Affective symptoms and risk of progression to mild cognitive impairment or dementia in subjective cognitive decline: A systematic review and meta-analysis

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Counts:

Abstract: 197

Main Text: 3667

Figures & tables: 5

References: 42

Declarations of interest: none

Abstract

Aims: To systematically review the literature on outcomes for individuals with subjective cognitive decline (SCD) with concurrent affective symptoms. To conduct a meta-analysis to establish whether either higher depressive symptoms or higher levels of anxiety increased the risk of progression SCD to mild cognitive impairment (MCI) or dementia.

Methods: Five databases were searched from inception to February 2021 for longitudinal studies of older adults with SCD, reporting depressive and anxiety symptoms at baseline and risk of MCI or dementia at follow-up. Data were extracted and pooled using a random-effects meta-analysis.

Results: Twelve studies were identified. Pooled effect sizes indicated higher depressive symptoms did not increase risk of clinical progression to either MCI (RR= 0.98; 95% CI: 0.75 − 1.26) or dementia (RR= 0.69; 95% CI: 0.27 − 1.79). However, presence of anxiety or SCD-related worry did significantly increase risk of progression from subjective to objective cognitive impairment by 40% (RR= 1.40; 95% CI:1.20 − 1.63).

Conclusions: Affective symptoms in the form of anxiety, but not depressive symptoms, increase the risk of progression to objective cognitive impairment in individuals with SCD. Further research should focus on establishing whether psychological interventions aimed at reducing anxiety and worry also reduce the risk of clinical progression.

1. Introduction

Subjective cognitive decline (SCD) is the perception of a persistent decline in cognitive abilities often in, but not limited to, the memory domain in the absence of objective neuropsychological indictors of decline (Jessen et al., 2014). Although SCD is relatively common (Holmen et al., 2013; Mitchell, 2008),in the last decade it has come to prominence within the field of aging research because of its utility in predicting subsequent mild cognitive impairment (MCI) and dementia (Mendonça et al., 2016; Mitchell et al., 2014). Various terms have been used interchangeably in the literature to describe the concept of a self-perceived decline in cognition including, 'subjective cognitive complaints', 'subjective memory decline' and 'self-reported cognitive impairment'. However, this use of multiple interchangeable terms led to difficulty in comparing and combining findings from research studies (Jessen et al., 2014). To try to address these difficulties, an international working group initiative proposed and reached a consensus definition for SCD as well as a subgroup (SCD *plus*) describing a specific profile conferring a higher risk of subsequent decline (Jessen et al., 2014).

SCD is a relatively common experience which increases with age (Mitchell, 2008) with studies reporting prevalence rates of between 50-80% in older community-dwelling individuals (Balash et al., 2013; Holmen et al., 2013). Evidence from longitudinal studies suggests that SCD predicts MCI and dementia (Hessen et al., 2017). A meta-analysis combining the results from 28 studies found that individuals with SCD have up to two times the risk of progressing to dementia when compared to those without SCD (Mitchell et al., 2014) and another review found that in 16 out of 17 studies SCD was consistently associated with a higher risk of progression to cognitive impairment (Mendonça et al., 2016). When neurobiological changes are taken into account, for example in individuals with elevated

beta-amyloid burden as well as SCD, then this increases to a fivefold increased risk of progression (Buckley et al., 2016).

The observation that in some instances SCD progresses to MCI which in turn may further progress to dementia has led some researchers to propose the continuum hypothesis of dementia (Cheng et al., 2017; Sperling et al., 2011). This theory proposes that within the continuum between normal cognition and dementia, SCD is one of the earliest indicators of neurobiological changes which may ultimately result in dementia. However, it is also clear that SCD in not an indicator of future cognitive decline for most individuals. In fact, some authors have reported overall conversion rates as low as 14% when individuals are followed up over six years (Hessen et al., 2017) while others have highlighted the lack of temporal stability of the construct with up to 70% of SCD cases following an inconsistent pattern over time (Roehr et al., 2016). One reason for the lack of predictive validity of SCD is due to the aetiological heterogeneity of the construct. The subjective experience of a decline in cognition is also closely associated with other factors such as personality (Pearman and Storandt, 2005) and affective symptoms (Balash et al., 2013). Currently it is unclear how anxiety and depressive symptoms interact, if at all, with SCD or the progression of cognitive impairment.

In the case of depressive symptoms, this has been widely studied in relation to dementia risk and is considered to be a putative risk factor for incident dementia (Livingston et al., 2020). Meta-analyses have shown that depressive episodes can elevate the risk of dementia by up to two-fold (Prince et al., 2014). The Lancet Commission on dementia further reports that if late life depression were to be eliminated there would be a corresponding reduction in dementia prevalence of 4% (Livingston et al., 2020). Although depression has been highlighted as an important modifiable risk factor in dementia prevention less attention has been focused on anxiety.

