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Review article

The influence of education in predicting conversion from Subjective cognitive decline (SCD) to objective cognitive impairment: A systematic review and meta-analysis

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ABSTRACT

Background: Subjective cognitive decline (SCD) is considered a pre-symptomatic stage of dementia characterized by cognitive complaints. The ability of education to reduce the risk of dementia is well known. Our objective is to investigate the influence of education on the risk of progression from SCD to MCI or dementia.
Methods: Prospective longitudinal studies of adults (≥50 years) with SCD evaluating progression to objective cognitive decline, MCI, or dementia were selected. Pooled estimates (random effects model) and 95 % confidence intervals were calculated, exploring heterogeneity. Standardized education differences, Odds Ratio, or Hazard Ratio between converters and non-converters were estimated.
Results: The systematic review carried out showed that high education, as well as other cognitive reserve proxies, delays cognitive decline. The first meta-analysis showed a significant association of SCD with conversion in both high and low education strata. A second meta-analysis considering education as a continuous variable found that SCD converters showed two years less education than non-converters.
Conclusions: Our results suggest that education has a delaying effect against cognitive decline progression. The presumed improvement in accurately detecting cognitive decline associated with better metacognitive skills in higher-educated SCD participants does not seem to neutralize the incremental risk of objective cognitive decline associated with lower educational attainment.

1. Introduction

Subjective Cognitive Decline (SCD) is considered a pre-symptomatic stage of Alzheimer's Disease (AD) characterized by persistent Subjective Cognitive Complaints (SCCs) that cannot be explained by medical conditions or substance use and without evidence of objective cognitive impairment (Jessen et al., 2014, 2020). SCD has been proposed as the transitional stage between Cognitively Unimpaired (CU) and Mild cognitive impairment (MCI) (Jack et al., 2018). The presence of SCCs is a relevant criterion for MCI diagnosis (Albert et al., 2011; Petersen et al., 1999) and a risk factor for cognitive decline and dementia (Mendonça et al., 2016; Pereiro et al., 2021). Greater SCCs were found to be linked to a heightened risk of objective cognitive decline (Dufouil et al., 2005; Numbers et al., 2021). Accordingly, meta-analytical evidence supports that SCD participants show an increased risk of progression to MCI and dementia (Mitchell et al., 2014; Pike et al., 2021).

Current research on dementia risk factors is also interested in the variables that reduce the chances of cognitive symptoms associated with this disease (Silva et al., 2019). Cognitive Reserve (CR) refers to the variables capable of delaying the onset of symptoms even in the presence of neurodegeneration (Stern et al., 2020). Education is the proxy that has proven to be the most relevant within this construct (Roe et al.,

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2007; Valenzuela, Sachdev, 2006).

There is considerable evidence about the association between higher educational attainment and lower risk of MCI (Liu et al., 2022; Roe et al., 2007; Tervo et al., 2004) and dementia (Mungas et al., 2018; Robitaille et al., 2018; Stern et al., 2020; Xu et al., 2016). A meta-analytic study involving 69 studies showed that the incidence and prevalence of AD and dementia significantly decreased in older adults with high educational levels compared to those with a low level of education (Meng, D'Arcy, 2012). This is highly consistent with the CR hypothesis, which proposes that individuals with more cognitive abilities and brain-stimulating experiences can better cope with neurological damage and aging-related changes (Stern, 2009).

Notwithstanding, recent studies have shown a stage-dependent effect of CR on cognitive functioning. According to Soldan et al., (2017), higher CR is associated with improved cognitive performance and delayed onset of symptoms in individuals with MCI. Another study (Zahodne et al., 2019) revealed that the positive impact of education on cognitive protection might be stronger in the initial stages of age-related brain issues such as CU or SCD. However, in later stages, the negative cognitive effects of brain damage in people with high reserve could be increased due to the critical overflow of the compensatory capacity of CR. Accordingly, other studies (Amieva et al., 2014; Mungas et al., 2018; Ye et al., 2013; Yu et al., 2012) have shown that with increasing neurodegeneration, the compensatory effects of higher education are lowered as more developed functional networks that support resilience could become more sensitive to brain damage, potentially leading to faster cognitive decline.

Research on the role of education in SCD progression to MCI and dementia has been scarce (Montemurro et al., 2021). Most of the available evidence shows that higher education in SCD participants can lower the risk of progression to objective cognitive decline (Crumley et al., 2014; Hao et al., 2017, 2019; Yang et al., 2020). Complementary to this, some studies have shown that participants with a lower level of education are more likely to report SCCs (Stewart et al., 2008; Bolla et al.; 1991). However, some inconsistent results were found and other studies have informed that higher education in SCD participants increases the risk of AD (Aghjayan et al., 2016; Jonker et al., 2000; Rabin et al., 2017), by a better estimation of cognitive changes associated to increased metacognitive skills in higher educational levels (Hertzog et al., 2008).

Our objectives were to conduct: a) a systematic review of the longitudinal association between cognitive worsening, progression to MCI or dementia, and education (alone or with other CR proxies); and b) a meta-analysis on the influence of education on the estimation of the risk of progression of SCD to MCI or dementia.

2. Methods

2.1. PICO evaluation

The review question was formed using the PICO statement (Cumpston et al., 2021):

- P (Population): cognitively unimpaired participants aged 50 years or more with SCD.
- I (Intervention): no intervention/exposure, observational (cohort study).
- C (Comparison): level of education of the participants who progress to MCI and/or dementia versus those who do not.
- O (Outcome): risk of progression to MCI and/or dementia.

Review question: How much education affects the validity of SCD in predicting the progression to MCI or conversion to dementia in older adults?

2.2. Search strategy

Our systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA 2020) (Page et al., 2021) (eTable1 in the supplement) and MOOSE (Stroup et al., 2000) guidelines (eTable2 in the supplement). A protocol was also registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 24 October 2022, with the registration number CRD42022362750 (National Institute for Health Research, n.d.).

