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Subjective Cognitive Decline: Level of Risk for Future Dementia and Mild Cognitive Impairment, a Meta-Analysis of Longitudinal Studies

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Running title: SCD and cognitive decline

Abstract

Subjective Cognitive Decline (SCD) in older adults has been identified as a risk factor for dementia, although the literature is inconsistent, and it is unclear which factors moderate progression from SCD to dementia. Through separate meta-analyses, we aimed to determine if SCD increased the risk of developing dementia or mild cognitive impairment (MCI). Furthermore, we examined several possible moderators. Longitudinal studies of participants with SCD at baseline, with data regarding incident dementia or MCI, were extracted from MEDLINE and PsycINFO. Articles were excluded if SCD occurred solely in the context of dementia, MCI, or as part of a specific disease. Pooled estimates were calculated using a random-effects model, with moderator analyses examining whether risk varied according to SCD definition, demographics, genetics, recruitment source, and follow-up duration. Risk of study bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies(QUADAS)-2 tool. 46 studies with more than 74, 000 unique participants were included. SCD was associated with increased risk of developing dementia (HR = 1.90, 95% CI: 1.52-2.36; OR = 2.48, 95% CI: 1.97-3.14) and MCI (HR = 1.73, 95% CI: 1.18-2.52; OR = 1.83, 95% CI: 1.56-2.16). None of the potential moderating factors examined influenced the HR or OR of developing dementia. In contrast, including worry in the definition of SCD, younger age, and recruitment source impacted the OR of developing MCI, with clinic samples demonstrating highest risk. SCD thus represents an at-risk phase, ideal for early intervention, with further research required to identify effective interventions for risk reduction, and cognitive-behavioural interventions for cognitive management. PROSPERO, protocol number: CRD42016037993

Keywords: subjective memory changes; memory complaints; Alzheimer's disease; mild cognitive impairment; dementia; risk factors

Declarations

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Conflicts of interest/Competing interests

None. The funding source had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Availability of data and material

Data is available from Kerryn Pike on reasonable request.

Code availability

Not applicable

Authors' contributions

Kerryn Pike had the idea for the review. Literature search, data-extraction, and quality analysis were performed by Kerryn Pike and Marina Cavuoto. Data analysis was performed by Kerryn Pike and Brad Wright. The first draft of the manuscript was written by Kerryn Pike and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Dementia is one of the most important current health issues, afflicting nearly 50 million worldwide (Prince et al., 2015), and with immense impact on the person, their family and caregivers, and society. Dementia is the leading cause of disability for older adults (Australian Institute of Health and Welfare, 2012), one of the leading causes of mortality (Alzheimer's Association, 2019; Australian Bureau of Statistics, 2016), and has an economic impact of > US$950 billion worldwide (Jia et al., 2018). Given that age is the greatest risk factor for dementia, and people are living longer, the impact of dementia is predicted to increase, with prevalence expected to triple by 2050 (Prince et al., 2015). Despite this, dementia remains the only disease in the top ten causes of death without a reliable method of prevention, slowing, or cure, and therefore interventions to alter the disease course are a top priority for governments and researchers alike.

Interventions will be most effective as early in the disease process as possible, when there is minimal pathology, and fewer behavioural and cognitive symptoms. This applies to both pharmacological treatments (e.g., Alzheimer's Drug Discovery Foundation, 2018), as well as nonpharmacological therapy (e.g., Bahar-Fuchs et al., 2019), such as cognitive-behavioural memory groups (e.g., LaTCH memory group; Kinsella et al., 2016), and risk reduction interventions (Isaacson et al., 2018; Livingston et al., 2020). Alzheimer’s disease (AD) is the most common cause of dementia (Alzheimer's Association, 2019), and, as such, has been researched the most extensively of all dementias. With the advent of reliable biomarkers, it has become clear that AD exists on a continuum of severity, with a long preclinical and prodromal period occurring for approximately 14 years (Vermunt et al., 2019) before symptoms become severe enough to meet criteria for AD dementia (Jack et al., 2018).

Current research guidelines identify six clinical stages of AD (Jack et al., 2018). AD dementia occurs in stages 4-6 (mild, moderate, and severe dementia). Stage 3, the most proximal stage to AD dementia, is the prodromal disease stage usually labelled mild cognitive impairment (MCI; Jack et al., 2018). In this stage, there is concern about cognitive change, which is supported by objective evidence of cognitive impairment, in the absence of dementia, and with relative preservation of functional independence. MCI is associated with approximately triple the risk of developing AD dementia within 2-5 years, although many cases of MCI never develop AD dementia, or any form of dementia (Petersen et al., 2018). Stage 2 reflects a transitional period for individuals with preclinical AD, where cognition is not completely normal (*vs* Stage 1 – no cognitive impairment) but they do not yet meet MCI criteria (Stage 3). In this stage, individuals experience a decline from their previous level of cognitive functioning, but performance remains within the expected normative range on objective neuropsychological tests (Jack et al., 2018). Change may be evident through subjective report of cognitive decline (SCD), or subtle evidence of decline on longitudinal testing, or both (Jack et al., 2018).

Recent work supports the proposition that SCD is one of the earliest symptoms of AD, which may reflect underlying brain changes consistent with AD, including β-amyloid imaging, atrophy, micro-structural changes, and functional activation changes (Chételat et al., 2010; Erk et al., 2011; Jessen et al., 2006; Meiberth et al., 2015; Rodda et al., 2009; Ryu et al., 2017). Furthermore, there is developing evidence that people with SCD demonstrate subtle reduction in cognition on everyday tasks that involve multiple cognitive domains (Lee et al., 2018; Pike et al., 2015). Most compelling regarding the role of SCD in preclinical AD is a meta-analysis reporting that SCD approximately doubles the chance of developing dementia (RR = 2.01 [1.76-2.44]; Mitchell et al., 2014).

Mitchell et al.'s (2014) findings on the relative risk of SCD for development of dementia were based on the synthesis of 14 studies (18, 830 participants), with an average follow up of 5 years. This duration is a relatively short period in the evolution of dementia, with studies suggesting SCD may occur up to 15 years prior to MCI (Molinuevo et al., 2017), which itself occurs several years before the diagnosis of dementia. Hence, follow-up studies of only 5 years may not identify people who would have developed dementia further down the track. Thus, it would be useful to know the relative risk of conversion to earlier stages in the AD process – i.e. MCI. Although Mitchell et al. (2014) reported on the annual conversion rate of people with SCD to MCI (6.67%), we do not know how this compares to older adults without SCD, as relative risks were not calculated. Understanding the relative risk of SCD for developing MCI is important because MCI is an earlier outcome in the disease process, circumventing the longer (and costlier) duration of follow-up required to detect dementia.

Despite evidence that SCD is a risk factor for dementia, it is unclear which factors impact the progression from SCD to dementia. SCD is highly heterogeneous, with many possible underlying causes besides preclinical dementia, including psychiatric disorders, neurological and medical conditions, and medication or substance effects (Jessen et al., 2014; Molinuevo et al., 2017). Therefore, it is important to identify factors that increase the risk that an individual presenting with SCD will develop objective cognitive decline and dementia, to ensure better targeting of therapy.

There is a high degree of heterogeneity in the way SCD is defined, including a wide variety of measures used to classify SCD, with very little overlap between studies (Rabin et al., 2015). Further analysis of how various aspects of SCD definition may influence outcome is crucial to advance the field. There is currently no consensus regarding the gold standard measurement of SCD (Molinuevo et al., 2017), thus any information regarding whether the type of measure used moderates the risk of future cognitive decline would help researchers choose appropriate measures. Studies vary in terms of whether SCD classification is based on a single question, response to a questionnaire, or based on clinical interview. Use of a single question to define SCD provides a dichotomised variable, whereas a continuous variable based on a scale provides more variability on important factors such as the frequency or severity of symptoms, although there is currently no agreed upon cut-off scores for the SCD threshold (Molinuevo et al., 2017).

Jessen et al. (2014) provided a list of factors suggested to increase the likelihood of preclinical AD in individuals with SCD, which largely focus on the way SCD is operationalised. Subjective decline in memory is more suggestive of preclinical AD, which is consistent with MCI research suggesting objective memory impairment relates to higher conversion to dementia, whereas objective impairment in non-memory domains may be more indicative of preclinical stages of atypical AD and non-AD dementia (Busse et al., 2006; Yaffe et al., 2006). Additionally, the likelihood that SCD represents preclinical AD is believed to be increased by onset of SCD within the last 5 years, age of onset >59 years, particular concerns or worry regarding SCD; perception that performance is worse than peers; persistence of SCD over time; seeking medical help for SCD; confirmation of decline by an informant, presence of the apolipoprotein E (APOE) ε4 genotype, and biomarker evidence for AD (Jessen et al., 2014; 2020).

Although the latest research criteria focus on decline in subjective cognition, many previous studies have not required decline in cognition. Instead, some studies have instead captured dissatisfaction with current cognition. Given the progressive nature of AD, it might be expected that definitions capturing perceived decline might carry a higher risk of future decline, however, this needs to be explored. A final important aspect of SCD classification to consider is whether and how psychiatric and mood associations were managed. An association between SCD in older adults and elevated symptoms of anxiety and depression is often reported (Buckley et al., 2013; Yates et al., 2017; Zlatar et al., 2018), but the relationship between SCD and psychiatric disorders is complex (Jessen et al., 2014; Rabin et al., 2017). Some of this complexity relates to different approaches in managing mood, including which aspects are managed (depression, anxiety, other psychiatric disorders), whether past history as well as current diagnosis or symptoms are considered, and whether it is an exclusion criterion, or recorded and controlled for in analyses. To date, whether mood moderates the relationship between SCD and decline over time is unclear.

In terms of demographic risk factors, AD dementia is associated with increased age (Prince et al., 2015), lower educational attainment (Livingston et al., 2020), and female gender (Mazure & Swendsen, 2016; Mielke et al., 2014). Similar demographic risk factors are observed for MCI, although gender differences are unclear (Petersen et al., 2018). It is important to establish whether demographic factors influence whether SCD leads to cognitive decline. Carriage of the ε4 allele of APOE is the strongest genetic risk factor for late-onset AD (Harold et al., 2009; Saunders et al., 1993), and Jessen et al. (2014) suggest it is a factor increasing the likelihood of preclinical AD pathology in individuals with SCD.

Another important factor is the population or setting from which SCD samples are recruited (Rodríguez-Gómez et al., 2015). Factors such as age, education, family history, level of concern regarding SCD, and change represented by SCD all vary by setting, and likely contribute to differences in the risk of MCI or dementia. In the current literature, people with MCI recruited from a memory clinic setting have a greater rate of conversion to dementia than those from epidemiological studies (Petersen et al., 2009). Similarly, Vermunt et al. (2019) reported shorter disease duration (or faster conversion from preclinical to clinical stages) in clinic settings. Mitchell et al. (2014) examined recruitment setting impact on annual conversion rate of people with SCD to dementia or MCI, and found no significant differences; although they did not examine impact of setting on relative risk – i.e. risk when compared to people without SCD. The SCD literature typically includes studies from three broad recruitment sources – memory clinics, volunteers from advertisements in the community, and volunteers from a randomly selected sample from the community. Given the findings in MCI, we would expect the relative risk to be highest in clinic samples, followed by community volunteers, and finally those from epidemiological studies. This is supported by the findings of a recent study demonstrating increased risk of incident MCI in people with SCD recruited from a memory clinic compared to those from a population study (Snitz et al., 2018).

Longitudinal studies vary greatly in their length of follow-up, which is important in the detection of outcomes given the evolving nature of AD. Given that cognitive decline and dementia are more common as one ages, it might be expected that longer duration follow-up would lead to higher risk of SCD leading to cognitive decline. On the other hand, the impact of duration might be the same for older adults without SCD – i.e. the relative risk of SCD may not change over time. Furthermore, there is some belief that the risk of SCD evolving to AD dementia is greatest within the first five years of SCD onset (Jessen et al., 2014; 2020). Thus, the relative risk of SCD leading to AD may be reduced in studies with longer follow-up, and duration of follow-up was considered an important variable to examine.

The final consideration was in terms of the relationship of SCD to risk of specific dementia subtypes. It might be expected that SCD would confer a different relative risk for different types of dementia, and that the moderating factors might vary, given different demographic, genetic, and symptom profiles of the different dementias.

Thus, although Mitchell et al.'s (2014) meta-analysis has provided highly useful information regarding the outcome of SCD, there are several important gaps that the current meta-analysis will address, as well as providing an update with the addition of papers published since March 2014. The primary objective of the current meta-analysis was to determine if, and to what degree, subjective cognitive decline (SCD) is a risk factor for future cognitive decline. We asked three separate, but related research questions: a) Is SCD a risk factor for the development of dementia; b) Is SCD a risk factor for the development of MCI; and c) Is SCD a risk factor for future changes in objective cognition? Due to the scale of literature involved, the question of whether SCD is a risk factor for future changes in objective cognitive will be addressed in a future manuscript. Our secondary objective in this study was to investigate potential sources of heterogeneity in the level of risk bestowed by SCD including how SCD was classified; demographic and genetic factors; recruitment source; and length of follow-up.

Methods

Protocol Registration

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). The protocol for the present meta-analysis is registered on the International Prospective Register of Systematic Reviews PROSPERO (http://www.crd.york.ac.uk/PROSPERO, protocol number: CRD42016037993), registration date 20th April 2016.

Eligibility Criteria

Studies were eligible for inclusion in the meta-analysis if they were published in English, involved a longitudinal (at least 6 months post-baseline) design, and measured SCD at baseline. SCD could be any form of subjectively reported cognitive impairment, i.e. decline or broader dissatisfaction with cognition. Furthermore, there needed to be comparison of at least one of the following outcome measures, related to level of baseline SCD: a) rate of incident dementia; b) rate of incident MCI. To ensure that articles were addressing SCD in an appropriate context (as a risk factor for future cognitive decline and dementia) we excluded articles with participants less than 18 years at baseline, those where SCD only occurred as part of MCI or dementia at baseline, and any regarding SCD occurring as part of another specific disease (for example following stroke, epilepsy, post-cancer). In order to obtain appropriate data for our research questions, articles not reporting data in an appropriate effect size were excluded (authors of these articles were contacted to try and obtain appropriate data), as were conference abstracts, and articles without a control group of participants without SCD. Finally, to ensure we were including independent data sets, we excluded any articles that were not reporting original, empirical studies (e.g. reviews, comments, erratum).

Search Strategy

Included articles were identified by a systematic search strategy of the Ovid MEDLINE (1946-present) and PsycINFO (1987- present) databases, up to 17th October 2020. A set of keywords was created for each database (see Appendix A) to identify longitudinal studies examining SCD within ageing. The searches were limited to articles published in English and concerning a human population. In addition, Mitchell et al.'s (2014) list of included studies was scrutinised for any additional studies missed by our search.

Study Selection

Two reviewers (KP and MC) independently screened the titles and abstracts of all articles to determine possible eligibility, and reasons for exclusion. Any disagreements were resolved by consensus, or the article was obtained for closer inspection. The two reviewers then each examined half of the articles retrieved for closer inspection to determine eligibility. Any unclear cases were discussed to reach consensus. Multiple reports from the same data set were identified, and only one report selected to be analysed for each of the research questions. The selection was made using the following criteria (in order): a) data provided in an appropriate format to calculate effect sizes; b) longer follow up period; c) larger sample size; d) most recent publication. Appendix B lists the reports identified from the same cohort and indicates included and excluded reports regarding the outcomes of dementia or MCI.