However, more recently research that investigates the role of anxiety has found evidence to suggest that anxiety is also linked to cognitive decline. Four recent reviews have identified anxiety (Becker et al., 2018; Gimson et al., 2018; Gulpers et al., 2016) or post-traumatic stress disorder (Günak et al., 2020) as independent risk factors for cognitive decline and dementia. With the results from one meta-analyses indicating that anxiety increases the risk of dementia by 57% (Gulpers et al., 2016).

Whilst Jessen's framework identifies depressive symptoms, anxiety and concerns about cognitive decline to be elevated in individuals with SCD and SCD plus there are no

meta-analytic studies investigating if higher affective symptoms increase the risk of clinical progression. Specifically, the question of whether individuals presenting with SCD and with higher depressive or anxiety symptoms are at greater risk of clinical progression than those with lower depressive or anxiety symptoms has not been addressed. Therefore, the aim of the current study was to conduct a systematic review and meta-analysis to ascertain whether higher levels of depressive symptoms or anxiety and SCD-related worry conferred a greater risk of cognitive decline in individuals with SCD.

2. Methods

2.1 Systematic search and study selection

Our systematic review protocol was completed in advance and registered on PROSPERO (Ref: CRD42020172432). Five databases (Medline, PubMed, PsycInfo, Embase and Web of Science) were searched from inception to 22nd February 2021. Keywords that were included as part of the search strategy were: ("self-reported/subjective cognitive complaints" OR "self-reported/subjective cognitive decline" OR "self-reported/subjective cognitive impairment" OR "self-reported/subjective cognitive difficulties" OR "self-reported/subjective memory complaints" OR "self-reported/subjective memory difficulties" OR "self-reported/subjective memory impairment" OR "self-reported/subjective memory decline") AND ("dementia" OR "Alzheimer's disease" OR "vascular dementia" OR "mild cognitive impairment" OR "cognitive dysfunction" OR "cognitive change" OR "mild cognitive complaints" OR "MCI"). Title and abstracts were screened for relevance and the remaining articles were subject to a full text screen. Review articles were excluded but the reference lists of two reviews(Mendonça et al., 2016; Mitchell et al., 2014) were hand searched for further relevant studies.

2.2 Study selection

Studies were included if they were published in peer-reviewed journals in English, were longitudinal cohort studies, included participants had normal cognition and SCD at baseline, reported depressive or anxiety symptoms at baseline and had an outcome of MCI or dementia at follow-up. One reviewer (RD) completed the title, abstract and full text screen for the full pool of studies, while a second reviewer (TW) independently rated 10% at each stage of the screening process. Inter-rater reliability was calculated for each stage of the screening process. Where more than one study reported data using the same population cohort, the study reporting the largest sample size was included in the final analysis.

2.3 Methodological quality assessment

Two reviewers (RD and TW) independently assessed the quality of all included papers using the Joanna Briggs Institute critical appraisal checklist for cohort studies (JBI assessment tool) (Moola et al., 2017). The JBI assessment tool uses a pragmatic approach to assess the risk of bias on 11 domains. These domains include: population recruited, measurement of risk factor, validity of risk factor measurement, management of confounders, whether the participants are outcome free at baseline, outcome measurement, validity of outcome measurement, follow-up time, attrition levels, strategies to deal with attrition and statistical analysis. Each domain was assessed as 'yes', 'no', 'unclear' or 'not applicable' corresponding to 'low', 'high', and 'medium' risk of bias. Studies were given an overall 'low' risk of bias if all or the majority of domains assessed were rated as 'low'. Similarly, studies were given overall ratings of 'medium' and 'high' risk of bias depending on the number of domains that were rated as 'high' risk of bias. For the purposes of the current review, it was determined in advance that studies with nine or more quality domains rated as 'low' risk would be given an overall low risk of bias rating. Studies with between eight and six quality domains rated 'low' risk would be given an overall medium risk of bias rating and studies with five or fewer items rated 'low' risk would be given an overall high risk of bias rating.