Four databases (Web of Science - WOS, PubMed, SCOPUS, and PsycINFO) were searched for published articles between September 1993 (the earliest study found) and June 14, 2022. The keywords used were: ("subjective memory complaints" OR "Subjective Cognitive decline" OR "Memory complaints" OR "Cognitive complaints") AND (education OR "cognitive reserve" OR "educational level" OR "years of schooling") AND (aging OR elderly OR "older adults" OR ageing) AND (progression OR conver* OR evolution OR Risk) (eAppendix in the supplement). Titles were screened first, followed by abstracts and full-text articles. References were compiled using Mendeley Desktop 1.19.8, with duplicates removed using the same software.

2.3. Study selection

Two reviewers (S.A. and C.L.-S.) independently screened titles, abstracts, and full-text articles. Rayyan QCRI (Ouzzani et al., 2016) was used for screening titles and abstracts. An overall consensus of 84 % was reached between the reviewers. Any disagreements regarding eligibility were resolved by consensus meetings, or if necessary, with a third reviewer (S.C.M.).

Inclusion criteria were: (1) Analyse the risk of objective cognitive decline, progression to MCI or conversion to dementia or any impact on cognitive performance due to level of education in SCD participants; (2) Participants aged 50 years or more; (3) SCD diagnosed by any procedure (question/s, questionnaires/spontaneous self-reports on the presence of memory complaints); (4) Education informed by range or number of years; (5) Empirical longitudinal or follow-up studies.

Exclusion criteria were: (1): Studies focused on demented or MCI patients; (2) Participants from a special population were included (e.g., participants with a history of stroke, people with cancer, Fabry disease, cognitive frailty); (3) The criteria or evaluation to determine SCD, MCI or dementia were not specified; (4) Education was not considered as CR measure; (5) Studies lacking separate education data to assess the risk of onset of objective cognitive decline, MCI progression, or dementia conversion in SCD participants.

Furthermore, for the meta-analysis, those studies that do not separately provide quantitative data on the educational level of SCD participants who remain stable and those who progress towards more or less severe forms of objective cognitive impairment were excluded.

2.4. Data abstraction

A standardized Excel spreadsheet was designed including the following variables: study information (i.e., first author, year), substantive characteristics (i.e., country, mean age, percentage of women, years of education, depressive symptoms, personality traits), methodological characteristics (i.e., months of follow up, sample type, criteria used for SCD/MCI/dementia and results. This section includes the mean and Standard Deviation (SD) of years of education of converters and non-converters SCD participants. Besides, parameters such as Hazard Ratio (HR) and Odds Ratio (OR) for converters vs. non-converters stratified by educational level were also included. One reviewer (S.A.) extracted the data from all included studies. The abstracted data were discussed with a second reviewer (S.C.M.) and any disagreements were resolved by consensus or by a third researcher (A.X.P.).

In the study, converters refer to participants with SCD who progress

to any cognitive decline, MCI, or dementia during the follow-up period. Conversely, non-converters refer to participants with SCD who do not progress to objective cognitive decline, MCI, or dementia during the follow-up period.

2.5. Quality scale used

Study quality was assessed using the quality assessment tool for observational cohort and cross-sectional studies from the National Heart, Lung and Blood Institute (eTable3 in supplement). This tool consists of 14 questions on which quality is determined. Each item was responded as "yes", "no", or "cannot determine" and an overall rating for each study was provided as "good", "fair" or "poor". For articles classified as "good", 11 or more "yes" answers (11/14 that is, 78.5 % positive answers) were required. Furthermore, for a "fair" rating, 10 or more "yes" answers (10/14 that is, 71 % positive answers) were required. Finally, for a "poor" rating, 9 or fewer "yes" answers to the scale items were considered. Two reviewers (S.A.) and (S.C.M.) independently assessed the quality of all included papers. Disagreements were reconciled with the original reviewers and if required, with an independent party (A.X.P.).

2.6. Meta-analysis

The meta-analysis was conducted using the "meta" command in STATA v17 (College Station, TX) (Harris et al., 2008). A visual summary was generated using forest plots. The analysis used a random effects model implemented using the DerSimonian-Laird method. Heterogeneity was quantified using the tau-squared (T^2) and I-squared (I^2) parameters (Higgins et al., 2003), and tested against the null hypothesis of no heterogeneity using the Q-test.

The primary analysis estimated the relative risk for SCD for conversion with stratification by education level as a binary variable (low versus high education). The aggregate outcome is labeled as "conversion" in the analysis and includes the onset of documented objective cognitive impairment, MCI, or dementia in SCD participants. This meta-analysis was based on the pooling of reported ratio-based measures (one study reported hazard ratios and three others reported odds ratios), again using the DerSimonian-Laird method. The estimates were then back-transformed after fitting the meta-analytic model.

A secondary analysis compared the mean education level in samples with SCD who subsequently demonstrated objective cognitive decline, MCI, or dementia versus those who did not. These meta-analytic models estimated the mean difference in education between converters and non-converters groups.

3. Results

3.1. Identification of studies

A total of 657 articles were identified from the initial database search and 1 from the manual search. A flowchart of the process according to PRISMA is shown in Fig. 1.

Out of those 657 articles identified from databases, 247 were excluded as duplicates, and 365 were removed after screening for title and abstract based on the inclusion and exclusion criteria: a) Being a review, systematic review, meta-analysis, or case studies (1.13 %; *N*= 4); b) Studies focused on demented or MCI patients (30.95 %; *N*= 113); c) Participants belonging to a special population are included (10.73 %; *N*= 39); d) Studies not specifying criteria or evaluation methods for determining SCD, MCI, and/or dementia (30.95 %; *N*= 113); e) Education is not considered as CR measure (14.24 %; *N*= 52); and f) Studies lacking separate education data to assess the risk of onset of objective cognitive decline, MCI progression, or dementia conversion in SCD participants (12 %; *N*= 44).