Data Extraction

Two reviewers (KP and MC) each independently extracted and coded data from half of the included articles, using a data collection form and associated coding manual. The form and manual were piloted on a random selection of 3 studies prior to conducting the full review. The reviewers independently confirmed the accuracy of the other reviewer's data extractions, and discrepancies were discussed and resolved by consensus. The following data were extracted:

a) Outcome. We were interested in two different outcomes, and each individual study may have provided information regarding either or both outcomes. Sample size of the SCD and control groups were extracted for all outcomes where possible. Data extracted according to each outcome was as follows:
    i) Rate of incident dementia. Data was extracted as either number of people with and without SCD who developed dementia; hazard ratio; odds ratio; or relative risk ratio of developing dementia. The type of incident dementia, as percentage of Alzheimer's dementia, was extracted where available.
    ii) Rate of incident MCI. Data was extracted as either number of people with and without SCD who developed MCI; hazard ratio; odds ratio; or relative risk ratio of developing MCI.
b) Potential moderators: Data on factors which might influence the size of the relationship between SCD and risk of future decline were also extracted from each study including how SCD was diagnosed (including whether decline or worry was captured in the definition;

whether SCD was defined using a single question, multiple questions or a scale, interview, or assumed due to presentation at a memory clinic), sample characteristics (age, education, gender, APOE genotype, country), recruitment source (representative community sample, volunteers from community, volunteers from a clinic), and length of follow up. Whether mood was considered was also extracted in terms of whether studies excluded participants based on mood (current symptoms, current mood disorder, past mood disorder), or controlled for mood statistically in the reported effect size.

Twenty-five authors were contacted via email in cases of incomplete data relating to calculation of appropriate effect sizes, cohort overlap, follow-up duration, or to clarify measurement of SCD. Seven authors responded and provided the requested data (Ebenau et al., 2020; Jorm et al., 1997; Kryscio et al., 2014; Maruta & Martins, 2019; St John & Montgomery, 2002; van Harten et al., 2018), including Tomata et al. (2016) who provided a copy of a then in-press article (Tomata et al., 2017) which provided relevant data, and was included in the synthesis.

Risk of Bias in Individual Studies

During data extraction, the two reviewers (KP, MC) also assessed risk of bias of each individual study, thus performing the initial assessment on half of the articles and cross-checking those of the other reviewer, with discrepancies resolved through discussion. Risk of bias items were part of the data extraction form and piloted as above. The methodological quality of each study was assessed using the (QUADAS)-2 tool (Whiting et al., 2011), modified to be specific to the content of the current review. The QUADAS-2 tool consists of four domains which are assessed in terms of risk of bias: patient selection, index test (SCD), reference standard (diagnosis of dementia or MCI), and patient flow and timing. The signalling questions used to help judge the risk of bias within each domain are provided in Appendix C. If the answers to any of these questions was negative, then the study was assigned a high level of bias. The first three domains are also considered in terms of applicability to the review question. QUADAS-2 was not used to generate summary quality scores, because of the well-established issues with such scores (Cooper, 2010; Whiting et al., 2005), but was used to produce a narrative summary and table describing the level of bias (high, low, unclear) for each included study according to each domain.

Data Analysis

Comprehensive Meta-Analysis (CMA) Version 3.0 (Borenstein et al., 2013) was used to perform the data synthesis. Separate data syntheses were performed according to each outcome (dementia; MCI) and effect size type. Specifically, odds ratio, relative risk, and raw data were combined using the formulae embedded in the CMA software and the hazard ratios were examined separately as this measure involves time-to-event data and censoring other variables earlier in the analysis and as such, combining with effect measures such as odd or risk ratios is not appropriate (Deeks, Higgins, & Altman, 2021l). We planned to examine development of incident Alzheimer's disease compared to other dementias separately if there were sufficient data. All syntheses used random effects models, given the expected heterogeneity in the included studies. Heterogeneity was assessed using I^2, tau, and Cochran's Q statistic, with I^2 values of .25, .50, and .75 corresponding with low, moderate, and high levels, respectively (Higgins et al., 2003). Publication bias was assessed visually with separate funnel plots for each analysis, as well as quantified using Egger's regression test (Egger et al., 1997) and Duval and Tweedie's (2000) trim and fill. The fail-safe *N* (Rosenthal, 1979) was used to determine the robustness of the findings by computing how many additional studies with an effect size of 0 would render significant findings non-significant. Sensitivity analyses were run, excluding studies with high levels of bias, to determine any impact on overall findings.

Moderators of effect sizes were examined for the following covariates: SCD definition (SCD question type [single question, multiple questions, scale, interview, presentation to clinic], cognitive domain, decline in SCD definition, worry in SCD definition, control of mood disturbance; subgroup analysis); demographic and genetic factors (age, education, gender, APOE genotype; meta-regression); recruitment source (subgroup analysis); and follow-up duration (meta-regression). Control of mood disturbance was examined as a dichotomous moderator, with studies that controlled mood disturbance either statistically or by exclusion criteria grouped together and compared to those with no control. Given that multiple tests of moderation may inflate Type 1 error (Higgins and Thompson, 2004), we chose a conservative alpha level of .01 as the criterion for statistical significance for these analyses.

Results

Study Selection

The literature searches yielded 4, 296 potentially relevant records to examine. Initial screening of the titles and abstracts of these papers, and exclusion of duplicates, resulted in 174 papers where the full text was retrieved for closer inspection. Reapplication of the exclusion criteria resulted in 64 papers eligible for inclusion in the quantitative synthesis, 46 of which had data relating to dementia or MCI as an outcome and are included in the current paper. More detail is provided in the PRISMA flow chart in Figure 1.

(Fig 1 approximately here)

Characteristics of Included Studies

Incident Dementia. Thirty-seven included studies provided effect size data relevant to development of incident dementia (see Table 1). Fifteen studies provided hazard ratio data, and 22 studies provided odds ratio, or data that could be used to calculate an odds ratio, hence two separate syntheses were performed, overall representing 70, 022 participants. As shown in Table 1, studies came from a range of countries including 9 from North America, 22 from Europe, 2 from Australia, and 4 from Asia with sample size ranging from 26-13,974.   Average baseline age of participants was 73 years (mean range 60-83), with 61% female (mean range 37-86%), 11 years education (mean range 1-18), and 28% APOE e4 carriers (mean range 7-55). Twenty-one of the studies recruited randomly from the community, 7 recruited volunteers from the community, and 9 recruited from specialist memory clinics. Average prevalence of SCD in the sample was 44% (range 5-84%). Average follow up duration varied from 12 – 180 months (average 5.2 years). Average progression to dementia was 10% (range 1-23%).

(Table 1 approximately here)

Included studies also varied in the way that SCD was defined, as shown in Table 2. Method of defining SCD varied, with 16 studies using response to a single targeted question, 13 using response to a few questions or specific SCD scale, 3 using clinical interview in conjunction with a scale, and 5 studies assuming SCD based on presentation to a memory clinic or report to a medical professional. Thirty-one studies focused on episodic memory as the domain of SCD. Thirteen of the studies included specific reference to cognitive decline and 7 included concern or worry. Four studies excluded participants at baseline with current mood disorder, another 3 studies excluded past or current mood disorder, an eighth study excluded participants with elevated symptoms on the Geriatric Depression Scale at baseline, and another excluded participants with past mood disorder, baseline mood disorder, or baseline elevated symptoms on the Hamilton Depression Scale. An additional 11 studies did not exclude based on mood disturbance, but controlled for it statistically when calculating the effect size.

(Table 2 approximately here)

Incident MCI. Fifteen included studies provided effect size data relevant to development of incident MCI (see Table 3). Four studies provided hazard ratio data, and 11 studies provided odds ratio, or data that could be used to calculate an odds ratio, hence two separate syntheses were performed, overall representing 14, 278 participants. As shown in Table 3, studies were all from North American or European countries, with sample size ranging from 32-4414. Average baseline age of participants was 73 years (mean range 61-81), with 61% female (mean range 44-76%), 12.8 years education (mean range 8-17), and 28% APOE e4 carriers (mean range 19-55). Five of the included studies recruited randomly from the community, six recruited volunteers from the community, and four recruited from specialist memory clinics. Average prevalence of SCD across studies was 46% (range 10-77%). Average follow up duration varied from 13 – 96 months (mean 4 years). Average progression to MCI was 15% (range 7-48%).

(Table 3 approximately here)

Included studies also varied in the way that SCD was defined, as shown in Table 4. Six studies used response to a single targeted question to define SCD, 4 studies used clinical interview (3 also including a scale), with 3 studies using a scale alone, another using a few questions, and another study assuming SCD based on presentation to a memory clinic. Ten studies focused on episodic memory as the domain of SCD. Eight of the studies included specific reference to cognitive decline and 5 included concern or worry. Two studies excluded participants at baseline with current mood disorder, a third study excluded participants with past mood disorder, baseline mood disorder, or baseline elevated symptoms on the Hamilton Depression Scale, and another study excluded participants with baseline elevated symptoms on the Geriatric Depression Scale. A further two studies did not exclude based on mood disturbance, but controlled for it statistically when calculating the effect size.

(Table 4 approximately here)

Risk of Bias Within Studies

Incident Dementia. Overall judgement of risk of bias within the 37 incident dementia studies was assessed using the QUADAS-2 assessment tool, with results presented in Table 5. Regarding patient selection, all 15 studies using hazard ratio had low risk of bias, as did 64% of the studies using odds ratio. Most of the studies with a high risk of bias used different recruitment sources or techniques for people with SCD compared with controls, and did not ensure the two groups were equivalent on baseline demographics (Devanand et al., 2005; Ebenau et al., 2020; Nunes et al., 2010; Reisberg et al., 2010; Schofield et al., 1997; Selnes et al., 2013; Sluimer et al., 2008). Although Wilson et al. (2008) recruited SCD and controls from the same source, recruitment was limited to nuns, priests, and monks, and may not be representative of the general population. Regarding index test, or how SCD was identified, only 3 of the hazard ratio studies, and 7 of the odd ratio studies had a low risk of bias. For most of the studies with a high risk of bias, it was unclear how cognitive impairment at baseline was screened, and therefore the possibility of MCI cases within the baseline sample could not be ruled out. Reisberg et al. (2010) had an unclear risk of bias, as details regarding how MCI and dementia diagnoses were made at baseline were unclear.   Only 1 (hazard ratio) study (and none of the odds ratio studies) had a high risk of bias regarding reference standard, or how dementia was diagnosed. Waldorff et al. (2012) were judged to have a high risk of bias) as they relied on hospital-based diagnoses of dementia using a national hospital register (and hence may have missed cases). Two hazard ratio studies also had an unclear level of bias. Wang et al. (2004) was judged to have an unclear level of bias as it was not evident whether the team reaching consensus on dementia diagnosis were blind to baseline SCD or control status. Tsutsumimoto et al. (2017) were also judged to have an unclear level of bias as they mentioned that dementia status was monitored monthly, but it was unclear how this was achieved. In terms of flow and timing, most of the studies had an unclear risk of bias, as they either did not report attrition or follow-up rates at all, or did not report whether there were differences in attrition between participants with SCD and those without. St John and Montgomery (2002) had a high risk of bias in flow and timing, as although they did not report differences in attrition between SCD and controls, they did report higher mortality in SCD. Palmer et al. (2003) reported less attrition (fewer refused or had moved) from their SCD than -control group, which may have led to greater undetected dementia in the control group. In contrast, Ebenau et al. (2000) reported higher attrition in their SCD group (only 49% completed follow-up) compared to their control group (98% completed). Liew (2019) also reported statistically significantly higher attrition in SCD than controls, although this was a relatively small difference (25% of the follow-up sample had SCD, compared with 30% of those who dropped out). In terms of applicability to the research question, none of the studies included were considered to have biases substantial enough to warrant exclusion from this meta-analysis. The impact of study bias will be examined, however, by running separate analyses excluding those studies with high risk of bias (see section on *Sensitivity Analyses*).

(Table 5 approximately here)

Incident MCI. Overall judgement of risk of bias within the 15 incident MCI studies was assessed using the QUADAS-2 assessment tool, with results presented in Table 6. Regarding patient selection, all the hazard ratio studies, and half the odds ratio studies had low risk of bias. The studies with a high risk of bias had the same issue as the incident dementia studies – that is they used different recruitment sources for people with SCD compared with controls, sometimes with different screening criteria, and did not ensure the two groups were equivalent on baseline demographics (Reisberg et al., 2010; Rolstad et al., 2013; Selnes et al., 2013; Sluimer et al., 2008). Gifford et al.'s (2014) level of bias was unclear as it could not be determined if SCD and controls came from the same source or whether baseline demographics were equivalent. Regarding index test, or how SCD was identified, all but three (odds ratio) studies had a low risk of bias. Reisberg et al. (2010) had an unclear risk of bias, as details were unclear regarding how cognitive impairment (MCI and dementia diagnoses) was ruled out at baseline. Lobo et al. (2008) were judged as having a high risk of bias in identifying SCD, perhaps unsurprising given that their aim was to examine the association of baseline "non-cognitive" psychopathological symptoms with incident MCI. Within their measures of baseline symptoms, however, there were questions regarding concentration difficulties, subjective slowness, difficulties in thinking, and observed slowing. High risk of bias was determined as Lobo et al. (2008) only reported odds ratios for statistically significant baseline items. Maruta et al. (2019) were also judged as having a high risk of bias, as cognitive impairment at baseline was screened using MMSE only, hence MCI cases may have been included. All the included studies had a low risk of bias regarding reference standard, or how MCI was diagnosed, as they all applied appropriate consensus criteria, often in a team review. In terms of flow and timing, most of the studies had an unclear risk of bias, as they either did not report attrition or follow-up rates at all, or did not report whether there were differences in attrition between participants with SCD and those without. St John and Montgomery (2002) had a high risk of bias in flow and timing, as although they did not report differences in attrition between SCD and controls, they did report higher mortality in SCD. In terms of applicability to the research question, none of the studies included were considered to have biases substantial enough to warrant exclusion from this meta-analysis.

(Table 6 approximately here)

Results of Individual Studies and Synthesis of Results

Incident Dementia. The 15 studies reporting hazard ratios for incident dementia all reported increased risk (hazard ratio>1) for participants with SCD, as shown in Figure 2. Hazard ratio estimates varied from 1.10 to 6.00. Overall, people with SCD demonstrated almost twice the probability of developing incident dementia compared to those without SCD (HR = 1.90, 95% CI: 1.52-2.36). As expected, there was significant heterogeneity between studies (Q = 221.05, p<.001; I^2 = 93.67, Tau = 0.377), which was further explored with moderator analyses.

(Figure 2 approximately here)

Similarly, Figure 3 demonstrates that the 22 studies reporting odds ratios for incident dementia also all reported increased risk (odds ratio>1) for participants with SCD. Odds ratio estimates varied considerably, from 1.05 to 15.84. Overall, the odds of developing incident dementia were two and a half times more for people with SCD compared to those without (OR = 2.48, 95% CI: 1.97-3.14). Significant heterogeneity between studies was observed as expected (Q = 92.70, p<.001; I^2 = 77.35, Tau = 0.375), and investigated with moderator analyses.

(Figure 3 approximately here)

Incident MCI. All 4 studies reporting hazard ratio of incident MCI reported increased risk (hazard ratio>1) for people with SCD, as shown in Figure 4. Hazard ratio estimates ranged from 1.18 to 3.10. Overall, people with SCD demonstrated almost twice the probability of developing incident MCI compared to those without SCD (HR = 1.73, 95% CI: 1.18-2.52). As anticipated, there was significant heterogeneity between studies (Q = 12.45, p=.006; I^2 = 75.90, Tau = 0.321), which was inspected with moderator analyses.

(Figure 4 approximately here)

All, except one (Maruta et al., 2019), of the 11 studies reporting odds ratio for incident MCI also reported increased risk (odds ratio>1) of incident MCI for participants with SCD, as shown in Figure 5. Odds ratio estimates ranged considerably, from 0.95 to 17.71, and overall people with SCD demonstrated almost twice the odds of developing incident MCI compared to those without SCD (OR = 1.83, 95% CI: 1.56-2.16). As expected, there was significant heterogeneity between studies (Q = 20.54, p=.025; I^2 = 51.32, Tau = 0.287). This was examined with moderator analyses.