2.4 Data extraction and measure of effect size

Two researchers (RD and AJ) extracted all the data presented in Table 1. Disagreements were resolved through consensus meetings. Where studies reported odds ratios (OR), these estimates were extracted directly. In studies reporting hazard ratios (HR)

these figures were extracted and interpreted as relative risks (RR) as per the guidelines provided by the Cochrane handbook (Higgins and Green, 2011). In studies which reported a HR relative to a different reference group than the one of interest for the current study, the estimates were transformed so that the reference group was SCD with no or sub clinical affective symptoms. In studies where it was not possible to transform the data the author of the study was contacted and frequency data requested. The frequency data were used to calculate the OR. Where studies reported means and standard deviations for affective symptoms for those who progressed to MCI or dementia and for those who remained stable, these data were also extracted. The standardised mean difference (SMD) was calculated and subsequently transformed to an OR. In this way, all the estimates were transformed to or interpreted as RR and pooled for the meta-analysis.

2.5 Meta-analysis

In the first instance, two meta-analyses were run to calculate the risk of cognitive progression (combining MCI and dementia outcomes) in people with SCD with depressive symptoms and separately for anxiety or SCD-related worry. An inverse variance weighted random-effects model was used to account for heterogeneity (Higgins and Green, 2011). In cases where significant, $p < 0.1$ (Higgins et al., 2021), levels of heterogeneity rendered the results uninterpretable, planned sub-group analyses were run separately for the outcomes of MCI or dementia. Publication bias was assessed by plotting the standard error of each estimate against its log risk ratio for each study to produce funnel plots. Egger's test was used to assess for funnel plot asymmetry. All analyses were performed using RStudio (2016) software version 1.1.419 and the metafor package for R (Viechtbauer, 2010). The robvis package in R (McGuinness and Higgins, 2020) was used to create a plot of study risk of bias.

3. Results

3.1 Study selection

A total of 6647 articles were identified from the initial database search. After removing duplicates and screening on title and abstract, 192 articles were subjected to a full text examination. This resulted in 25 studies meeting inclusion criteria (see Figure 1 for the

PRISMA flow diagram). There was an overall agreement level of 97% for the title and abstract stage and a 94% level of agreement at the full text stage. Disagreements were resolved by discussion in consensus meetings. Thirteen studies were identified as having overlapping cohorts and excluded and leaving 12 studies.

Eight of these studies (Bessi et al., 2018; Hong et al., 2015; Jessen et al., 2010; Kim et al., 2006; Liew, 2019; Mazzeo et al., 2020; Reisberg et al., 2010; Yue et al., 2021) reported data on individuals with SCD and depressive symptoms. Two studies (Luck et al., 2020; Snitz et al., 2018) reported data on SCD-related worry. One study reported data on anxiety (Liew, 2020) and one study (Fernández-Blázquez et al., 2016) reported both depressive symptoms and state anxiety symptoms and the relevant estimates were used in the separate depression and anxiety meta-analyses. Thus, the results from nine studies were pooled for the depression analysis and four pooled for the anxiety and SCD-related worry analysis.

Insert figure 1 about here

3.2 Characteristics of the studies

The characteristics of all included studies are presented in Table 1. The year of baseline data collection ranged from 1984 to 2019 with follow-up periods ranging from 0.5 to 27.2 years. Sample sizes in the studies ranged from 53-13462. The mean age of the study samples ranged from 61.3 to 79.7 years and all the study populations comprised a greater proportion of females (range 52.6% to 78.3%). Nine of the 12 studies met criteria for low risk of bias, two for medium risk (Fernández-Blázquez et al., 2016; Jessen et al., 2010) and one for high risk of bias (Kim et al., 2006) (See Table 2 for risk of bias assessment for all studies).

A range of different measures of SCD were used by the studies. Five studies (Hong et al., 2015; Jessen et al., 2010; Liew, 2020, 2019; Luck et al., 2020) used a single item question. Two studies (Fernández-Blázquez et al., 2016; Yue et al., 2021) use the SCD-I framework (Jessen et al., 2014). Two studies (Bessi et al., 2018; Mazzeo et al., 2020) used a measure of SCD which was defined as a self-perceived decline in four out of five everyday activities. One study (Kim et al., 2006) used a subset of questions from the Geriatric Mental State Schedule which taps into presence and severity of memory difficulties and SCD was operationalised as a score >3. One study (Reisberg et al., 2010) used the Global Deterioration Scale for age-associated cognitive decline and dementia. One study (Snitz et al., 2018) used a 16-item

questionnaire related to memory self-appraisal. All studies conducted comprehensive neuropsychological assessments to screen for normal cognition at baseline.