Forty-five studies were selected for a subsequent full-text review. Of those, 34 were excluded for (a) Absence of empirical longitudinal or follow-up studies (38.23 %; *N*=13); (b) Studies focused on demented or MCI patients (14.70 %; *N*=5); (c) Participants belonging to a special population are included (8.82 %; *N*=3); (d) Education not informed by range or number of years (32.34 %; *N*=11); (e) Being a systematic review or meta-analysis (2.94 %; *N*=1); and (f) Not specifying the criteria or evaluation to determine SCD, MCI or dementia (2.94 %; *N*=1).

Finally, 12 studies (11 identified from databases and 1 from manual search) were included in the systematic review (Bessi et al., 2018; Chary et al., 2013; Jia et al., 2021; Lojo-Seoane et al., 2018; 2020; Mazzeo et al., 2019; Mondini et al., 2022; Qi et al., 2018; Silva et al., 2014; Van den Kommer et al., 2008; Van Oijen et al., 2007; Yun et al., 2020).

However, 10 articles were selected for the meta-analysis after the exclusion of the manuscripts that do not separately provide quantitative data on the educational level of SCD participants who remain stable and those who progress towards more or less severe forms of objective cognitive impairment (Van den Kommer et al., 2008; Yun et al., 2020).

3.2. Characteristics of the studies

Studies included in the systematic review were published between 2007 and 2022. Three of the 12 studies were from Italy, two from Spain, two from China, two from the Netherlands, and one from Portugal, France, and Korea. Further, the follow-up periods ranged from 18 to 512 months and the mean age of the study sample ranged from 61.3 to 78.2. All of them included more women than men (percentage of females ranging from 51.20 % to 70.77 %). Seven studies were clinic-based and five were community-based. The main characteristics of the studies selected are summarized in Table 1.

All studies included neuropsychological evaluation and the Mini-Mental State Examination (MMSE; Folstein et al., 1975) was the most frequent instrument to evaluate global cognition.

Regarding SCD identification, seven studies used single questions (Chary et al., 2013; Jia et al., 2021; Mondini et al., 2022; Qi et al., 2018; Van den Kommer et al., 2008; Van Oijen et al., 2007; Yun et al., 2020); three studies used a specific questionnaire (Bessi et al., 2018; Mazzeo et al., 2019; Silva et al., 2014); and two used spontaneous SCC self-reports (Lojo-Seoane et al., 2018, 2020). Only two of the aforementioned studies (Bessi et al., 2018; Mazzeo et al., 2019) verified compliance with the SCD-I Working Group criteria (Jessen et al., 2014).

Regarding dementia diagnosis, the following criteria were used in the selected studies: a) the Diagnostic and Statistical Manual of Mental Disorders-Third Edition-Revised (APA, 1987) (Van Oijen et al., 2007; Jia et al., 2021; Chary et al., 2013); b) the Diagnostic and Statistical Manual of Mental Disorders-Third Edition-Fourth Edition Diagnostic and Statistical Manual of Mental Disorders (APA, 2000) (Silva et al., 2014); c) Alzheimer's Disease and Related Disorders Association (NINCDS-A-DRADA; McKhann et al., 1984) and/or the National Institute of Neurological and Communicative Disorders and Stroke and/or the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRADA; McKhann et al., 1984) (Lojo-Seoane et al., 2018, 2020); d) the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN; Erkinjuntti, 1994) (Van Oijen et al., 2007); e) the NIA-AA criteria (Jack et al., 2018) (Bessi et al., 2018; Mazzeo et al., 2019; Qi et al., 2018); and e) the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5; American Psychiatric Association, 2013) (Yun et al., 2020).

Eight studies included a sample of SCD participants who progressed to MCI and/or dementia (Bessi et al., 2018; Chary et al., 2013; Jia et al., 2021; Mazzeo et al., 2019; Qi et al., 2018; Silva et al., 2014; Van Oijen et al., 2007; Yun et al., 2020), while the remaining four studies tested whether SCD participants experienced objective cognitive decline at follow-up (Lojo-Seoane et al., 2018, 2020; Mondini et al., 2022; Van den Kommer et al., 2008).