(Figure 5 approximately here)

Risk of Bias Across Studies

Incident Dementia. Visual inspection of the funnel plot for the hazard ratio synthesis (Appendix D, Fig D1) demonstrated asymmetry, suggesting there may be some publication bias, with small studies with positive effects published but not those with negative effects. This was supported by a statistically significant Egger's regression test, p<.001. Despite this, the fail-safe N estimate suggests the findings were robust as a minimum of 1172 additional studies with a ratio of 1 would be required to render the current finding non-significant. Duval and Tweedie's (2000) trim and fill was performed (Appendix D, Fig D1) to create an imputed HR estimate = 1.25 (95% CI = 1.02-1.53). This suggests mild impact of publication bias on the results.

In contrast, visual inspection of the funnel plot for the odds ratio synthesis demonstrated minimal asymmetry (Appendix D, Fig D2), supported by a non-significant Egger's regression test. In this instance, the fail-safe N estimate = 1318. Given the low risk of publication bias, trim and fill was not performed in this instance.

Incident MCI. Visual inspection of the funnel plot for the hazard ratio synthesis (Appendix D, Fig D3) demonstrated some asymmetry, with a statistically significant Egger's regression test, *p*=.01. Despite this, the fail-safe *N* estimate suggests the findings were robust as a minimum of 29 additional studies with a ratio of 1 would be required to render the current finding non-significant. Duval and Tweedie's (2000) trim and fill was performed (Appendix D, Fig D3) to create an imputed HR estimate = 1.57 (95% CI = 1.10-2.24). This suggests a minimal impact of publication bias on the results.

Visual inspection of the funnel plot for the odds ratio synthesis (Appendix D, Figure D4) demonstrated some asymmetry, suggesting there may be some publication bias, supported by a statistically significant Egger's regression test, *p*=.05. Impact of this bias on the overall findings is unlikely, however, given the fail-safe *N* estimate of 167 additional studies. Duval & Tweedie's (2000) trim and fill was performed (Appendix D, Figure D4) to create an imputed OR estimate = 1.81 (95% CI = 1.33-2.45). This suggests a minimal impact of publication bias on the results.

Overall. We also recorded whether there were biases due to multiple outcome measures being reported from the same cohort – i.e., reporting risk of developing dementia and MCI, which would not be entirely independent estimates. Six publications provided odds ratio (or the data to calculate) for both incident dementia and incident MCI (; Kryscio et al., 2014; Maruta et al., 2019; Reisberg et al., 2010; Selnes et al., 2013; Sluimer et al., 2008; St John & Montgomery, 2002). Furthermore, the same cohort (AgeCoDe) was used by Heser et al., (2019) and Luck, Riedel-Heller et al. (2010) to report HR for incident dementia, and OR for incident MCI respectively. Similarly, Liew (2019) and Gifford et al., (2014) used the same cohort (NACC) to report HR for incident dementia and OR for incident MCI, respectively. Finally, Luck et al. (2015) and Luck, Luppa, et al.

(2010) both used the Leipzig cohort to report HR for incident dementia and incident MCI, respectively.

Sensitivity Analyses

Incident Dementia. Regarding the HR studies, all but two had a high risk of bias in at least one domain. None had patient selection bias, flow and timing was unclear for most, and all but 3 had index test bias, so sensitivity analyses were not appropriate based on these domains. There was 1 study with a high risk of bias in the reference standard, and a sensitivity analysis was conducted excluding this study, resulting in an adjusted HR = 1.86 [1.49-2.32], which was not significantly different from the original estimate.

In terms of the OR studies, all but 1 study had high risk of bias in at least one domain. A sensitivity analysis was conducted excluding the 8 studies with high risk of bias in patient selection, which demonstrated OR = 2.35 [1.80-3.08]. A separate sensitivity analysis was conducted excluding the 14 studies with high risk of index test bias, resulting in an OR = 2.70 [1.91-3.81]. A third sensitivity analysis was conducted, excluding the 3 studies with high bias in terms of flow and timing, resulting in an OR = 2.52 [1.93-3.30]. Note that none of these sensitivity analyses resulted in ORs that were significantly different from the original estimate.

Incident MCI. The four HR studies for incident MCI all had low risk across the first three domains, with unknown risk in flow and timing. Given this, no sensitivity analyses were conducted.

In contrast, 7 of the 10 included OR studies for incident MCI had high risk of bias, each within a single domain. Four of these were in patient selection, with 2 studies having high risk of bias in index test and 1 study for flow. Given that the main area of bias was around patient selection, a sensitivity analysis was conducted excluding the 4 studies with high risk of bias in patient selection, which demonstrated OR = 1.82 [1.46-2.27], very similar to the original estimate (OR = 1.83, 95% CI: 1.56-2.162).

Moderator Analyses

Incident Dementia. We had planned to run subgroup analyses according to different dementia types, but there was insufficient data, as most studies either did not report the type of dementia, or solely investigated Alzheimer's disease dementia. We first examined the effect of SCD definition on risk of incident dementia, using a series of subgroup analyses (see Appendix E, Table E1). In terms of HR, type of questions used was not a significant moderator; Q = 1.44, (df = 2), p = .487, nor was decline; Q = 1.15, (df = 1), p = .284, nor was mood; Q = 1.12 (df = 1), p =.290. In contrast, the inclusion of worry in the definition was a significant moderator, Q = 65.76, (df = 1), p<.001, resulting in a lower HR (1.10 [1.07 – 1.13] compared to 1.92 [1.68-2.18]). This result should be treated with caution, however, as only one study included worry in its definition of SCD. We were unable to examine the effect of SCD in different domains of cognition, as 11/15 studies only investigated episodic memory, 2 investigated memory plus other domains, and 2 studies used any cognitive domain.

In terms of the OR studies of incident dementia, type of question used to define SCD was also not a significant moderator; Q = 1.60, (df = 3), p = .660, nor was decline, Q = 4.85, (df = 1), p = .028. Similarly, mood was not a significant moderator; Q = 1.85 (df = 1), p=.174; nor was worry; Q = 1.73 (df = 1), p=.188. Moderation by cognitive domain could not be conducted as 1 study did not state what domain was used, 2 used any domain, 1 used language, and the remainder used episodic memory (16 studies) or episodic memory plus other domains (2 studies).

We next conducted meta-regressions (Appendix E, Table E2) to examine whether the demographic or genetic factors were moderators for HR of incident dementia, finding that none of them were: age (*k* = 15; R^2 analog = 0.39, *Q* = 0.19 (*df* = 1), *p*=.666); gender (*k* = 15; R^2 analog = 0.00 , *Q* = 0.23 (*df* = 1), *p*=.630), education (*k* = 5; R^2 analog = 0.00, *Q* = 0.01 (*df* = 1), *p*=.915); or APOE e4 carriage (*k* =4; R^2 analog = 1.00, *Q* = 5.90, (*df* = 1), *p* = .015). Similarly, none of the demographic or genetic factors were moderators for OR of incident dementia: age (*k* = 20; R^2 analog = 0.23, *Q* = 2.18 (*df* = 1), *p*=.140); education (*k* = 11; R^2 analog = 0.00, *Q* = 0.09 (*df* = 1), *p* =.768); gender (*k* = 21; R^2 analog= 0.00, *Q* = 1.07 (*df* = 1), *p* =.300); or APOE e4 carriage (*k*=8; R^2 analog= 0.00, *Q* = 0.75, (*df* = 1), *p* = .385).

In terms of recruitment source, subgroup analysis (Appendix E, Table E1) revealed that this did not impact on HR for incident dementia, *Q* = 0.42, (*df* = 2), *p*=.811, or OR for incident dementia, *Q* = 4.46, (*df* = 2), *p* = .107.

The final moderator analyses assessed whether duration of follow-up (entered as a continuous covariate in separate meta-regressions; Appendix E, Table E2) moderated the effect of SCD on incident dementia. These revealed no significant moderating effect of follow-up duration for either the HR (*k* = 15; R^2 analog= 0.23, *Q* = 0.49 (*df* = 1), *p*=.482) or OR (*k* = 21; R^2 analog = 0.06, *Q* = 0.96 (*df* = 1), *p*=.327) incident dementia studies.

Incident MCI. A series of separate subgroup analyses (Appendix E, Table E1) were conducted to examine the effect of SCD definition on risk of incident MCI. In terms of HR, type of questions used was not a significant moderator; *Q* = 0.02 (*df* = 1), *p*=.884, nor was worry; *Q* = 0.07 (*df*=1), *p* = .795, nor was decline; *Q* = 0.02, (*df* = 1), *p* = .884, nor was mood; *Q* = 1.345 (*df* = 1), *p* =.246. We were unable to examine the impact of cognitive domain, as 2 studies asked about episodic memory plus other areas, 1 about episodic memory alone, and the other about any cognitive change. Similarly, for the OR synthesis, type of questions used was not a significant moderator; Q = 9.26 (df = 3), p=.026, nor was decline; Q = 1.90 (df = 1), p =.168; nor mood; Q = 0.55 (df = 1), p =.460. In contrast, inclusion of worry in the definition of SCD was a significant moderator, Q = 9.28, (df=1), p = .002, with studies including worry reporting significantly higher OR (5.94, [2.87-12.31]) than those that did not (OR = 1.82 [1.46-2.27]). We were again unable to examine the effect of SCD in different domains of cognition, as 6/10 studies only asked about episodic memory, 1 asked about memory plus other domains, 1 asked about attention, 1 about language, and 2 did not state the cognitive domain.

We then examined the moderating effect of demographic and genetic factors. Separate meta-regressions were conducted for age, years of education, gender (% female), and APOE status (% e4 carriers; Appendix E, Table E2). For the HR analyses, meta-regressions could not be conducted for education or APOE status as there were fewer than 4 studies reporting on these variables. Neither age (k = 4; R^2 analog = 0.00, Q = 0.33 (df = 1), p =.566), nor gender (k = 4; R^2 analog = 0.00, Q = 0.54 (df = 1), p =.464), were found to have a moderating effect on HR for developing MCI. In contrast, for the OR analyses, age was found to significantly moderate the relationship between SCD and incident MCI (k = 10), with the unexplained variance dropping from T^2 =0.0900 to T^2 =0.0122, and age explaining 86% of this decrease (R^2 analog = 0.86, Q = 8.56, (df = 1), p = .003). As shown in Figure 6, younger average age of SCD participants was significantly associated with increased OR of incident MCI. In contrast, there were no significant moderating effects of education (k = 8; R^2 analog = 0.51, Q = 2.90 (df = 1), p =.089), gender (k = 11; R^2 analog = 0.00, Q = 0.08 (df = 1), p =.776), or APOE e4 carriage (k =4; R^2 analog = 1.00, Q = 3.15, (df = 1), p = .076).

(Figure 6 approximately here)

We then examined the impact of recruitment source using a subgroup analysis (Appendix E, Table E1), finding that recruitment source was a significant moderator of the relationship between

SCD and incident MCI when examining OR, Q = 9.91, (df = 2), p=.007. As shown in Figure 5, participants recruited from a clinic setting, compared to random recruitment from the community, had significantly greater odds of developing MCI (2.97 [2.08-4.25] compared with 1.56 [1.29-1.90]). Participants from the community who volunteered for studies (rather than being randomly recruited) had a risk somewhere in between these two groups, although not statistically significantly different. Note that for HR, there was no impact of recruitment source, Q = 2.32, (df = 1), p=.127, but in this case we were only comparing 3 randomly recruited community samples with 1 volunteer sample.

The final moderator analysis examined the effect of follow-up duration (Appendix E, Table E2). Consistent with the incident dementia findings, follow-up duration did not moderate the relationship between SCD and incident MCI (k=10; R^2 analog = 0.14, Q = 1.58 (df = 1), p=.209).

Discussion

This set of meta-analyses aimed to provide an updated estimate of the dementia risk conferred by SCD; to provide an estimate of the risk of developing MCI conferred by SCD; and importantly, to explore factors moderating these levels of risk. SCD was associated with approximately double the risk of developing both dementia (HR = 1.90, 95% CI: 1.52-2.36; OR = 2.48, 95% CI: 1.97-3.14) and MCI (HR = 1.73, 95% CI: 1.18-2.52; OR = 1.83, 95% CI: 1.56-2.16). Our findings are consistent with Mitchell et al.'s (2014) earlier synthesis of 14 studies of risk of dementia (18, 830 participants), but represent a larger sample (22 studies, 25, 546 participants for OR; 15 studies, 44, 476 participants for HR), with a similar average follow up of 5.2 years.

We also built on Mitchell et al.'s (2014) findings, by extending our analysis to risk for developing MCI. MCI is a newer concept than dementia, thus there were fewer studies (11 for OR, 4 HR), and overall the follow-up was shorter (average = 4.0 years). Despite this, we also found that SCD approximately doubled the risk of developing MCI. This finding is perhaps somewhat surprising, as we would have expected that the risk of developing MCI would be greater than that of developing dementia, given that a) MCI is an earlier stage on the pathway to dementia, and b) MCI (like SCD) can occur for reasons in addition to underlying neurodegenerative disease. Our results may reflect the shorter average time frame for MCI follow up compared to dementia, and a reduction in incident MCI due to further transition to dementia from the six studies reporting both incident dementia and MCI.

Moderators of the Risk of Developing Dementia or MCI

Although SCD is a risk factor for future cognitive decline, many people with SCD do not develop dementia or MCI, and there is little understanding of moderating factors. Indeed, as expected, there were high levels of heterogeneity within our syntheses, suggesting important moderating effects. Better understanding of moderating factors is important clinically, in terms of providing clients with more accurate estimates of prognosis. It is also important for research studies – for example so that clinical trials can target recruitment at SCD with the highest risk of conversion. Our meta-analyses aimed to directly address this, by examining key potential moderators for decline to dementia and MCI. Despite our extensive examination of moderators, however, most of the potential sources of heterogeneity examined did not moderate the level of risk, including education, gender, genetics, follow-up duration, and most aspects of SCD definition. Indeed, there was only one likely spurious moderator found in the incident dementia studies. For the incident MCI studies, three significant moderators of the OR were found – recruitment source, age, and inclusion of worry in the definition of SCD.

Recruitment Source. Recruitment source moderated the OR of developing MCI, such that SCD samples recruited from a clinic setting had the greatest risk of developing MCI, with the lowest risk in samples recruited randomly from the community, and volunteer community samples falling in between. Of note, however, people with SCD from any of these settings had an elevated risk of decline compared to people without SCD. In contrast, while recruitment source was not a moderator for the HR of developing MCI or dementia, there were few HR studies recruiting from clinics or volunteers, suggesting these findings are less reliable. In terms of the OR of developing dementia, the findings for recruitment source were in the same direction as reported for MCI, but the effect sizes for the different groups were not significantly different to one another, likely due to small sample sizes and large confidence intervals within the clinic samples. Similarly, Mitchell et al. (2014) reported no significant impact of recruitment setting, comparing clinics to community setting and examining annual conversion rate, although again, their results were in the direction that the risk is higher for SCD in clinic than community settings. Overall, our findings suggest recruitment source is an important moderator that should be considered, despite lack of power to consistently demonstrate significant differences. These findings are consistent with the MCI literature, which reports greater risk of conversion to dementia in patients recruited from clinics versus epidemiological studies (Petersen et al., 2009).

Method of Defining SCD. Methods of defining SCD are far from unanimous (Rabin et al., 2015), and more information regarding key descriptors that increase risk of future decline would be helpful for both clinical practice and research. Despite the large number of studies and participants included in our meta-analyses, we found that most of the examined aspects of definition did not moderate risk. Firstly, in terms of whether the general method used to elicit SCD – be it assumption based on presentation to a clinic; a positive response to a single question, multiple questions, or scale; or elicited via clinical interview–moderated the level of risk of future decline, we found no association with risk of dementia or MCI (using OR or HR).