Insert table 1 about here

3.3 Meta-analyses

SCD, depressive symptoms and risk of clinical progression

There was heterogeneity in how clinical progression was defined and measured across the studies. Three studies (Hong et al., 2015; Liew, 2019; Reisberg et al., 2010) collapsed dementia and MCI outcomes into an overall clinical progression outcome, four studies (Bessi et al., 2018; Fernández-Blázquez et al., 2016; Jessen et al., 2010; Yue et al., 2021) used MCI, and two studies (Kim et al., 2006; Mazzeo et al., 2020) specified dementia as the outcome. In the first instance, data from all nine studies were combined, representing the pooled relative risk of individuals with SCD and depressive symptoms and clinical progression to MCI and or dementia. The pooled result was non-significant (RR = 0.90; 95% CI: 0.62 − 1.30) with significant levels of heterogeneity (χ^2 = 32.56, *df* = 8, *p* < 0.0001, I^2 = 80.17%). Planned sub-group analysis were thus carried out, separating the groups by outcome.

SCD, depressive symptoms and risk of MCI

The effect sizes of the four studies reporting results with MCI as the outcome were pooled. Pooling these three studies reduced the heterogeneity to non-significant levels (χ^2 = 3.27, *df* = 3, *p* = 0.35, I^2 = 0%) and indicated that higher depressive symptoms did not significantly increase the risk of MCI in individuals with SCD (RR = 0.98; 95% CI: 0.75 − 1.26) (Figure 2).

Insert Figure 2 about here

SCD, depressive symptoms and risk of dementia

The effect sizes of two studies reporting results with dementia as the outcome were pooled. Pooling these studies reduced the heterogeneity to non-significant levels (χ^2 = 2.66, *df* = 1, *p* = .10, I^2 = 62.35%) and indicated that higher depressive symptoms did not significantly increase the risk of dementia in individuals with SCD (RR = 0.69; 95% CI: 0.27 – 1.79) (Figure 3).

Insert Figure 3 about here

SCD, depressive symptoms and risk of cognitive progression

Three studies reported results using a single combined outcome of MCI and dementia. The pooled result was non-significant (RR = 0.88; 95% CI: 0.35 – 2.20) with significant levels of heterogeneity (χ^2 = 14.89, *df* = 2, *p* <.001, I^2 =91.63%) (Figure 4).

Insert Figure 4 about here

Anxiety and SCD-related worry *and risk of cognitive progression*

Four studies reported effect sizes for individuals with and without SCD-related worry (Luck et al., 2020; Snitz et al., 2018) or state anxiety (Fernández-Blázquez et al., 2016; Liew, 2020). Two of these studies (Fernández-Blázquez et al., 2016; Snitz et al., 2018) had MCI as an outcome, one study (Luck et al., 2020) had dementia as the outcome and one study (Liew, 2020) reported a combined depression and MCI outcome. The effect sizes of all four studies were pooled in a meta-analysis. The pooled result indicated that individuals with higher levels of anxiety or SCD-related worry were at a significantly increased risk of cognitive progression to either MCI or dementia (RR= 1.40; 95% CI:1.20 – 1.63). The level of heterogeneity in this model was non-significant (χ^2 = 5.54, *df* = 3, *p*= 0.14, I^2 = 52.55%) (Figure 5).

Insert Figure 5 about here

Post-hoc sensitivity analyses were conducted to assess the pooled effect of anxiety and SCD-related worry separately. In both cases, anxiety (RR= 1.26; 95% CI:1.14 – 1.40) and SCD-related worry (RR= 1.51; 95% CI:1.34 – 1.70) increased the risk of clinical progression. In both cases the overall level of heterogeneity was reduced and remained non-significant (anxiety: χ^2 = 0.41, *df* = 1, *p*= 0.52, I^2 = 0%; SCD-related worry: χ^2 = 0.28, *df* = 1, *p*= 0.59, I^2 = 0%;)

3.4 Publication bias

A funnel plot and Egger's test was used to assess publication bias separately for the depression and anxiety and SCD-related worry studies (Figure 7 & 8). For both sets of analyses the funnel plots appeared relatively symmetrical and the Egger's test was non-significant (depression studies: *z* = -0.91, *p* = 0.36; anxiety and SCD-related worry studies: *z* = 0.95, *p* = 0.34) indicating low likelihood of publication bias.

4. Discussion

This systematic review and meta-analysis aimed to establish within the group of individuals with SCD if greater depressive or anxiety symptoms elevated the risk of subsequently developing MCI and dementia. The results indicated that within the group of individuals with SCD, those with higher levels of depressive symptoms were not at a greater risk of progression to either MCI or dementia. On the other hand, if SCD was coupled with anxiety or worry then there was an elevated risk of progression to MCI or dementia when compared to individuals with SCD lower levels of anxiety. SCD-related worry is a known risk factor for clinical progression; however, this study is the first to identify that higher levels of anxiety may also be an exacerbating factor. The results are important as they identify a

subgroup of individuals within the SCD group who appear to be at greater risk of cognitive progression and also potentially identify a target for intervention.