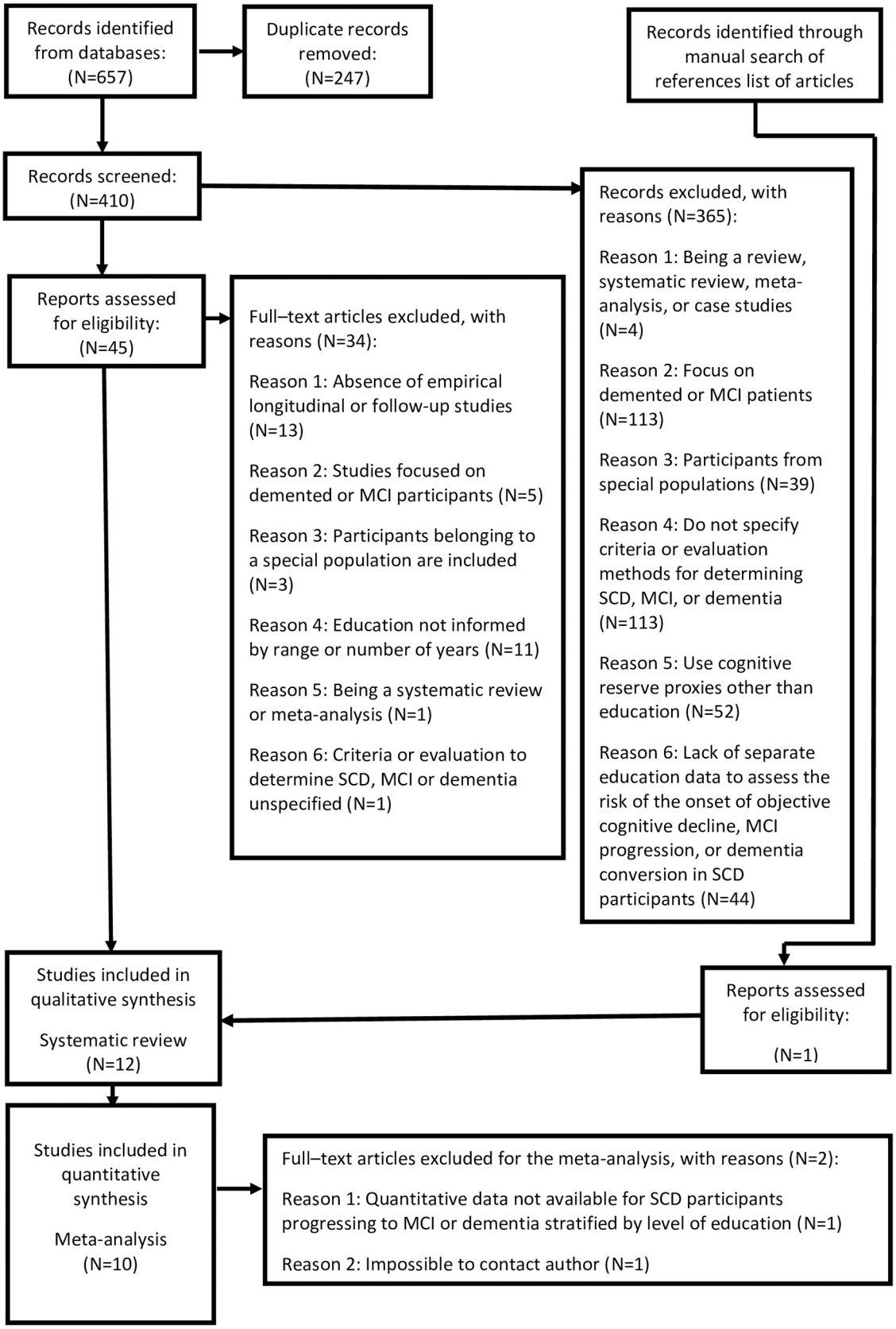

Fig. 1. Flowchart of the process of article selection and inclusion.

Table 1
. Summary of characteristics of included studies.

Study	Country (Continent)	N	Mean age	% of females	Level of Education or CR measure	Sample	Follow-up (months)	SCC measurement	Diagnostic Criteria (MCI/ Dementia)	Outcome	Results
Bessi et al. (2018)	Italy (Europe)	109	64.6	67.88 %	Higher education (+13 years) CR: TIB test CR proxy: Intellectual activities	Clinical	84	Memory Assessment Clinics-Questionnaire (20 items), Criteria: SCD-I Working Group	MCI and Dementia: NIA-AA criteria	Both MCI and Dementia	SCD participants who converted to MCI/ dementia had lower average education levels compared to those who did not convert.
Chary et al. (2013)	France (Europe)	2882	74.7	58.70 %	Two groups: LEL (<elementary school diploma) and HEL (Secondary school or University)	Community	240	"Do you frequently have 1. forgetfulness in activities of daily living; 2. difficulties in retaining or remembering new simple information; 3. difficulties in retrieving or remembering old memories and 4. difficulties in finding words"	Dementia: A, B, and C, DSM-III-R, AD, vascular dementia, or other types	Dementia	SCD participants with high education levels showed a slightly increased likelihood of converting to dementia compared to those with low education levels.
Jia et al. (2021)	China (Asia)	940	72	51.20 %	Three groups: Lower (≤10), Intermediate (>10 and <12) and Higher education (≥12) CR proxies: Early life education, mid-life occupation, and late-life cognitive activities	Community	24	"Have you tended to forget things recently?" and "Do you have to make more effort to remember things than you used to?	Dementia: DSM-III-R	Dementia	SCD participants with low education levels had a substantially higher risk of converting to dementia compared to those with high education levels.
Lojo-Seoane et al. (2018)	Spain (Europe)	189	66.68	67.67 %	Range from basic schooling to university studies (mean: 9.63 ± 4.45) CR: CRIq questionnaire	Clinical	18.67	Participants spontaneously reported that their memory was not as good as before	Dementia: DSM IV and/or NINCDS-ADRADA	Cognitive decline	SCD participants who converted to any cognitive decline had lower average education levels compared to those who did not convert.
Lojo-Seoane et al. (2020)	Spain (Europe)	164	65.86	68.40 %	Range from basic schooling to university studies (mean: 9.64 ± 4.58) CR: CRIq questionnaire	Clinical	36	Participants spontaneously reported that their memory was not as good as before	Dementia: DSM IV and/or NINCDS-ADRADA	Cognitive decline	SCD participants who converted to any cognitive decline had lower average education levels compared to

(*continued on next page*)

Table 1 (*continued*)

Study	Country (Continent)	N	Mean age	% of females	Level of Education or CR measure	Sample	Follow-up (months)	SCC measurement	Diagnostic Criteria (MCI/ Dementia)	Outcome	Results
											those who did not convert.
Mazzeo et al. (2019)	Italy (Europe)	154	61.3	70.77 %	Higher education (+13 years) CR: TIB test CR proxy: Premorbid intelligence	Community	84	Memory Assessment Clinics-Questionnaire (20 items), Criteria: SCD-I Working Group	MCI and Dementia: NIA-AA criteria	Both MCI and Dementia	SCD participants who converted to MCI/ dementia had lower average education levels compared to those who did not convert.
Mondini et al. (2022)	Italy (Europe)	507	78.2	65.23 %	Mean years of education: 6.99 ± 3.85 CR proxies: Education and occupation	Clinical	36+	Identified based on psychometric data, anamnestic and clinical information, Esame Neuropsicologico Breve 2 (ENB−2) battery assessment	NR	Cognitive decline	SCD participants who converted to any cognitive decline had higher average education levels compared to those who did not convert.
Qi et al. (2018)	China (Asia)	1713	71.1	69.60 %	Three groups: Illiterate, Primary school, and Junior high school or above	Clinical	512	Participants "Do you think that you have any problems with your memory?", Informants "Do you believe the subject has any problems with memory?"	MCI and Dementia: NIA-AA	Both MCI and Dementia	SCD participants with high education had a higher likelihood of progressing to MCI and converting to dementia. Low-education participants had a similar likelihood for both MCI and dementia.
Silva et al. (2014)	Portugal (Europe)	133	68.2	58.64 %	Formally educated participants	Clinical	24	SMC (25 items)	Dementia: DSM-IV-TR	Dementia	SCD participants who converted to dementia had lower education levels compared to non-converters.
Van den Kommer et al. (2008)	Netherlands (Europe)	169	73	NR	Two groups: Low education (≤Elementary education) and High education (>elementary school)	Community	36	Question asking if the patients have memory complaints or not.	NR	Cognitive decline	SCD participants with higher education had a significantly increased risk of progressing to any cognitive decline, while those with lower