Secondly, the conceptual framework for SCD proposed by (Jessen et al., 2014) uses “persistent decline in cognitive capacity in comparison with a previously normal status” as the first criteria for SCD, arguing that the idea of decline rather than impairment is important in the context of SCD as a possible symptom of a progressive disease. In our meta-analyses, we included studies where SCD could be any form of subjectively reported cognitive impairment, i.e., decline or broader dissatisfaction with cognition. We expected that studies including decline in their SCD definition would be associated with a higher risk of developing dementia and MCI, but our findings were not as hypothesised, with no moderating effect of decline for OR or HR of developing MCI or dementia.

Thirdly, Jessen et al. (2014; 2020) suggest that concerns or worries associated with SCD increase the likelihood that SCD is due to preclinical AD. Our synthesis on OR risk for MCI supported this concept, with studies defining SCD with the inclusion of worry leading to a greater OR of MCI. This finding may be confounded by recruitment source, as three of four studies including worry recruited from clinics. In contrast, there was no impact of including worry on HR of MCI, although only 1 study reported including worry, or OR of dementia. For HR of dementia, worry was a moderator, although in the opposite direction, but this was based on a single study including worry (and 14 not), thus is not terribly convincing.

Fourthly, SCD is recognised to have a complex relationship with depression, anxiety, and other psychiatric disorders (Jessen et al., 2014; Rabin et al., 2017). Our meta-analyses found that whether studies controlled for mood disturbance was not a moderator of the risk of developing either dementia or MCI. This finding must be considered in light of the variability in how studies assessed or controlled for mood disturbance– ranging from no consideration, through exclusion of participants with a past history, current diagnoses, or high current symptoms, to those that controlled for the effect of mood symptoms statistically. Due to the small number of studies controlling mood disturbance, our analyses focused on whether controlling mood disturbance, using any method, changed the level of risk. The findings suggest that, regardless of association with mood or psychiatric disorder, SCD is associated with increased risk of future cognitive decline, suggesting a more inclusive approach is warranted in the future. Furthermore, most studies focused on depression, but there is emerging evidence for consideration of anxiety and other psychiatric disorders. Future research should continue to consider the interaction of mood and psychiatric disorders, as well as subclinical symptoms, on the presentation of SCD.

Finally, domains of cognition impacted in SCD was another area of SCD definition we aimed to examine, however, were unable to do so due to the lack of variability in studies. Almost all studies to date have defined SCD based on memory, which is the domain thought most likely to be impacted in preclinical AD (Jessen et al., 2014). More research is needed to determine if SCD in domains other than memory are similarly at increased risk of developing MCI and dementia.

Demographic and Genetic Moderators. We also examined whether various demographic factors moderated risk of decline. The only demographic factor found to moderate risk was age, and it only did so for OR of MCI, not for HR of MCI or either of the dementia analyses. Our findings suggested that younger people (under 70 years) with SCD were at greater risk of developing MCI than older people. These findings may be understood in the context that for people in their eighties, there is greater variability in the underlying causes of SCD, but in those in their fifties or sixties, noticing subjective change is more likely to prelude objective cognitive impairment (MCI). It suggests clinicians should also take memory concerns in those under 70 seriously, as our findings suggest they have a higher risk of developing objective decline in the next few years. It will be important for research studies to continue including people in their fifties and sixties when examining SCD and preclinical dementia, as perhaps SCD at any age continues to be a risk factor for incident dementia. Our findings may be confounded by recruitment source – as the younger cohorts are more likely to have come through clinics. Another point to consider is that age moderated risk of MCI but not dementia. This may be because longer time frames are needed to determine whether age moderates risk of dementia as well. It may also reflect the varied aetiology of MCI – as well as reflecting prodromal AD, MCI also can be due to other types of neurodegenerative disorders (and few of the dementia studies included anything but AD), and can also be due to causes other than dementia (Petersen et al., 2018).

We also examined whether female gender or lower education – factors which have been associated with increased risk of MCI and dementia generally - moderated risk of SCD leading to MCI or dementia, but found no moderating effects. This is despite emerging literature suggesting SCD in individuals with higher levels of education may be more likely to lead to AD dementia (Rabin et al., 2017). Note that many studies did not report educational data that could be included in our moderation analysis, meaning that we could not analyse education as a moderator for HR for incident MCI, and there were only 4 studies reporting education in the HR for incident dementia, and only 5 for OR incident MCI. These findings are thus less reliable than other moderators with more data, and future researchers are encouraged to conduct their own moderation analyses to provide a better estimate of this relationship.

Our next possible moderator examined was APOE genotype, the strongest genetic risk factor for AD dementia (Harold et al., 2009; Saunders et al., 1993). Surprisingly, APOE genotype was not a moderator for any of the syntheses. One reason for this may have been that relatively few studies reported it (7/15 incident MCI studies; 11/37 incident dementia studies). As with education, this means that our estimates for these analyses are not as reliable. Indeed, 2/3 analyses demonstrated trends of a moderating effect of APOE genotype, which did not reach our *a priori* criteria for statistical significance. As techniques for measuring genotype become less invasive (indeed it can now be measured via saliva swab, rather than requiring a blood test), more studies might include it routinely when examining SCD, enabling a better estimate of whether SCD and APOE interact to increase risk of future cognitive decline. Another reason for the lack of moderation by APOE ε4 carriage is that ε4 may be most potent in conjunction with other risk factors (particularly vascular risk factors such as diabetes, e.g., Li et al., 2020). Further research of the interaction of other established risk factors for dementia (Livingston et al., 2020) and their relationship with SCD will be useful.

Follow-up Duration. Duration of follow-up was the final moderator examined. Given the association between increasing age and increasing risk of MCI and dementia (Petersen et al., 2018; Prince et al., 2015), as well as enabling more time for neurodegenerative processes to reveal themselves, longer follow-up was expected to be associated with greater risk. Our results, however, found no moderating effect of follow-up duration on HR of MCI, OR of MCI, OR of dementia, or HR of dementia. Our findings suggest that although the risk of developing dementia or MCI may increase with length of follow up, SCD does not seem to alter this relationship. This is despite a wide range of study durations, from 12 months up to 15 years, although the average duration of studies is still relatively short (5.2 years for dementia; 4.0 years for MCI). Note that although we were hoping to extend the average follow-up duration compared to Mitchell et al.'s (2014) analysis, and focused on including studies with longer duration where possible, the average length of follow-up of dementia studies barely increased. It is unclear, however, how attrition impacts these findings, as most studies either did not report attrition rates at all, or did not do so separately for SCD compared to those without SCD. It is possible, given findings in MCI (e.g., Kinsella et al., 2016), that there would be higher attrition from the SCD group, particularly those with cognitive decline who are developing dementia or MCI. This may lead to an underestimate of the risks with greater duration when attrition would have more of an impact.

Limitations and Future Directions

Our meta-analyses had several limitations, including those where no or very few studies addressed an issue, and those related to the quality of available studies. We were unable to examine the relationship between SCD and the risk of different dementia subtypes, or moderators of any risk, as almost all studies focused on AD dementia, or unspecified dementia. We were also unable to look at level of risk according to cognitive domain within SCD, as most studies focused on memory. Although we covered many important moderators, there are myriad other factors that could have been examined, including race or ethnicity, and emerging potential moderators such as personality (Bessi et al., 2018; Koller et al., 2019) or sleep (Cavuoto et al., 2016; Manousakis et al., 2018). Furthermore, we did not examine some of the factors suggested by Jessen et al. (2014; 2020) to increase risk for AD including corroborative informant report, length of SCD, age of onset, comparison to peers, persistence of SCD, seeking medical help, or biomarker evidence of AD. Examination of these factors will be important for future research. Another potentially fruitful direction would to be examine broader moderators such as prevalence of SCD in the sample and overall progression of the sample. We found that these broad descriptive characteristics varied greatly among the included samples. Reasons for this will include differences in some of our other moderators such as different recruitment sources, demographic factors, particularly age, and how SCD was defined. It may be that a combination of factors impacting SCD prevalence and overall sample progression may moderate the association between SCD and cognitive decline, more so than individual factors. Given that SCD is an early stage in the neurodegenerative process, we had also originally planned to look at the risk of objective cognitive decline (not necessarily sufficient to meet MCI criteria), however, the size of the literature meant that this analysis will appear in a forthcoming review.

Another limitation of our study is the potential circularity of examining whether SCD can predict MCI, when one of the core criteria for MCI is usually subjective cognitive changes. Our premise is not completely circular, given that we are asking whether SCD at one time point leads to MCI at some future point. SCD is not an entirely stable concept (Roehr et al., 2016), and hence, just because someone reports SCD at one timepoint does not mean they will still report it 1 year, or 15 years down the track. Presumably, the studies of incident MCI gathered a measure of cognitive complaints, where that was part of their criteria, at the follow-up time point. Unfortunately, this was not an element that was extracted from the individual studies. Another method that many studies use to reduce the circularity in this argument is to use different measures to assess SCD at baseline compared to the subjective cognitive change needed for an MCI diagnosis at follow-up. Again, unfortunately, this was not a variable that was extracted during the meta-analysis. Future studies might like to examine whether these factors do impact the findings.

Regarding limitations within the included studies, there was some publication bias evident in the HR and OR MCI syntheses and dementia HR synthesis, however the results were found to be robust to bias. Overlapping cohorts were used to estimate the risk of developing MCI and dementia in many cases (there were only six MCI cohorts not also used to calculate dementia risk), however, the large synthesis with robust findings that SCD leads to increased risk of cognitive decline – whether of MCI or dementia – suggests this is not overly concerning. The main biases in the included studies were selection biases, often around differences in recruitment sources and screening criteria for the SCD participants compared to those without SCD. Other studies did not clearly exclude MCI at baseline to enable determination of risk of SCD without cognitive compromise. Finally, most studies did not report attrition, or specify whether it differed between groups. All these factors are areas that future studies should consider in their study design. The other factor is the lack of consistency in the field regarding definition of SCD. This has been recognised with multiple efforts to improve this issue (e.g., Jessen et al., 2014), but was rife for the studies included in this meta-analysis. Despite the inconsistencies in how SCD was defined, however, we found that SCD was related to increased risk of both MCI and dementia, and for the most part, the way it was defined did not moderate this.

Clinical Implications and Conclusion

In summary, we found that SCD approximately doubles the risk of developing both MCI and dementia. People reporting SCD at younger ages (i.e., in their sixties rather than eighties) appear at increased risk of developing MCI, as do those who are concerned or worried about their cognitive changes. Recruitment source is also an important moderator for the development of MCI, with SCD patients recruited through a clinic demonstrating five times the risk of developing MCI, compared to controls. Nevertheless, people with SCD in the general community still have an increased risk (approximately double) of developing dementia and MCI compared to those without SCD. SCD thus represents an important marker of cognitive health in older age, and an ideal phase for early intervention, including risk reduction, and cognitive-behavioural interventions (Bhome et al., 2018; Livingston et al., 2020; Pike et al., 2018; Pike et al., 2021). A key component of these interventions is psychoeducation that although SCD increases the risk of future MCI or dementia, many people with SCD will not experience either of these conditions (Pike et al., 2021).

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Tables

Table 1. Descriptive characteristics of included studies with dementia outcome.

										N				%	
Study	**Country**	**Cohort**	**Recruitment Setting**	**Total N**	**Baseline Age**	**Gender (%F)**	**Edu**	**APOE (%e4)**	**Follow-up (months)**	**SCD**	**Controls**	**SCD developed dementia**	**Controls developed dementia**	**SCD prevalence**	**Overall rate of progression**
Brodaty (2017)	Australia	SMAS	Community	618	78.7[e]	56.1[e]	11.6[e]	NR	72.0	227	391	34	48	36.7	13.3
Devanand (2005)	USA	NYSPI & CPMC	Clinic	115	67.1	55.0	15.1	28.0	49.7	58	57	1	0	50.4	0.9
Ebenau (2020)	Netherlands	SCIENCe	Clinic	463	60.0	41.0	NR	35.4	36.0	342	121	22	1	73.9	5.0
Gruters (2019)	Netherlands	BBACL	Clinic	405	70.0	37.4	NR	NR	60.0	342	63	83	11	84.4	23.2
Heser (2019)[c]	Germany	AgeCoDe	Volunteer	2422	79.6[e]	64.2[e]	NR	NR	156.0	1393	1029	NR	NR	57.5	N/A
Heun (2006)	Germany	UM & UoB FSAD	Volunteer	615	68.1[e]	59.8[e]	NR	27.3[e]	56.4	310	305	24	14	50.4	6.2
Jorm (1997)	Australia	CLS	Community	504	NR	NR	NR	NR	43.2	349	155	21	4	69.2	5.0
Jungwirth (2009)	Austria	VITA	Community	478	78.3[e]	60.6[e]	NR	NR	30.0	NR	NR	NR	NR	N/A	N/A
Kim (2006)	S. Korea	10/66 DDCRP	Community	553	71.4	65.9	2.6	14.1	28.8	<135	<551	NR	NR	N/A	N/A
Kryscio (2014)[a]	USA	BRAiNS	Volunteer	531	73.2[e]	63.1[e]	16.0[e]	30.3[e]	NR	296	235	70	18	55.7	16.6
Liew (2019)[c]	USA	NACC	Clinic	10219	72[e]	65.3[e]	16.0[e]	NR	52.8	2605	7614	NR	NR	25.5	N/A
Luck (2015)[b]	Germany	LLSA	Community	443	82.3[e]	73.8[e]	NR	NR	64.8	162	281	30	28	36.6	13.1
Maruta (2019)[a]	Portugal	MA	Volunteer	275	65.6	76.0	8.3	NR	58.8	26	249	2	5	9.5	2.5
Montlahuc (2011)	France	3C Study	Community	8169	74.0[e]	61.4[e]	NR	NR	80.4	1494	6675	NR	NR	18.3	N/A
Nunes (2010)	Portugal	Memory Clinic	Clinic	26	65.9	66.7	10.4	6.7	42.0	15	11	2	0	57.7	7.7
Palmer (2003)	Sweden	Kungsholmen	Community	1417	81.3	76.0	NR	NR	40.8	457	960	104	100	32.3	14.4
Peres (2011)	France	Paquid	Community	2901	74.8[e]	58.5[e]	NR	NR	180.0	1788	1113	NR	NR	61.6	N/A

Rabin (2012)	USA	EAS	Community	627	78.5[e]	60.0[e]	13.8[e]	NR	39.6	NR	NR	NR	NR	N/A	N/A
Reisberg (2010)[a]	USA	CBH	Volunteer	213	67.5	65.0	15.6	NR	81.6	166	47	19	2	77.9	9.9
Ronnlund (2015)	Sweden	Betula	Community	2010	71.5[e]	55.6[e]	8.3[e]	27.8[e]	120.0	1048	901	NR	NR	52.1	N/A
Sacuiu (2018)	Sweden	PPSW/ H70	Community	921	74.9	78.7	NR	25.4	144.0	300	621	81	70	32.6	16.4
Schmand (1997)	Netherlands	AMSTEL	Community	2114	74.3[e]	62.9[e]	NR	NR	48.0	NR	NR	NR	NR	N/A	N/A
Schofield (1997)	USA	NMAP	Clinic	169	75.4	86.0	6.6	NR	12.0	70	99	20	8	41.4	16.6
Selnes (2013)[a]	Norway	UHMCO	Clinic	32	61.3	72.7	NR	55.0	30.0	11	21	3	0	34.4	9.4
Sluimer (2008)[a]	Netherlands	VUMC	Clinic	37	NR	44.4	NR	NR	21.6	27	10	4	0	73.0	10.8
St John (2002)[a]	Canada	MSHA/CSHA	Community	998	77.0	56.3	9.3	NR	60.0	185	813	22	64	18.5	8.6
Tobiansky (1995)	England	GOS	Community	433	74.6[e]	63.0[e]	NR	NR	24.0	84	349	7	24	19.4	7.2
Tomata (2017)	Japan	Ohsaki	Community	13974	73.8[e]	55.1[e]	NR	NR	68.4	5190	8784	740	489	37.1	8.8
Tsutsumimoto (2017)	Japan	OSHPE	Community	2925	71.6	46.8	11.6	NR	24.0	2006	919	37	3	68.6	1.4
van den Kommer (2009)	Sweden	OCTO-Twin	Community	521	83.3[e]	67.3[e]	NR	26.0[e]	24.0	NR	NR	NR	NR	N/A	N/A
van Oijen (2007)	Netherlands	Rotterdam	Community	6927	71.6	62.5	NR	26.8	129.6	NR	NR	NR	NR	N/A	N/A
van Wanrooij (2019)	Netherlands	preDIVA	Community	3423	74.3[e]	54.6[e]	NR	NR	80.4	601	2822	86	146	17.6	6.8
Verdelho (2011)	European[d]	LADIS	Clinic	587	74.2	55.0	9.4	NR	36.0	399	239	NR	NR	68.0	N/A
Waldorff (2012)	Denmark	GP Clinics CPH	Community	758	74.8[e]	61.4[e]	NR	NR	48.0	177	581	NR	NR	23.4	N/A
Wang (2000)	Taiwan	KINDS	Community	543	72.7	58.0	1.2	NR	36.0	265	275	5	5	48.8	1.8
Wang (2004)	USA	ACT	Volunteer	1739	76.1	44.8	NR	NR	62.4	79	1660	13	113	4.5	7.2
Wilson (2008)	USA	ROS	Volunteer	917	74.8[e]	68.5[e]	18.0[e]	NR	93.6	272	645	82	108	29.7	20.7

Note. [a]These studies also reported OR for incident MCI. [b]Additional publication from this study reported HR for incident MCI. [c]Additional publication from this study reported OR for incident MCI. [d]Multinational European includes Finland, Austria, Portugal, Netherlands, Sweden, France, Germany, Denmark, UK, Italy. [e] Characteristics are for SCD group, unless separate data was not provided.

