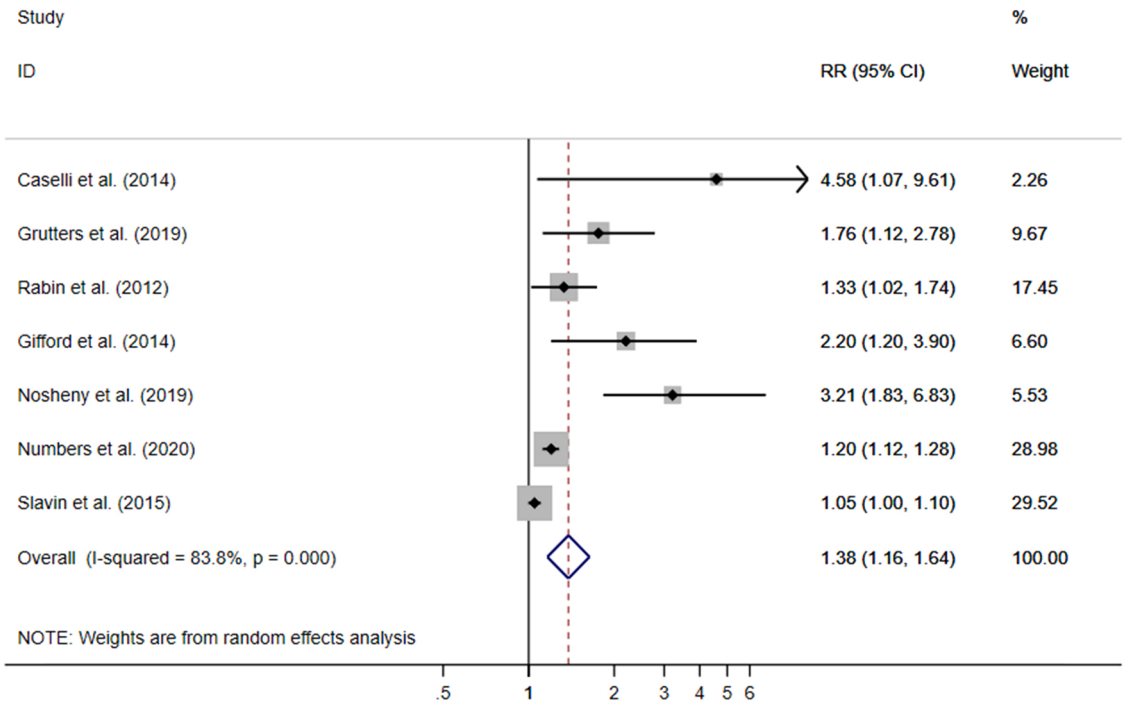


**Fig. 3.** Forest plot displaying a random-effects meta-analysis of relative risk of transition to MCI/dementia from informant-reported SCCs.

et al., 2020; Slavin et al., 2015).

## 5. Limitations

The studies included in this systematic-review were heterogeneous in terms of methodology and analytical methods. Consequently, meta-analysis was only performed for measures of association between self-reported and informant-reported cognitive decline as a predictor of transition to MCI/dementia. The pooled analysis included studies reporting odds ratios and hazard ratios. While both parameters seek to quantify the relative risk, differences can occur when an outcome is not rare or when the data are censored. Therefore, pooled estimates should be viewed with some caution. However, the association was consistently in the direction of increased risk, especially in the group with informant-reported cognitive decline, and the findings of the meta-analysis help to confirm that the reported data are unlikely to arise due to sampling variability. Another limitation of the study was that the number of studies was too small to enable use of funnel plots or other methods to detect publication bias. More prospective longitudinal studies comparing the predictive value of both reports are needed.

## 6. Conclusions

This meta-analytical study confirmed that both self-reported and informant-reported SCCs are associated with an elevated risk of transition to MCI or dementia in CU older adults. The association appears stronger and more robust for informant-reported than for self-reported SCCs, although the overlapping confidence intervals of the two pooled estimates presented here preclude the decisive conclusion that informant-reported SCCs are more predictive. The informant-reported SCCs may provide important details for distinguishing normal aging from objectified cognitive impairment and progression to dementia. Further research on this topic is required to determine which specific subtype of self-reported and informant-reported SCCs is associated with clinical transition.

## CRediT authorship contribution statement

**Lucía Pérez-Blanco:** Methodology, Writing – original draft. **Alba Felpete:** Methodology. **Scott B. Patten:** Methodology. **Sabela C. Mallo:** Methodology. **Arturo X. Pereiro:** Writing – review & editing. **María Campos-Magdaleno:** Writing – review & editing. **Onésimo Juncos-Rabadán:** Methodology, Writing – review & editing.

## Declaration of interest

The authors have no conflicts of interest to report.

## Data Availability

Any data generated in the analysis process can be requested from the corresponding author.

## Acknowledgments

This work was supported though FEDER founds by the Spanish National Research Agency (Spanish 'Ministry of Science, Innovation and Universities) (Project Ref. PSI2017-89389-C2-1-R), FEDER founds ('A way to make Europe') by the Spanish AEI (Doi: 10.13039/501100011033; Refs. PID2020-114521RB-C21 and PSI2017-89389-C2-1-R) and by the Galician Government (Consellería de Cultura, Educación e Ordenación Universitaria; axudas para a consolidación e estruturación de unidades de investigación competitivas do Sistema Universitario de Galicia; GI-1807-USC: Ref. ED431C 2021/04).

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101772.

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