(*continued on next page*)

Table 1 (*continued*)

Study	Country (Continent)	N	Mean age	% of females	Level of Education or CR measure	Sample	Follow-up (months)	SCC measurement	Diagnostic Criteria (MCI/ Dementia)	Outcome	Results
											education had a lower risk of not converting to any cognitive decline.
van Oijen et al. (2007)	Netherlands (Europe)	1309	69.5	60 %	Four groups: "Low, Low-intermediate, High-intermediate, and High education"	Community	108	Single question "Do you have memory complaints?"	Dementia: DSM-III-R, AD: NINCDS-ADRADA, vascular NINDS-AIREN	Dementia	SCD participants with high education levels had a higher risk of converting to dementia compared to those with low education levels.
Yun et al. (2020)	Korea (Asia)	107	66.6	37.38 %	Mean years of education: 8.56 ± 4.75	Clinical	60	CDR Assessment: "Do you have problems with your memory or thinking?"	Dementia: DSM 5	Dementia	Education level was not significantly associated with dementia conversion in SCD participants.

Note: N: Number of participants with Subjective Cognitive Decline; Basic schooling: 0–4 years of education; University studies: + 13 years of education; Low education: primary education; Low-intermediate education: primary education plus not completed higher education with persons with lower vocational education; High-intermediate education: intermediate vocational education with persons with general secondary education; High education: higher vocational education or university training; MCI: Mild Cognitive Impairment; NR: Not reported; SMC: Subjective Memory Complaints Scale; NIA-AA: National Institute on Aging-Alzheimer's Association; DSM -III-R: Diagnostic and statistical manual of mental disorders-Third edition-Revised; AD: Alzheimer's Disease; DSM IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; NINCDS/ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences; DSM 5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; TIB: Test di Intelligenza Breve; CRIq: Cognitive Reserve Index questionnaire

Six studies use, in addition to education, other proxy measures of CR. Among these, one study considered intelligence (Mazzeo et al., 2019) or intellectual activities as additional measures of CR (Bessi et al.,2018). Jia et al. (2021) combined early-life education, mid-life occupational complexity, and late-life cognitive activities as measures of CR, similar to Mondini et al. (2022) and Lojo-Seoane et al. (2018, 2020) that used education and occupation as main proxies of CR.

In the meta-analysis, education was operationalized as a categorical variable in four studies (Chary et al., 2013; Jia et al., 2021; Qi et al., 2018; Van Oijen et al., 2007) and as a continuous variable (i.e., years of schooling) in six studies (Bessi et al., 2018; Lojo-Seoane et al., 2018, 2020; Mazzeo et al., 2019; Mondini et al., 2022; Silva et al., 2014). Among the studies that considered education as a categorical variable: (a) one considered a binary classification approach (i.e., low education: below the elementary school and high education: secondary school or university) (Chary et al., 2013); (b) two adopted a three-tiered classification system (i.e., lower education: $\leq$10 years, intermediate education: >10 and <12 years, and higher education: $\geq$12 years in Jia et al., 2021) and illiterate, primary school, and junior high school or above in Qi et al., 2018); and (c) one employed an even higher number of categories (i.e., low, low-intermediate, high-intermediate, and high education levels) (Van Oijen et al., 2007).

3.3. Quality assessment

Regarding the quality of the selected studies for the systematic review, eight studies (66.67 %) were rated as good quality (Bessi et al., 2018; Chary et al., 2013; Lojo-Seoane et al., 2018, 2020; Mazzeo et al., 2019; Silva et al., 2014; Van den Kommer et al., 2008; Yun et al., 2020), while two studies (16.67 %) were qualified as fair (Qi et al., 2018; Van Oijen et al., 2007) and two (16.67 %) as poor quality (Jia et al., 2021; Mondini et al., 2022) (see eTable3 in the supplement).

All the studies met the quality criteria evaluated through the following questions: (a) "Was the research question or objective in this paper clearly stated?"; (b) "Was the study population specified and defined?"; (c) "Was the participation rate of eligible persons at least 50 %?"; (d) "Were all the subjects selected or recruited from the same or similar populations (including the same period?"; (e) Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?"; (f) "For the analyses in this paper, were the exposure(s) of interest measured before the outcome(s) being measured?"; and (g) "Was the exposure(s) assessed more than once over time?".

Only one study (8.33 %) provided a sample size justification, power description, or variance and effect estimates (Chary et al., 2013), and none reported blinding strategies to conceal participants' status from outcome assessors.

3.4. Systematic review

Almost all selected studies concluded that education alone or together with other CR proxies decreases the risk of progression toward objective cognitive impairment (Bessi et al., 2018; Jia et al., 2021; Lojo-Seoane et al., 2018, 2020; Mazzeo et al., 2019; Mondini et al., 2022; Qi et al., 2018; Silva et al., 2014; Van den Kommer et al., 2008; Yun et al., 2020). Some of them reported that SCD participants with

higher CR delayed the onset of MCI (Mazzeo et al., 2019) or dementia (Bessi et al., 2018, Jia et al., 2021) by 2–9 years in comparison to those with lower CR. Consistent with the previous results, other studies found that: a) a high level of CR predicts better levels of cognitive performance after three years compared to participants with a low level of CR (Lojo-Seoane et al., 2018, 2020; Mondini et al., 2022) and b) lower education in SCD participants increased the risk of progression to objective cognitive decline more than three years of follow-up (Van den Kommer et al., 2008; Qi et al., 2018) or conversion to dementia after more than two years of follow-up (Silva et al., 2014; Yun et al., 2020).