Abbreviations: N, number of participants; Edu, years of education; APOE, Apolipoprotein E; N/A, Not Available; NR, Not Reported; SMAS, Sydney Memory and Ageing Study; NYSPICPMC, New York State Psychiatric Institute and Columbia Presbyterian Medical Center; SCIENCe, Amsterdam Dementia Cohort and Subjective Cognitive Impairment Cohort; BBACL, Biobank Alzheimer Center Limburg; AgeCoDe, Ageing, Cognition and Dementia in Primary Care Patients; UM & UB, University Mainz & University of Bonn family study AD; CLS, Canberra longitudinal study; VITA, ViennaTransDanube Aging study; S. Korea, South Korea; 10/66 DDCRP, 10/66 Dementia in Developing Countries Research Program; BRAiNS, Biologically Resilient Adults in Neurological Studies; NACC, National Alzheimer's Coordinating Center; LLSA, Leipzig Longitudinal Study of the Aged; MA, Mindful Aging: Avoiding Age-Related Cognitive Decline; 3C Study, Three-City Study; CBH, Centre for Brain Health; PPSW, Prospective Population Study of Women; H70, H70 Birth Cohort Study; AMSTEL, Amsterdam Study of the Elderly; NMAP, North Manhattan Aging Project; UHMCO, University Hospital based Memory Clinic in Oslo;; VUMC, Vrije Universiteit Medical Centre Alzheimer Centre; MSHA/CSHA, Manitoba Study of Health and Aging/Canadian Study of Health and Aging; GOS, Gospel Oak Study; Ohsaki, Ohsaki Cohort 2006 Study; OSHPE, Obu Study of Health Promotion for the Elderly); preDIVA, Prevention of Dementia by Intensive Vascular Care; LADIS, Leukoaraiosis and Disability; OCTO-Twin, Origins of Variance in the Old-Old: Octogenarian Twins; GP clinics CPH, General Practitioner clinics in Copenhagen, Denmark; KINDS, Kinmen Neurological Disorders Survey; ACT, Adult Changes in Thoughts; ROS, Religious Orders Study.

Table 2. Definition of Subjective Cognitive Decline (SCD) used by included studies with dementia outcome.

Study	**Method**	**Name of Scale**	**Domain(s)**	**Worry?**	**Decline?**	**Mood disturbance controlled**
Brodaty (2017)	Scale	MAC-Q	Episodic memory	No	Yes	No
Devanand (2005)	Presented to memory clinic		Episodic memory	Yes	Yes	Yes[a]
Ebenau (2020)	Presented to memory clinic		Any cognitive change	Yes	No	Yes[a]
Gruters (2019)	Scale	SCFQ	Episodic memory	No	Yes	Yes[a,e]
Heser (2019)	Single question		Episodic memory	No	Yes	Yes[e]
Huen (2006)	A few questions		Episodic memory	No	No	Yes[b]
Jorm (1997)	Single question		Episodic memory	No	Yes	Yes[e]
Jungwirth (2009)	A few questions		Episodic memory	No	Yes	No
Kim (2006)	Scale	GMSS	Episodic memory	No	Yes	No
Kryscio (2014)	Single question		Episodic memory	No	Yes	Yes[b]
Liew (2019)	Single question		Episodic memory	No	Yes	Yes[e]
Luck (2015)	Single question		Episodic memory	No	No	Yes[e]
Maruta (2019)	A few questions		Language	No	No	No
Montlahuc (2011)	Reported to medical professional		Any cognitive change	No	No	No

Nunes (2010)	Presented to memory clinic		Any cognitive change	Yes	Unclear	Yes[c]
Palmer (2003)	Single question		Episodic memory	No	No	No
Peres (2011)	A few questions		Episodic memory plus	No	No	No
Rabin (2012)	Addition of multiple scales	10 items from CERAD Clinical History Questionnaire, Albert Einstein HSA, and GDepS	Episodic memory	Yes	Yes	Yes[e]
Reisberg (2010)	Interview with scale(s)	GDS/BCRS	Episodic memory	Yes	No	Yes[d]
Ronnlund (2015)	Single question		Episodic memory	No	Yes	Yes[e]
Sacuiu (2018)	Scale	CPRS	Any cognitive change	No	No	Yes[e]
Schmand (1997)	Interview with scale(s)	CAMDEX SMC scale	Episodic memory plus	No	No	No
Schofield (1997)	Single question		Episodic memory	No	No	Yes[e]
Selnes (2013)	Interview with scale(s)	GDS	Episodic memory	Yes	No	No
Sluimer (2008)	Presented to memory clinic		Unstated	Yes	Yes	No
St John (2002)	Single question		Episodic memory	No	Yes	Yes[e]

Tobiansky (1995)	Scale	Short-CARE, SMI scale	Episodic memory plus	No	No	Yes[b]
Tomata (2016)	A few questions		Episodic memory	No	No	No
Tsutsumimoto (2017)	Scale	CAMDEX SMC Scale	Episodic memory	No	No	No
van den Kommer (2009)	Single question		Episodic memory	No	No	No
van Oijen (2007)	Single question		Episodic memory	No	No	No
van Wanrooij (2019)	Single question		Episodic memory	No	No	No
Verdelho (2011)	Single question		Episodic memory	No	No	Yes[e]
Waldorf (2012)	Single question		Episodic memory	No	No	No
Wang (2000)	Single question		Episodic memory	No	No	Yes[b]
Wang (2004)	Scale	SMRS	Episodic memory plus	No	Yes	Yes[e]
Wilson (2008)	Single question		Episodic memory	No	No	No

Note. [a] Exclude past or current mood disorder; [b]exclude current (baseline) mood disorder; [c]exclude baseline elevated mood symptoms; [d]exclude past, baseline, and elevated symptoms on scale; [e]mood controlled statistically in reported effect size. BCRS = Brief Cognitive Rating Scale; CAMDEX = Cambridge Mental Disorders of the Elderly Examination; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CPRS = Comprehensive Psychopathological Rating Scale; GDepS = Geriatric Depression Scale; GDS = Global Deterioration Scale; GMSS = Geriatric Mental State Schedule; HSA = Health Self-Assessment Form (unpublished); MAC-Q = Memory Assessment Complaints Questionnaire; SCFQ = Subjective Cognitive Functioning questionnaire; Short-CARE = shortened version of the Comprehensive Assessment and Referral Evaluation; SMC = Subjective Memory Complaints; SMI = Subjective Memory Impairment; SMRS = Subjective Memory Rating Scale.

Table 3. Descriptive characteristics of included studies with mild cognitive impairment outcome.

										N				%	
Study	**Country**	**Cohort**	**Recruitment Setting**	**Total N**	**Baseline Age**	**Gender (%F)**	**Edu**	**APOE (%e4)**	**Follow-up (months)**	**SCD**	**Controls**	**SCD developed MCI**	**Controls developed MCI**	**SCD Prevalence**	**Overall rate of progression**
Fernandez-Blazquez (2016)	Spain	Vallecas	Volunteer	608	74.1	61.0	11.0	18.9	13.1	428	185	31	9	70.4	6.6
Gifford (2014)[b]	USA	NACC	Clinic	4414	72.7	65.4	16.0	NR	42.0	975	3439	NR	NR	22.1	N/A
Kryscio (2014)[a]	USA	BRAiNS	Volunteer	531	73.2[c]	63.1[c]	16.0[c]	30.3[c]	NR	296	235	72	33	55.7	19.8
Lobo (2008)	Spain	ZARADEMP	Community	1654	73.5[c]	57.7[c]	7.9[c]	NR	24.0	NR	NR	NR	NR	N/A	N/A
Luck, Luppa (2010)[b]	Germany	LLSA	Community	463	81.0[c]	72.3[c]	NR	NR	96.0	NR	NR	NR	NR	N/A	N/A
Luck, Riedel-Heller (2010)[b]	Germany	AgeCoDe	Volunteer	2331	79.5[c]	65.1[c]	NR	20.3[c]	36.0	1214	1117	210	140	52.1	15.0
Maruta (2019)[a]	Portugal	MA	Volunteer	275	65.6	76.0	8.3	NR	58.8	26	249	2	20	9.5	8.0
Nosheny (2019)	USA, Canada	ADNI	Volunteer	420	73.8[c]	52.4[c]	16.5[c]	27.9[c]	NR	NR	NR	NR	NR	N/A	N/A
Reisberg (2010)[a]	USA	CBH	Volunteer	213	67.5	65.0	15.6	NR	81.6	166	47	19	2	77.9	9.9
Rolstad (2013)	Sweden	GMCI	Clinic	129	60.9	53.6	13.2	NR	24.0	82	47	21	3	63.6	18.6
Selnes (2013)[a]	Norway	UHMCO	Clinic	32	61.3	72.7	NR	55.0	30.0	11	21	3	0	34.4	9.4
Sluimer (2008)[a]	Netherlands	VUMC	Clinic	37	NR	44.4	NR	NR	21.6	27	10	3	0	73.0	8.1
Snitz (2018)	USA	MY-HAT	Community	1181	78.3	60.0	12.8	20.7	37.1	592	589	299	269	50.1	48.1
St John (2002)[a]	Canada	MSHA/CSHA	Community	905	77.0	56.3	9.3	NR	60.0	156	8749	22	56	17.2	8.6

van Harten (2018)	USA	Mayo	Community	1085	80.3	51.3	14.3	25.7	96.0	267	843	NR	NR	24.6	N/A

Note. [a]These studies also reported OR for incident dementia. [b]Additional publication from these studies reported HR for incident dementia. Characteristics are for SCD group, unless separate data was not provided[c].

Abbreviations: N, number of participants; EDU, years of education; APOE, Apolipoprotein E; N/A, Not Available; NR, Not Reported; NACC, National Alzheimer's Coordinating Center; BRAiNS, Biologically Resilient Adults in Neurological Studies; LLSA, Leipzig Longitudinal Study of the Aged; AgeCoDe, Ageing, Cognition and Dementia in Primary Care Patients; MA, Mindful Aging: Avoiding Age-Related Cognitive Decline; ADNI, Alzheimer's Disease Neuroimaging Initiative; CBH, Centre for Brain Health; GMCI, Gothenburg Mild Cognitive Impairment; UHMCO, University Hospital based Memory Clinic in Oslo; VUMC, Vrije Universiteit Medical Centre Alzheimer Centre; MY-HAT, Monongahela-Youghiogheny Health Aging Team; MSHA/CSHA, Manitoba Study of Health and Aging/Canadian Study of Health and Aging; Mayo, Mayo Clinic Study of Aging.

Table 4. Definition of Subjective Cognitive Decline (SCD) used by included studies with mild cognitive impairment outcome.

Study	Method	Name of Scale	Domain(s)	Worry?	Decline?	Mood disturbance controlled
Fernandez-Blazquez (2016)	Addition of multiple scales	2 in-house scales	Episodic memory plus	No	Yes	No
Gifford (2014)	Interview		Unstated	No	No	No
Kryscio (2014)	Single question		Episodic memory	No	Yes	Yes[a]
Lobo (2008)	Single question		Attention	No	No	Yes[c]
Luck, Luppa (2010)	Single question		Episodic memory	No	No	No
Luck, Riedel-Heller (2010)	Single question		Episodic memory	No	Yes	No
Maruta (2019)	A few questions		Language	No	No	No
Nosheny (2019)	Scale	E-Cog	Episodic memory plus	No	Yes	Yes[d]
Reisberg (2010)	Interview with scale(s)	GDS/BCRS	Episodic memory	Yes	No	Yes[b]
Rolstad (2013)	Interview with scale(s)	GDS	Episodic memory	Yes	Yes	Yes[a]
Selnes (2013)	Interview with scale(s)	GDS	Episodic memory	Yes	No	No
Sluimer (2008)	Presented to memory clinic		Unstated	Yes	Yes	No
Snitz (2018)	Scale	MYHAT memory complaints	Episodic memory	No	Yes	No

St John (2002)	Single question	Episodic memory	No	Yes	No
van Harten (2018)	Single question	Any cognitive change	Yes	No	Yes[c]

Note. [a]Exclude current (baseline) mood disorder; [b]exclude past, baseline, and elevated symptoms on scale; [c]mood controlled statistically in reported effect size; [d]exclude elevated symptoms on scale. BCRS = Brief Cognitive Rating Scale; ECog = Everyday Cognition; GDS = Global Deterioration Scale; MYHAT = Monongahela-Youghiogheny Healthy Aging Team

Table 5. QUADAS results showing risk of bias within studies examining incidental dementia

	Risk of Bias			
Study	Patient Selection	Index Test SCD	Reference Standard	Flow and Timing
Brodaty (2017)	L	H	L	?
Devanand (2005)	H	L	L	?
Ebenau (2020)	H	L	L	H
Gruters (2019)	L	H	L	?
Heser (2019)	L	L	L	?
Heun (2006)	L	H	L	?
Jorm (1997)	L	H	L	?
Jungwirth (2009)	L	H	L	?
Kim (2006)	L	H	L	L
Kryscio (2014)	L	L	L	?
Liew (2019)	L	L	L	H
Luck (2015)	L	H	L	?
Maruta (2019)	L	H	L	?
Montlahuc (2011)	L	H	L	?
Nunes (2010)	H	L	L	L
Palmer (2003)	L	H	L	H
Peres (2011)	L	H	L	?
Rabin (2012)	L	H	L	?
Reisberg (2010)	H	?	L	L
Ronnlund (2015)	L	H	L	?
Sacuiu (2018)	L	H	L	L
Schmand (1997)	L	H	L	?
Schofield (1997)	H	H	L	L

Selnes (2013)	H	L	L	L
Sluimer (2008)	H	L	L	?
St John (2002)	L	L	L	H
Tobiansky (1995)	L	H	L	?
Tomata (2017)	L	H	L	?
Tsutsumimoto (2017)	L	L	?	?
van den Kommer (2009)	L	H	L	?
van Oijen (2007)	L	H	L	?
van Wanrooij (2019)	L	H	L	L
Verdelho (2011)	L	H	L	?
Waldorff (2012)	L	H	H	L
Wang (2000)	L	H	L	?
Wang (2004)	L	H	?	L
Wilson (2008)	H	H	L	?

Note. L = Low Risk; H = High Risk; ? = Unclear Risk.

Table 6. QUADAS results showing risk of bias within studies examining incidental mild cognitive impairment.

Study	Risk of Bias			
	Patient Selection	Index Test SCD	Reference Standard	Flow and Timing
Fernandez-Blazquez (2016)	L	L	L	?
Gifford (2014)	?	L	L	?
Kryscio (2014)	L	L	L	?
Lobo (2008)	L	H	L	?
Luck, Luppa (2010)	L	L	L	?
Luck, Riedel-Heller (2010)	L	L	L	?
Maruta (2019)	L	H	L	?
Nosheny (2019)	L	L	L	?
Reisberg (2010)	H	?	L	L
Rolstad (2013)	H	L	L	?
Selnes (2013)	H	L	L	L
Sluimer (2008)	H	L	L	?
Snitz (2018)	L	L	L	?
St John (2002)	L	L	L	H
van Harten (2018)	L	L	L	?

Note. L = Low Risk; H = High Risk; ? = Unclear Risk.

Figures

Figure Captions

*Figure 1***.** PRISMA flow chart showing the number of citations retrieved, and the number of studies included in the meta-analysis.

Note. 16 studies extracted for quantitative synthesis only provided data for the outcome of cognitive decline, thus were not included in the current synthesis.

Figure 2. Forest plot of hazard ratios that subjective cognitive decline leads to incident dementia.

Figure 3. Forest plot of odds ratios that subjective cognitive decline leads to incident dementia, showing moderator effect of recruitment source.

Figure 4. Forest plot of hazard ratios that subjective cognitive decline leads to incident mild cognitive impairment, showing moderator effect of recruitment source.

Figure 5. Forest plot of odds ratios that subjective cognitive decline leads to incident mild cognitive impairment, showing moderator effect of recruitment source.

Figure 6. Age as a moderator of the risk of subjective cognitive decline for incident mild cognitive impairment.

Figure 1.

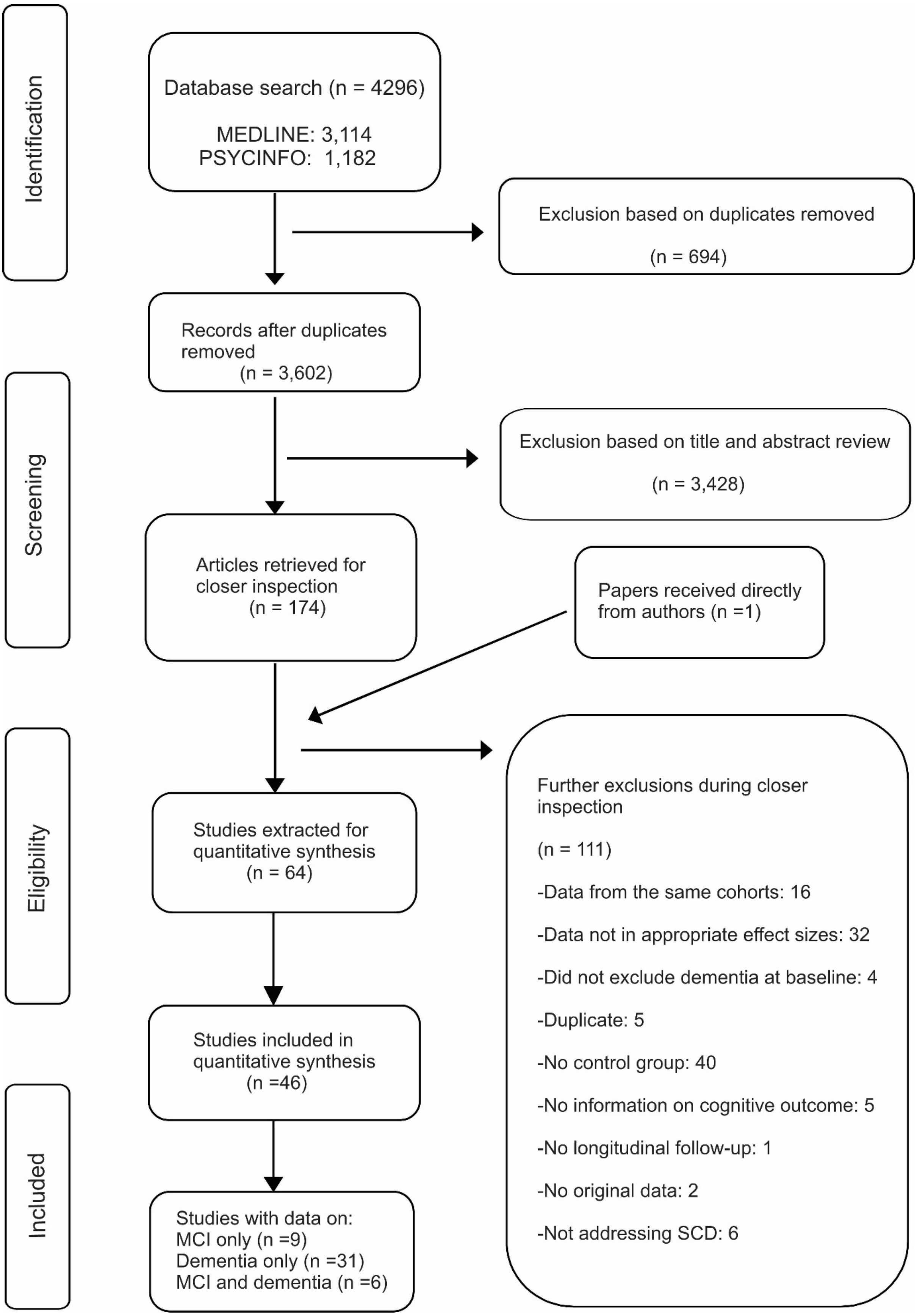

Identification
Screening
Eligibility
Included
Database search (n = 4296)
MEDLINE: 3,114
PSYCINFO: 1,182
Exclusion based on duplicates removed
(n = 694)
Records after duplicates removed
(n = 3,602)
Exclusion based on title and abstract review
(n = 3,428)
Articles retrieved for closer inspection
(n = 174)
Papers received directly from authors (n =1)
Further exclusions during closer inspection
(n = 111)
-Data from the same cohorts: 16
-Data not in appropriate effect sizes: 32
-Did not exclude dementia at baseline: 4
-Duplicate: 5
-No control group: 40
-No information on cognitive outcome: 5
-No longitudinal follow-up: 1
-No original data: 2
-Not addressing SCD: 6
Studies extracted for quantitative synthesis
(n = 64)
Studies included in quantitative synthesis
(n =46)
Studies with data on:
MCI only (n =9)
Dementia only (n =31)
MCI and dementia (n =6)

Figure 2.

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Gruters (2019)	1.260	0.652	2.436	0.687	0.492
Heser (2019)	1.760	1.401	2.211	4.854	0.000
Liew (2019)	2.000	1.700	2.353	8.359	0.000
Luck (2015)	1.820	1.069	3.098	2.207	0.027
Montlahuc (2011)	2.040	1.720	2.420	8.190	0.000
Peres (2011)	1.500	1.253	1.795	4.426	0.000
Rabin (2012)	1.100	1.070	1.131	6.756	0.000
Ronnlund (2015)	1.480	1.187	1.845	3.483	0.000
Sacuiu (2018)	1.800	1.298	2.496	3.523	0.000
Tsutsumimoto (2017)	4.950	1.520	16.115	2.656	0.008
Van Wanrooij (2019)	2.970	2.266	3.893	7.885	0.000
Van Oijen (2007)	1.710	1.408	2.077	5.409	0.000
Verdelho (2011)	2.200	1.185	4.084	2.498	0.012
Waldorff (2012)	2.630	1.482	4.667	3.305	0.001
Wang (2004)	6.000	2.049	17.566	3.269	0.001
	1.895	1.522	2.359	5.716	0.000

Statistics for each study

Hazard ratio and 95% CI

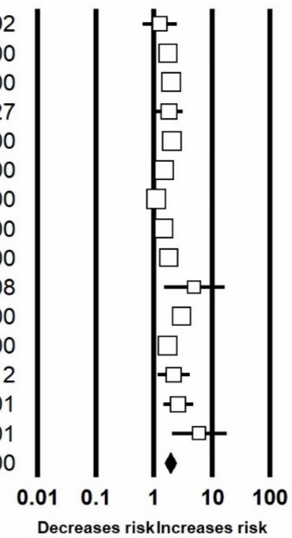


Figure 3.

Study name	Statistics for each study					
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Brodaty (2017)	1.300	0.802	2.106	1.066	0.287
Devanand (2005)	3.000	0.120	75.191	0.668	0.504
Ebenau (2020)	8.250	1.100	61.879	2.053	0.040
Heun (2006)	2.680	1.111	6.465	2.194	0.028
Jorm (1997)	2.417	0.815	7.163	1.592	0.111
Jungwirth (2009)	1.370	1.207	1.556	4.857	0.000
Kim (2006)	3.120	1.090	8.930	2.121	0.034
Kryscio (2014)	3.734	2.153	6.475	4.691	0.000
Maruta (2019)	4.067	0.748	22.096	1.624	0.104
Nunes (2010)	4.259	0.185	98.069	0.906	0.365
Palmer (2003)	2.534	1.875	3.424	6.050	0.000
Reisberg (2010)	2.908	0.652	12.966	1.400	0.162
Schmand (1997)	2.630	1.798	3.846	4.986	0.000
Schofield (1997)	4.550	1.869	11.075	3.338	0.001
Selnes (2013)	15.842	0.743	337.869	1.770	0.077
Sluimer (2008)	4.021	0.198	81.660	0.906	0.365
St John (2002)	1.780	1.081	2.932	2.265	0.024
Tobiansky (1995)	4.260	1.630	11.133	2.957	0.003
Tomata (2017)	2.821	2.502	3.180	16.954	0.000
Van den Kommer (2009	3.260	2.001	5.312	4.744	0.000
Wang (2000)	1.050	0.300	3.669	0.076	0.939
Wilson (2008)	2.146	1.541	2.989	4.517	0.000
	2.482	1.965	3.136	7.625	0.000

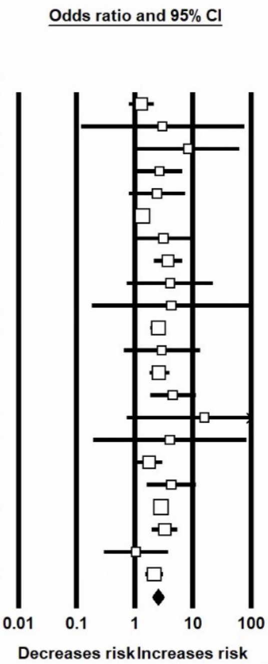


Figure 4.

Study name	Statistics for each study				
	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Luck (2010a)	1.920	1.280	2.880	3.153	0.002
Nosheny (2019)	3.100	1.391	6.910	2.767	0.006
Snitz (2018)	1.180	0.997	1.396	1.928	0.054
van Harten (2018)	1.870	1.298	2.695	3.357	0.001
	1.728	1.184	2.523	2.835	0.005

Hazard ratio and 95% CI

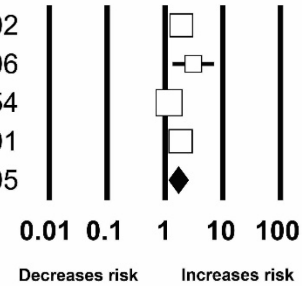


Figure 5.

Group by Recruitment source	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
1. Community	Lobo (2008)	1.710	1.170	2.500	2.770	0.006
1. Community	Luck (2010b)	1.420	1.107	1.822	2.760	0.006
1. Community	St John (2002)	2.032	1.200	3.440	2.638	0.008
1. Community		1.564	1.289	1.898	4.529	0.000
2. Volunteer	Fernandez (2016)	1.546	0.721	3.317	1.120	0.263
2. Volunteer	Kryscio (2014)	1.968	1.250	3.097	2.923	0.003
2. Volunteer	Maruta (2019)	0.954	0.210	4.333	-0.061	0.952
2. Volunteer	Reisberg (2010)	6.278	2.364	16.675	3.686	0.000
2. Volunteer		2.167	1.174	4.001	2.473	0.013
3. Clinic	Gifford (2014)	2.760	1.892	4.025	5.273	0.000
3. Clinic	Rolstad (2013)	5.049	1.418	17.985	2.498	0.012
3. Clinic	Selnes (2013)	17.706	0.824	380.561	1.836	0.066
3. Clinic	Sluimer (2008)	3.000	0.142	63.353	0.706	0.480
3. Clinic		2.972	2.080	4.246	5.983	0.000
Overall		1.834	1.556	2.160	7.247	0.000

Odds ratio and 95% CI

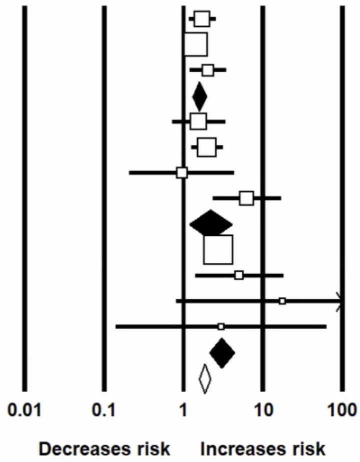
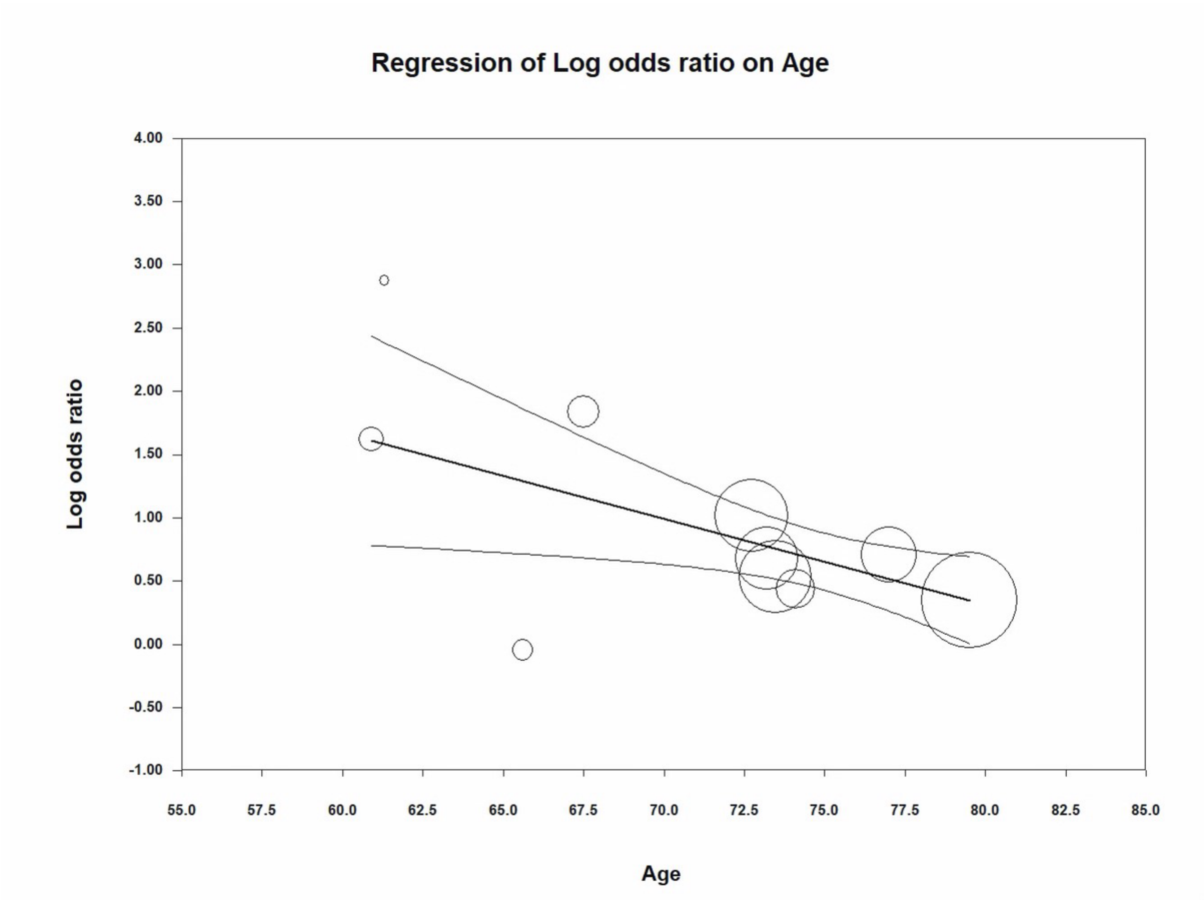


Figure 6.