Only 2 studies showed discrepant results pointing out that a higher educational level in SCD increased the risk of dementia after three years (Chary et al., 2013) or progression to AD after nine months of follow-up (Van Oijen et al., 2007).

3.5. Meta-analyses

Out of the 10 studies included in the meta-analysis, three reported sufficient data to meta-analyze conversion risk separately in low and high-education groups (Chary et al., 2013; Jia et al., 2021; Van Oijen et al., 2007). Besides, an additional study by Qi et al. (2018) did not report an overall conversion rate. Instead, it reported rates of conversion to MCI and dementia separately. Therefore, separate meta-analyses were conducted with the inclusion of Qi and colleagues' study (2018) for conversion to MCI and dementia. The result of this analysis showed a consistent association of SCD with conversion in both education strata. In the low education group, the pooled Risk Ratios (RRs) for SCD were, respectively, 1.61 (95 % CI 1.04–2.49, p = 0.03) and 1.62 (95 % CI 1.0 – 2.62, p = 0.05) depending on whether the results of the study by Qi et al. (2018) were incorporated or not. Some heterogeneity (I^2 approximately 63 % and the Q-test $p = 0.04$) was observed in both analyses for the low education stratum. Fig. 2 presents a forest plot for the low-education group that includes dementia conversion data from Qi et al. (2018).

Similarly, in the high education group, the combined RRs for SCD were respectively 1.40 (95 % CI 1.12 – 1.75, p < 0.001) and 1.58 (95 % CI 1.24 – 2.01, p < 0.001), depending on whether the results of the study by Qi et al. (2018) were incorporated or not (see Fig. 3).

Out of the ten studies included in the meta-analysis, six reported mean education level and the associated SD among converters and non-converters, though Bessi et al. (2018) separately reported mean education for those converting to MCI or dementia. Mean education level and SD were calculated as a weighted mean and weighted SD for Bessi et al. (2018), weighting these estimates by the number of converters to MCI and dementia. The mean differences are presented in the forest plot (Fig. 4). Despite the reversed direction of effect observed in the study reported by Mondini et al. (2022), there is no evidence of statistical heterogeneity, with both T^2 and I^2 rounding to zero and the I^2 estimate not being statistically significant according to the Q test ($Q = 3.86$, $df = 5$, $p = 0.57$). As displayed in Fig. 4, the confidence intervals associated with this study (Mondini et al., 2022) are consistent with a range of population values overlapping with those of the other studies. The pooled estimate of the mean difference was −2.0 ($z = -5.34$, $p < 0.001$) indicating that, on average, the converters had two fewer years of education than the non-converters in these studies. Judging by the confidence limits, the estimates in this literature are consistent with a difference as small as 1.3 years or as large as 2.7 years at the 95 % level of confidence.

Methodologically, the study developed by Mondini and colleagues (2022) was characterized by high attrition (95 %), creating the possibility of methodological heterogeneity, but also leading to imprecision. In a sensitivity analysis with this study excluded there was little change in the observed mean difference, which became −2.1 years (*95 % CI*: −1.4 – −2.9) in this analysis.

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis aimed at investigating the influence of education on the estimation of the risk of SCD progression towards objective cognitive impairment.

Among the selected studies for the systematic review, almost all studies (Bessi et al., 2018; Jia et al., 2021; Lojo-Seoane et al., 2018, 2020; Mazzeo et al., 2019; Mondini et al., 2022; Qi et al., 2018; Silva et al., 2014; Van den Kommer et al., 2008; Yun et al., 2020) consistently support the idea that higher education and other CR proxies are associated to later onset and reduced risk of objective cognitive decline, including progression to MCI or conversion to dementia. Furthermore, our results support that people with SCD with higher levels of education compared to those with lower education appeared to delay the progression of objective cognitive decline over a period ranging from two to nine years.

These results are consistent with those hypothesized from Stern's CR model (Stern et al., 2020), which proposes that higher education levels may enhance CR, which enables individuals to better counteract the gradual brain changes associated with aging and neurodegenerative diseases. Thus, they could be more resilient against the cognitive effects of AD and other dementias, potentially delaying the onset of the disease or reducing the severity of its symptoms.

Our results also coincide with previous longitudinal studies carried out in participants without cognitive impairment and with those that

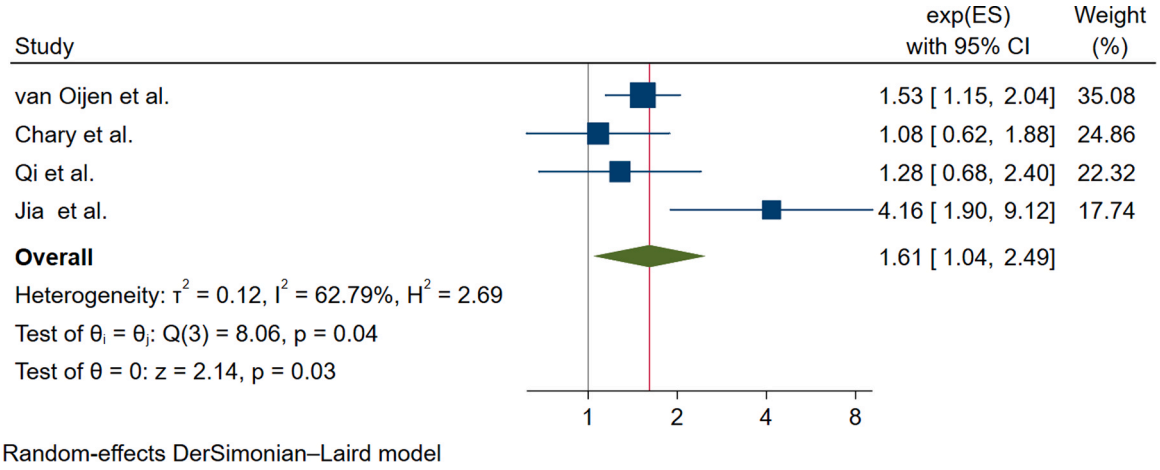

Fig. 2. Association of SCD with conversion to MCI or dementia: low education group. Note: All the studies reported OR except van Oijen et al. (2007) which reported HR.

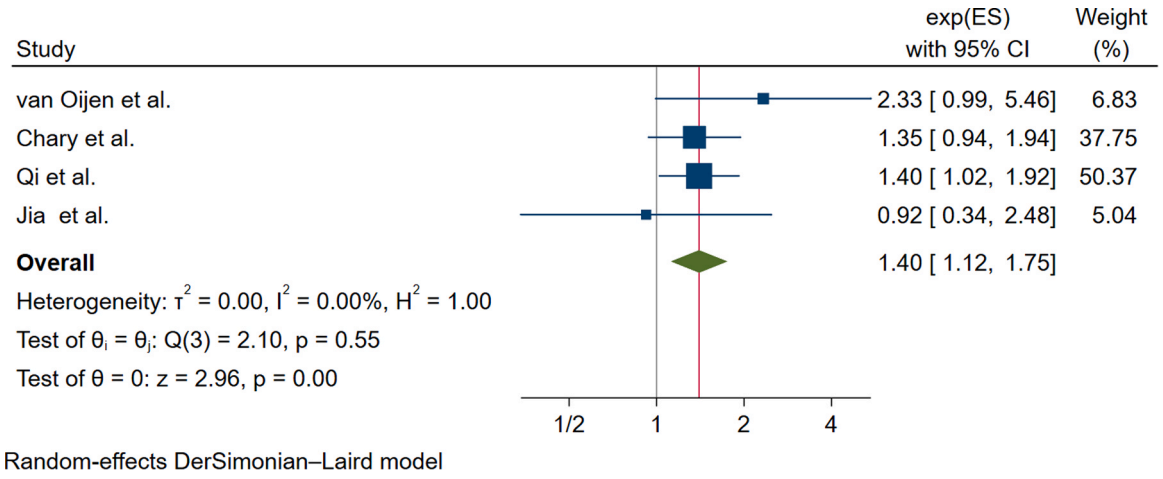

Fig. 3. Association of SCD with conversion to MCI or dementia: high education group. Note: All the studies reported OR except van Oijen et al. (2007) which reported HR.

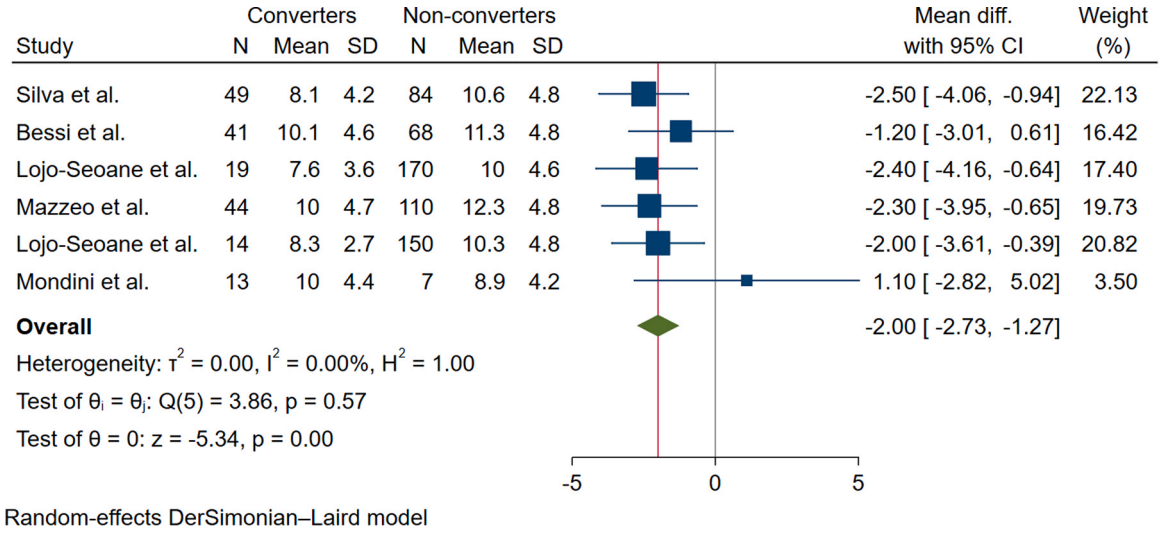

Fig. 4. Mean differences for years of education in SCD participants converters and non-converters in six longitudinal studies.

implement cross-sectional designs in SCD. Thus, Amieva et al. (2014) showed that cognitively normal individuals with higher education exhibited a slower decline over 15 years before meeting the criteria for dementia, whereas those with lower education experienced a more rapid cognitive decline of 7 years before dementia onset. Cross-sectional evidence also suggests that higher education in participants with SCD can reduce the risk of progression to objective cognitive decline, MCI, or dementia (Crumley et al., 2014; Hao et al., 2017, 2019; Yang et al., 2020).

However, the findings were not universally consistent. Two studies pointed out that higher education could, paradoxically, raise the risk of transition to AD or dementia (Chary et al., 2013; Van Oijen et al., 2007). These results agree with those reported in previous studies (Aghjayan et al., 2016; Jonker et al., 2000; Rabin et al., 2017) and could give some support to the hypothesis that predicts a better estimate of cognitive changes in older adults with higher education (Hertzog et al., 2008).