Regression of Log odds ratio on Age
Log odds ratio
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
-0.50
-1.00
55.0
57.5
60.0
62.5
65.0
67.5
70.0
72.5
75.0
77.5
80.0
82.5
85.0
Age

Appendices

Appendix A: MEDLINE and PsychINFO Search Strategies

Ovid MEDLINE (R) 1946 to Present, including In-Process & Other Non-Indexed Citations				
Subjective	Cognitive/ Memory	Decline	Ageing	Longitudinal studies
exp Self Report/ OR exp Diagnostic Self Evaluation/ OR exp Self-Assessment OR subjective.mp. OR self report.mp. OR self rated.mp.	exp Memory/ OR exp Cognition/ OR cognit*.mp. OR memory.mp.	exp Memory Disorders/ OR exp Cognition Disorders/ OR change*.mp. OR impairment*.mp. OR complaint*.mp. OR disorder*.mp. OR decline.mp. OR concern*.mp. OR difficult*.mp.	exp Aging/ OR exp Aged/ OR OR aging.mp. OR ageing.mp. OR aged.mp. OR elderly.mp OR older.mp	exp Longitudinal Studies/OR exp Prospective Studies/ OR exp Followup Studies/ OR follow up.mp. OR prospective.mp. OR longitudinal.mp.
With limits: English language, Human				

(((exp Self Report/ OR exp Diagnostic Self Evaluation/ OR exp Self-Assessment OR subjective.mp. OR self rated.mp. OR self report.mp.)

AND

(exp Memory/ OR exp Cognition/ OR exp OR cognit*.mp. OR memory.mp.)

AND

(exp Memory Disorders/ OR exp Cognition Disorders/ OR change*.mp. OR impairment*.mp. OR complaint*.mp. OR disorder*.mp. OR decline.mp. OR concern*.mp. OR difficult*.mp.))

OR ((exp Memory/ OR exp Cognition/ OR cognit*.mp. OR memory.mp.) AND complaint*.mp.))

AND (exp Aging/ OR exp Aged/ OR aging.mp. OR ageing.mp. OR aged.mp. OR elderly.mp OR older.mp)

AND (exp Longitudinal Studies/OR exp Prospective Studies/ OR exp Followup Studies/ OR follow up.mp. OR prospective.mp. OR longitudinal.mp.)

PsycINFO (1987 – present)				
Subjective	Cognitive/ Memory	Decline	Ageing	Longitudinal studies
exp Self Report/ OR exp Self Evaluation/ OR subjective.mp. OR self rated.mp. OR self report.mp.	exp Memory/ OR exp Cognition/ OR exp Cognitive Ability/ OR exp Cognitive Impairment/ OR cognit*.mp. OR memory.mp.	exp Memory Disorders/ OR exp Brain Disorders/ OR change*.mp. OR impairment*.mp. OR complaint*.mp. OR disorder*.mp. OR decline.mp. OR concern*.mp. OR difficult*.mp.	exp Aging/ OR aging.mp. OR ageing.mp. OR aged.mp. OR elderly.mp OR older.mp	exp Longitudinal Studies/OR exp Prospective Studies/ OR exp Followup Studies/ OR follow up.mp. OR prospective.mp. OR longitudinal.mp.
With limits: English language, Human				

(((exp Self Report/ OR exp Self Evaluation/ OR subjective.mp. OR self rated.mp. OR self report.mp.)

AND

(exp Memory/ OR exp Cognition/ OR exp Cognitive Ability/ OR exp Cognitive Impairment/ OR cognit*.mp. OR memory.mp.)

AND

(exp Memory Disorders/ OR exp Brain Disorders/ OR change*.mp. OR impairment*.mp. OR complaint*.mp. OR disorder*.mp. OR decline.mp. OR concern*.mp. OR difficult*.mp.))

OR ((exp Memory/ OR exp Cognition/ OR exp Cognitive Ability/ OR exp Cognitive Impairment/ OR cognit*.mp. OR memory.mp.) AND complaint*.mp.))

AND (exp Aging/ OR aging.mp. OR ageing.mp. OR aged.mp. OR elderly.mp OR older.mp)

AND (exp Longitudinal Studies/OR exp Prospective Studies/ OR exp Followup Studies/ OR follow up.mp. OR prospective.mp. OR longitudinal.mp.)

Appendix B: Retrieved Studies from the Same Cohort and Decisions Made re Inclusion

Cohort	Included in Meta-Analysis	Outcome	Rationale	Excluded Studies Retrieved for Closer Inspection
3C study	**Montlahuc et al (2011).** Self-rated health and risk of incident dementia: A community-based elderly cohort, the 3C Study. Neurology. Vol.77(15), 1457-1464.	Dementia	Appropriate effect size not provided in excluded study.	Stewart et al (2011). Longitudinal neuroimaging correlates of subjective memory impairment: 4-year prospective community study. The British Journal of Psychiatry. Vol.198(3), 199-205.

AgeCoDe	Heser et al. (2019). Subjective cognitive decline may be a stronger predictor of incident dementia in women than in men. Journal of Alzheimer's Disease. Vol. 68(4), 1469-1478. **Luck et al (2010).** Risk factors for incident mild cognitive impairment- Results from the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe). Acta Psychiatrica Scandinavica. Vol.121(4), 260-272.	Dementia & MCI	Heser (2019) has longest follow up (13 years) for development of dementia Luck (2010) has longest follow up (3 years) for development of MCI.	Jessen et al (2014)**.** AD dementia risk in late MCI, in early MCI, and in subjective memory impairment. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. Vol.10(1), 76-83. Roehr et al (2019). Is function in instrumental activities of daily living a useful feature in predicting Alzheimer's disease dementia in subjective cognitive decline? International journal of geriatric psychiatry. Vol 34(1), 193-203. Luck et al (2020). Determinants of incident dementia in different old age groups: Results of the prospective AgeCoDe/AgeQualiDe study. International Psychogeriatrics, Vol 32(5), 645-659. Wolfsgruber et al (2016). Differential risk of incident Alzheimer's disease dementia in stable versus unstable patterns of subjective cognitive decline. Journal of Alzheimer's Disease, Vol 54(3), 1135-1146. Heser et al (2020). Sex-specific associations between depressive symptoms and risk for subsequent dementia. Journal of Alzheimer's Disease, Vol 74(1), 151-161. Jessen et al (2010). Prediction of dementia by subjective memory impairment. Archives of General Psychiatry. Vol.67(4), 414-422. Heser et al (2013). Age of major depression onset, depressive symptoms, and risk for subsequent dementia: results of the German study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe). Psychological Medicine. Vol.43(8), 1597-1610. Jessen et al (2011). Prediction of dementia in primary care patients. PLoS ONE. Vol.6(2), e16852. Luck et al (2014). A hierarchy of predictors for dementia-free survival in old-age: Results of the AgeCoDe study. Acta Psychiatrica Scandinavica. Vol.129(1), 63-72.

				Roehr et al (2015). Mortality in incident dementia - results from the German Study on Aging, Cognition, and Dementia in Primary Care Patients. Acta Psychiatrica Scandinavica. Vol.132(4), 257-69.
AMSTEL	**Schmand et al (1997).** Subjective memory complaints in the elderly: depressive symptoms and future dementia. British Journal of Psychiatry. Vol.171(04), 373-376.	Dementia	Larger sample than Schmand (1996) and longer follow up than Geerlings (1999) and Lugtenburg (2016).	Geerlings et al (1999). Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. The American Journal of Psychiatry. Vol.156(4), 531-537. Schmand et al (1996). Subjective memory complaints may announce dementia. Neurology. Vol.46(1), 121-125. Lugtenburg et al (2016). Symptom Dimensions of Depression and 3-Year Incidence of Dementia: Results From the Amsterdam Study of the Elderly. Journal of Geriatric Psychiatry & Neurology. Vol.29(2), 99-107.
Betula	**Ronnlund et al (2015).** Subjective memory impairment in older adults predicts future dementia independent of baseline memory performance: Evidence from the Betula prospective cohort study. Alzheimer's & Dementia. Vol.11(11), 1385-1392.	Dementia	Larger sample, longer follow up.	Ronnlund et al (2015). Self-Reported Memory Failures: Associations with Future Dementia in a Population-Based Study with Long-Term Follow-Up. Journal of the American Geriatrics Society. Vol.63(9), 1766-1773.

CLS	**Jorm et al (1997).** Do cognitive complaints either predict future cognitive decline or reflect past cognitive decline? A longitudinal study of an elderly community sample. Psychological Medicine. Vol.27(1), 91-98.	Dementia	Jorm et al (1997) answers both cognitive change and dementia questions and examines subjective memory decline as well as subjective decline in other areas of cognition.	Jorm et al (2001). Memory complaints as a precursor of memory impairment in older people: A longitudinal analysis over 7-8 years. Psychological Medicine. Vol.31(3), 441-449.
CBH	**Reisberg et al (2010).** Outcome over seven years of healthy adults with and without subjective cognitive impairment. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. Vol.6(1), 11-24.	Dementia & MCI	More recent and provides data more appropriate to our questions.	Glodzik-Sobanska et al (2007). Subjective memory complaints: Presence, severity and future outcome in normal older subjects. Dementia and Geriatric Cognitive Disorders. Vol.24(3), 177-184.
Kungsholmen	**Palmer et al (2003).** Detection of Alzheimer's disease and dementia in the preclinical phase: population based cohort study. BMJ. Vol.326(7383), 245-247.	Dementia	Appropriate effect size not provided in Palmer et al. (2002); Palmer et al (2008). Larger sample than Berger et al (1999).	Palmer et al (2002). Differential evolution of cognitive impairment in nondemented older persons: Results from the Kungsholmen Project. The American Journal of Psychiatry. Vol.159(3), 436-442. Palmer et al (2008). Early symptoms and signs of cognitive deficits might not always be detectable in persons who develop Alzheimer's disease. International Psychogeriatrics. Vol.20(2), 252-258. Berger et al (1999). The occurrence of depressive symptoms in the preclinical phase of AD: A population-based study. Neurology. Vol.53(9), 1998-2002.

LADIS	**Verdelho et al (2011).** Self-perceived memory complaints predict progression to Alzheimer disease. The LADIS study. Journal of Alzheimer's Disease. Vol.27(3), 491-498.	Dementia	Appropriate effect size not provided in excluded study.	Verdelho et al (2013). Depressive symptoms predict cognitive decline and dementia in older people independently of cerebral white matter changes: the LADIS study. Journal of Neurology, Neurosurgery & Psychiatry. Vol.84(11), 1250-1254.
LLSA	**Luck et al (2015).** Incident subjective memory complaints and the risk of subsequent dementia. Acta Psychiatrica Scandinavica. Vol.131(4), 290-296. **Luck et al (2010).** Mild cognitive impairment: Incidence and risk factors: Results of the Leipzig Longitudinal Study of the Aged. Journal of the American Geriatrics Society. Vol.58(10), 1903-1910.	Dementia & MCI	Luck (2010) for risk of MCI, Luck (2015) for risk of dementia.	
MSHA/CSHA	**St John et al (2002).** Are cognitively intact seniors with subjective memory loss more likely to develop dementia? International Journal of Geriatric Psychiatry. Vol.17(9), 814-820.	Dementia & MCI	Excluded studies control for bilingualism or self rated health which is not as directly answering our research questions.	Yeung et al (2014). Is bilingualism associated with a lower risk of dementia in community-living older adults? Cross-sectional and prospective analyses. Alzheimer Disease and Associated Disorders. Vol.28(4), 326-332. St John et al (2013). Does self-rated health predict dementia? Journal of Geriatric Psychiatry and Neurology. Vol.26(1), 41-50.

NACC	**Gifford et al (2014).** The source of cognitive complaints predicts diagnostic conversion differentially among nondemented older adults. Alzheimer's & Dementia. Vol.10(3), 319-327. Liew (2019). Depression, subjective cognitive decline, and the risk of neurocognitive disorders. Alzheimer's Research & Therapy. Vol. 11(1), 70.	Dementia & MCI	Gifford (2014) for risk of MCI, Liew (2019) for risk of dementia. Gifford provides longest follow-up for MCI (3.5 years); Liew provides longest follow-up for dementia (4.4 years). Donovan, Dave, and Farias are cohorts of the NACC sample., hence smaller samples.	Donovan et al (2014). Subjective cognitive concerns and neuropsychiatric predictors of progression to the early clinical stages of Alzheimer's disease. The American Journal of Geriatric Psychiatry. Vol.22(12), 1642-1651. Dave (2009). Accuracy of subjective cognitive complaints in a longitudinal context: The effect of depression and dementia status. PhD thesis. Kielb et al (2017). Objective features of subjective cognitive decline in a United States national database. Alzheimer's & dementia. Vol. 13(12), 1337-1344. Stabler (2017). Conversion to mild cognitive impairment of cognitively normal older adults compared to research volunteers and clinic patients with baseline subjective memory complaints. PhD thesis. Farias et al (2017). Early functional limitations in cognitively normal older adults predict diagnostic conversion to mild cognitive impairment. Journal of the American Geriatrics Society. Vol. 65(6), 1152-1158.
Paquid	**Peres et al (2011).** Gender differences in the prodromal signs of dementia: Memory complaint and IADL-restriction. A prospective population-based cohort. Journal of Alzheimer's Disease. Vol.27(1), 39-47.	Dementia	Appropriate effect size not provided in excluded studies.	Amieva et al (2014). Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: a study of 20 years of cognitive decline. Brain. Vol. 137(4), 1167-1175. Amieva et al (2008). Prodromal Alzheimer's disease: Successive emergence of the clinical symptoms. Annals of Neurology. Vol.64(5), 492-498. Chary et al (2013). Short-versus long-term prediction of dementia among subjects with low and high educational levels. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. Vol.9(5), 562-571.

Rotterdam Study	**Van Oijen et al (2007).** Subjective memory complaints, education, and risk of Alzheimer's disease. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. Vol.3(2), 92-97.	Dementia	Appropriate effect size not provided in Den Heijer and Verlinden studies; van Oijen has longest follow up (10.8 years).	Licher et al (2019). Development and validation of a dementia risk prediction model in the general population: An analysis of three longitudinal studies. American Journal of Psychiatry. Vol 176(7), 543-551. Den Heijer et al (2006). Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people. Archives of General Psychiatry. Vol.63(1), 57-62. Verlinden et al (2016). Trajectories of decline in cognition and daily functioning in preclinical dementia. Alzheimer's & Dementia. Vol.12(2), 144-153.
SMAS	**Brodaty et al (2017).** Operationalizing the diagnostic criteria for mild cognitive impairment: The salience of objective measures in predicting incident dementia. American Journal of Geriatric Psychiatry. Vol. 25(5), 485-497.	Dementia	Brodaty has longest follow up (6 years).	Slavin et al (2015). Predicting cognitive, functional, and diagnostic change over 4 years using baseline subjective cognitive complaints in the Sydney Memory and Ageing Study. American Journal of Geriatric Psychiatry. Vol 23, 906-914.
Vallecas	**Fernandez-Blazques et al (2016).** Specific features of subjective cognitive decline predict faster conversion to mild cognitive impairment. Journal of Alzheimers Disease. Vol. 52, 271-281.	MCI	Excluded study does not provide data in appropriate effect size.	Avila-Villanueva et al (2018). Internal consistency over time of subjective cognitive decline: Drawing preclinical Alzheimer's disease trajectories. Journal of Alzheimer's Disease. Vol 66(1), 173-183.