The first meta-analysis calculated the risk of progression separately in low and high-education groups and pointed out that SCD is associated with a higher frequency of conversion irrespective of education level. The confidence interval leans more favorably toward those with lower education levels, suggesting a comparatively higher likelihood of progression in this subgroup. These results align with the CR hypothesis (Stern et al., 2020) and the available evidence on the reduction in the risk of progression or delay in the cognitive symptoms onset associated with education (Amieva et al., 2014; Ye et al., 2013; Yu et al., 2012), although it does not eliminate the possibility of suffering from dementia.

A second meta-analysis conducted by calculating standardized mean education differences between converters and non-converters indicated that converters had two years fewer of education than non-converters. Again, these findings are consistent CR hypothesis (Stern et al., 2020) showing that lower education/CR is associated with an increased risk and early onset of cognitive symptoms linked to dementia compared to higher education. However, our results do not support the hypothesis that the higher the educational level in SCD, the greater the risk of conversion to dementia (Aghjayan et al., 2016; Jonker et al., 2000; Rabin et al., 2017). This effect could be particularly evident in the more advanced stages of the disease when CR is exhausted, leading to a more rapid progression, especially among individuals with higher education levels (Mungas et al., 2018; Zahodne et al., 2019). However, this phenomenon does not seem to manifest itself in SCD, a stage in which complaints are interpreted as possible early symptoms of dementia.

In conclusion, our study provides valuable insights into the link between SCD and education and its progression to objective cognitive decline, MCI, or dementia. However, due to the limited studies available, our findings are tentative. Future research is necessary to fully understand the multifaceted and intricate relationship between

education and SCD (Rabin et al., 2017).

5. Strengths and limitations

5.1. This research possesses several strengths

Primarily, to our knowledge it is the first systematic review and MA that pioneers a comprehensive investigation into the influence of education on the predictive validity of SCCs for cognitive decline, MCI, and dementia.

The research methodology adheres rigorously to established guidelines, such as PRISMA (Page et al., 2021) and MOOSE (Stroup et al., 2000) protocols. The employed techniques are robust, involving multiple reviewers at each stage, with abstract and full-text evaluations, as well as study quality assessments. The statistical methods employed also reflect this rigor, as the pooled mean difference is quantified using appropriate measures of significance.

Despite the limited number of studies included, the meta-analysis results showed no heterogeneity and remained statistically significant, enhancing the robustness of the findings.

Finally, this study holds significant clinical relevance by highlighting the importance of early detection in individuals with SCD, especially concerning their education level. The findings emphasize the pivotal role of educational training in the later stages of life and its significance in preventing cognitive decline (Peeters et al., 2020).

In the realm of research, this study deepens our understanding of prediction and identifying key risk and delaying factors associated with the progression from SCD to dementia. These insights enhance our grasp on the complexities of this transition, thereby guiding future investigations and interventions effectively.

Despite the strengths of our systematic review and meta-analysis, some limitations should be considered.

Firstly, the studies incorporated in this systematic review were characterized by considerable heterogeneity in terms of their methodological approaches. This heterogeneity may introduce variations in the results so the findings should be handled with caution.

Additionally, it is also worth mentioning that, despite having contacted several authors to provide us with missing information and quantitative data for SCD participants progressing to MCI or dementia stratified by level of education, we did not get a response.

Further, a major limitation not only in our study but also in the broader field of SCD research, is the absence of a standardized measure for SCD due to its lack of operationalization. Studies employed in the meta-analysis used varied measures, ranging from single-item questions capturing subjective memory decline to utilizing the SCD-1 criteria outlined by the Jessen study (Jessen et al., 2014). The existence of diverse definitions and criteria might have introduced further heterogeneity in our study.

Another limitation of our study arises from the relatively limited number of studies available for inclusion. As a result, we were unable to employ funnel plots or other statistical methods to assess potential publication bias, which could impact the validity and generalizability of our findings.

Moreover, the quality assessment of the included studies revealed that while eight studies were rated as good, two were considered fair, and two of them were deemed poor in terms of quality. This discrepancy underscores the need for further development of high-quality studies on this subject to strengthen the reliability of conclusions.

Finally, in this meta-analysis, we considered studies regardless of whether participants progressed to cognitive decline, MCI, or dementia after the follow-up period (all of them were considered converters). Unfortunately, due to the insufficient number of studies to conduct separate meta-analyses, all the data regarding evolution to cognitive decline, MCI, or dementia were combined. Since the number of studies was small, we couldn't perform further analyses, such as by sample type or gender/sex.

6. Conclusions

In conclusion, our systematic review and meta-analysis suggest that education has a reducing effect on the probabilities of progression in SCD. Furthermore, the supposed greater accuracy in detecting truly cognitive decline attributed to participants with a high educational level and better metacognitive skills does not seem capable of neutralizing the positive effect of CR in SCD.

Understanding the influence of education on cognitive outcomes is crucial for promoting cognitive health among individuals as they age, and implementing educational activities at any stage of life may be an effective strategy for prevention. More research on the topic is essential to understand the evolution of this delaying effect and the variables that may enhance it.

CRediT authorship contribution statement

Sonali Arora: Methodology, Writing – original draft. **Scott B. Patten:** Methodology, Quantitative analysis. **Sabela C. Mallo:** Methodology, Writing-review, and editing. **Cristina Lojo-Seoane:** Methodology. **Alba Felpete:** Writing-Review and editing. **David Facal-Mayo:** Writing-review and editing. **Arturo X. Pereiro:** Methodology, Writing – review and editing.

Declaration of Competing Interest

The authors declare that they have no financial or personal relationships with other people or organizations that could inappropriately influence the work reported in this paper. The authors do not have any competing interests such as employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, or grants or other funding that could be perceived as conflicts of interest in connection with this work.

The authors confirm that there are no potential competing interests to disclose.

Data availability

Data will be made available on request.

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Disclosure statement

The authors have no conflicts of interest to report.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2024.102487.

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