VITA	**Jungwirth et al (2009).** Screening for Alzheimer's dementia at age 78 with short psychometric instruments. International Psychogeriatrics. Vol.21(3), 548-559.	Dementia	Jungwirth et al (2009) J Neural Transmission has longest follow up. BUT issues that controls includes possible AD. So include Jungwirth et al (2009) Int psychogeriatrics.	Jungwirth et al (2008). Do subjective memory complaints predict senile Alzheimer dementia? Wiener Medizinische Wochenschrift. Vol.158(3-4), 71-77. Jungwirth et al (2009). Prediction of Alzheimer dementia with short neuropsychological instruments. Journal of Neural Transmission. Vol.116(11), 1513-1521.

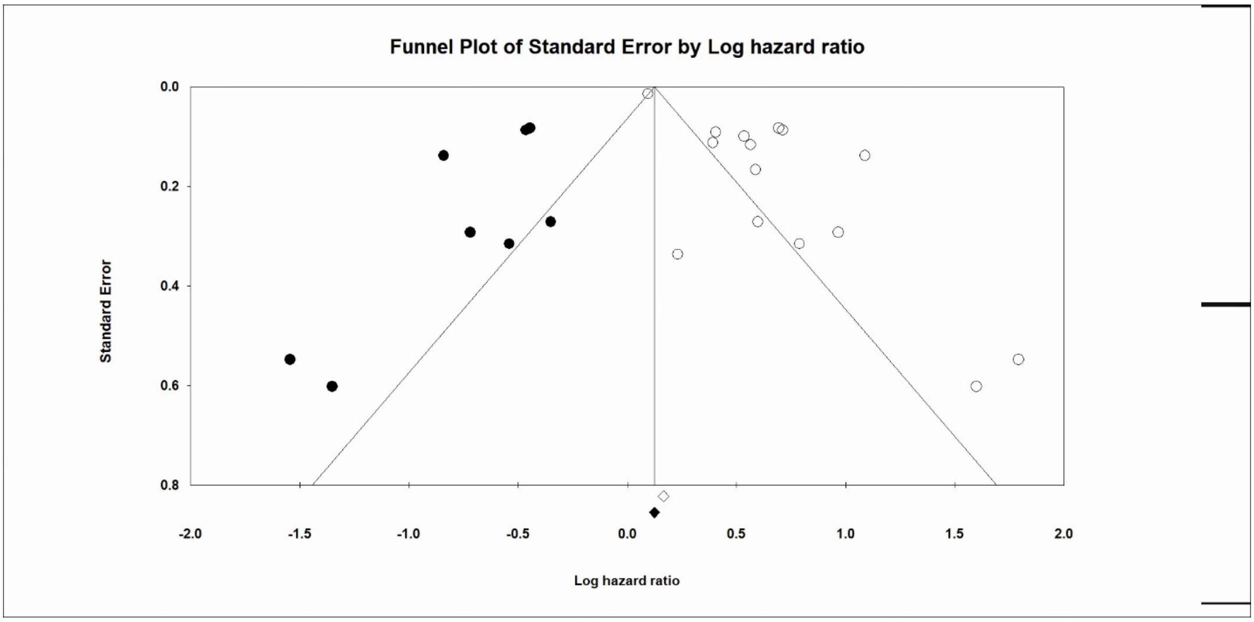
Abbreviations: 3C Study, Three-City Study; AgeCoDe, Ageing, Cognition and Dementia in Primary Care Patients; AMSTEL, Amsterdam Study of the Elderly; CLS – Canberra longitudinal study; CBH, Centre for Brain Health; LADIS, Leukoaraiosis and Disability; LLSA, Leipzig Longitudinal Study of the Aged; MSHA/CSHA, Manitoba Study of Health and Aging/Canadian Study of Health and Aging; NACC, National Alzheimer’s Coordinating Center; SMAS, Sydney Memory and Ageing Study; VITA, ViennaTransDanube Aging study.

Appendix C: Signalling Questions Used to Assess Risk of Bias in each QUADAS-2 Tool Domain

Domain	Signalling question(s)
Patient selection	1. Are the baseline demographics of controls and SCD well matched? 2. Was the same recruitment source used for controls and SCD? 3. Was the same screening process applied to controls and SCD?
Index test (SCD)	1. Does the definition of SCD capture the group of interest? 2. Was there sufficient screen of cognitive impairment at baseline?
Reference standard (outcome)	1. Was a valid outcome measure used? 2. Were those making the outcome diagnoses blind to SCD status? 3. Was there no selectivity in reporting of outcomes?
Patient flow and timing	1. Was attrition similar across SCD and controls?

Appendix D: Funnel Plots Assessing Publication Bias

Fig D1: Funnel plot of publication bias for incident dementia hazard ratio studies



Note. Solid black data points indicate imputed data using Duval & Tweedie’s trim and fill

Fig D2: Funnel plot of publication bias for incident dementia odds ratio studies

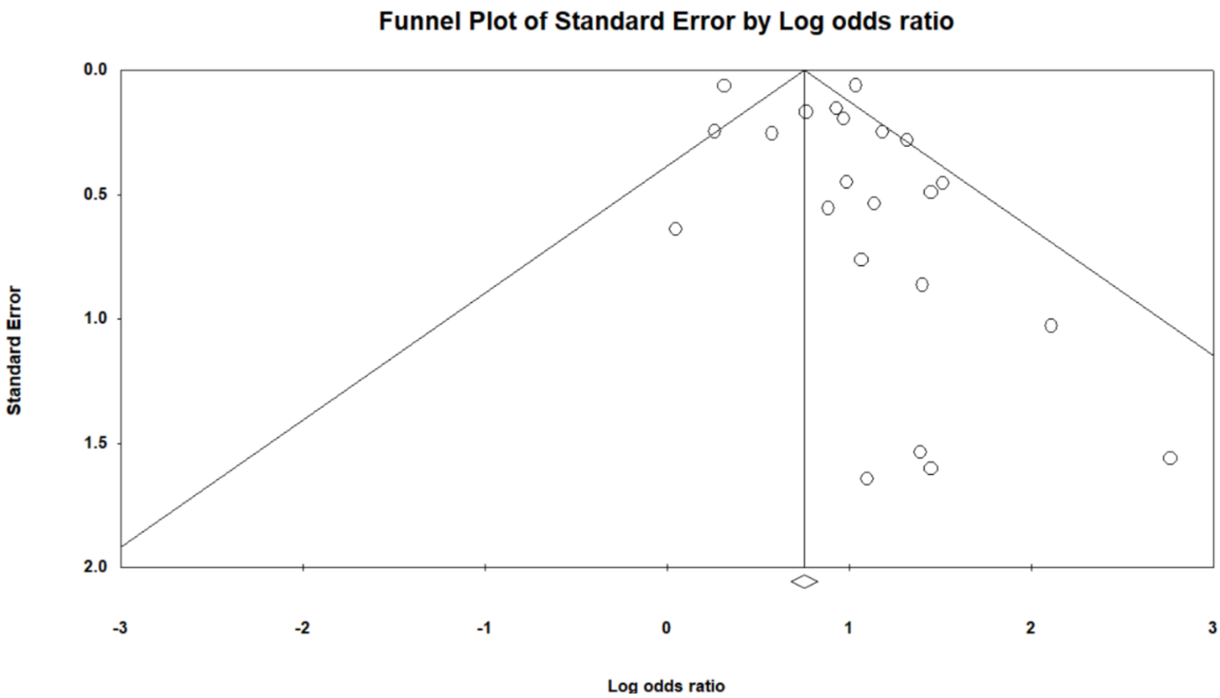
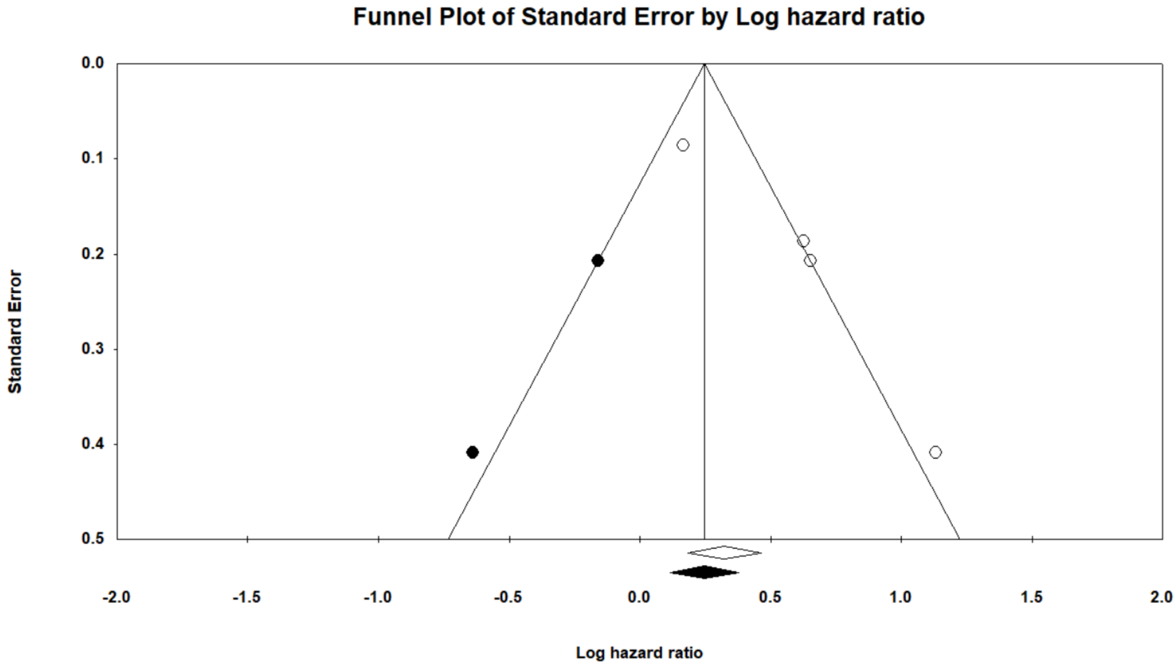
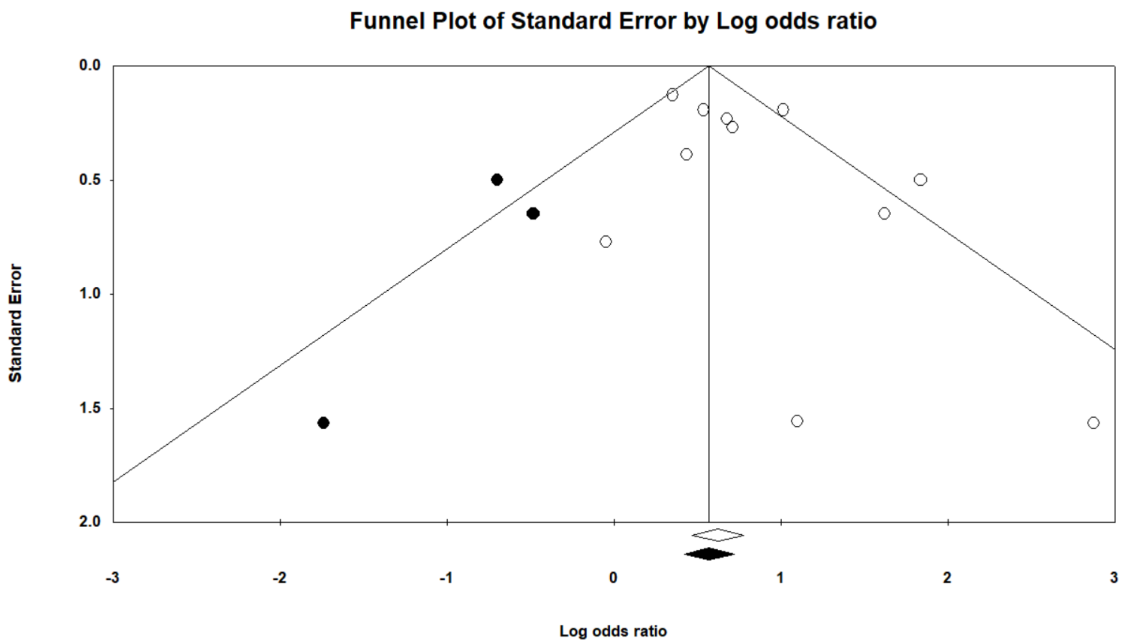


Fig D3: Funnel plot of publication bias for incident mild cognitive impairment hazard ratio studies



Note. Solid black data points indicate imputed data using Duval & Tweedie's trim and fill.

Fig D4: Funnel plot of publication bias for incident mild cognitive impairment odds ratio studies



Note. Solid black data points indicate imputed data using Duval & Tweedie's trim and fill.

Appendix E: Moderation analyses

Table E1. Subgroup moderator analyses: definition and recruitment source

Moderator	Outcome	*Q*	*df*	*p*
Type of question	HR dementia	1.44	2	.487
	OR dementia	1.60	3	.660
	HR MCI	0.02	1	.884
	OR MCI	9.26	3	.026
Decline in definition	HR dementia	1.15	1	.284
	OR dementia	4.85	1	.028
	HR MCI	0.02	1	.884
	OR MCI	1.90	1	.168
Mood	HR dementia	1.12	1	.290
	OR dementia	1.85	1	.174
	HR MCI	1.35	1	.246
	OR MCI	0.55	1	.460
Worry in definition	HR dementia*	65.76	1	<.001
	OR dementia	1.73	1	.188
	HR MCI	0.07	1	.795
	OR MCI*	9.28	1	.002
Recruitment source	HR dementia	0.42	2	.811
	OR dementia	4.46	2	.107
	HR MCI	2.32	1	.127
	OR MCI*	9.91	2	.007

Note. HR = Hazard ratio; OR = Odds ratio; MCI = mild cognitive impairment. $^{*}p<.01$.

Table E2. Meta-regression moderator analyses: Demographics, genetics, and duration of follow-up

Moderator	Outcome	*k*	R^2 analog	*Q*	*df*	*p*
Age	HR dementia	15	0.39	0.19	1	.666
	OR dementia	20	0.23	2.18	1	.140
	HR MCI	4	0.00	0.33	1	.566
	OR MCI*	10	0.86	8.56	1	.003
Gender	HR dementia	15	0.00	0.23	1	.630
	OR dementia	21	0.00	1.07	1	.300
	HR MCI	4	0.00	0.54	1	.464
	OR MCI	11	0.00	0.08	1	.776
Education[a]	HR dementia[a]	5	0.00	0.01	1	.915
	OR dementia	11	0.00	0.09	1	.768
	OR MCI	8	0.51	2.90	1	.089
APOE e4 carriage[a]	HR dementia	4	1.00	5.90	1	.015
	OR dementia	8	0.00	0.75	1	.385
	OR MCI	4	1.00	3.15	1	.076
Follow-up duration[a]	HR dementia	15	0.23	0.49	1	.482
	OR dementia	21	0.06	0.96	1	.327
	OR MCI	10	0.14	1.58	1	.209

Note. HR = Hazard ratio; OR = Odds ratio; MCI = mild cognitive impairment. *p<.01. [a]Meta-regression could not be conducted for HR MCI as education, APOE status, and follow-up duration were available for <4 studies.