4.1 Mechanisms and implications

It is clear from existing literature that depressive symptoms are associated with SCD (Açikgöz et al., 2014). However, the current study did not find evidence that higher depressive symptoms increased the risk of subsequent progression to MCI or dementia. One explanation for this finding may be due to aetiological differences within the group of individuals with SCD as a result of depressive symptoms and individuals with SCD as a result of being in the first phase of a dementia and with depressive symptoms. Across age groups depressive symptoms in their own right are widely reported as having a detrimental impact on cognition (McDermott and Ebmeier, 2009). In many cases the cognitive effects are resolved once the depressive symptoms have been treated or remit and, in older adults do not necessarily reflect an underlying subclinical dementia. In addition, individuals with higher depressive symptoms may be more vulnerable to negative interpretation biases which may heighten their experience of and lead to more reports of SCD. The studies included in the current review did not differentiate between individuals experiencing primarily depressive symptoms with resultant SCD and those experiencing primarily SCD and associated depressive symptoms. Future studies could focus on differentiating between these groups to better understand if having depressive symptoms as well as but separately to SCD poses a further risk to individuals with SCD in terms of cognitive progression.

Given the recommendations from the SCD working group (Jessen et al., 2014) that anxiety scores be captured as a distinct part of the framework for coding SCD, it is of note that measures of anxiety were not routinely reported by the studies included in this review. Only two studies reported a measure of anxiety and two captured rates of SCD-related worry. It is important to measure and report anxiety and SCD-related worry separately in the context of SCD as recommended by Jessen et al., (2014) as they may representative of different aspects of SCD. One explanation for the predictive utility of SCD-related worry is that it may be a more sensitive indicator of pre-clinical dementia than are offered by current objective measures and as such represent a symptom of preclinical dementia rather than a risk factor. Another plausible explanation for the overall finding of the elevated risk of clinical progression conferred by anxiety or SCD-related worry is offered by the cognitive debt hypothesis. This hypothesis proposes that worry or rumination in the form of repetitive

negative thinking has a detrimental physiological impact on brain structures via dysregulation of the hypothalamic-pituitary adrenal (HPA) axis (Marchant and Howard, 2015). Support for this theory comes from the finding that in cognitively intact individuals, repetitive negative thinking has been found to be associated with a steeper decline in cognition and higher levels of amyloid and tau pathology both of which are bio-markers of Alzheimer's disease (AD) (Marchant et al., 2020) and brain aging (Karim et al., 2021).

An important clinical implication of these results is the treatment of patients presenting to memory clinics with SCD and related worry. This group of people have traditionally been referred to as the 'worried well' and currently offered little in the way of clinical input or management. However, it is clear from the results of this study that this group are at an increased risk of further cognitive progression. Jessen et al., (2020), suggests that individuals with SCD actively seeking medical help should be offered tailored differential diagnosis and counselling to help them engage in pro-health activities. The results from this study should be incorporated into such treatment protocols with particular emphasis on anxiety reduction. In addition, to understand if interventions are useful in attenuating the risk of progression research needs be carried out to investigate if targeting anxiety and 'worry', using psychological interventions such as mindfulness, reduces cognitive decline and risk of dementia. A related area of research focus could be on assessing temporal trajectories of SCD. SCD trajectories are known to be unstable and, in this context, an important question to ask would be does anxiety reduction have impact on remission of SCD and facilitate more favourable outcomes? Answering these research questions could help to provide an evidence base for a tailored diagnosis and counselling approach as suggested by Jessen (2020).

4.2 Strengths and Limitations

A strength of the current study is that the majority of studies included were rated as low risk of bias. In addition, the analysis suggested that there was low risk that the results were affected by publication bias, indicating that these findings are relatively robust. A limitation of the current study and the SCD field in general is the lack of a standardised measure of SCD. Some studies included in this review used a single item question tapping into a person's experience of subjective decline in the memory domain whilst others used the SCD criteria as defined by Jessen and colleagues (2014). The publication of the established criteria means that studies completed and published prior to 2014 and some on-

going longitudinal cohort studies are still using legacy definitions of SCD. These older definitions of SCD are inherently diverse and have potentially introduced a degree of heterogeneity into the current review. However, no clear pattern of bias emerged based on the way SCD was assessed. Another limitation of note is the number of studies which measured anxiety and therefore contributed to the overall study findings. As this number is low the results of this study should be interpreted with caution and future studies should aim to replicate the current findings.

4.3 Conclusions

Higher depressive symptoms do not appear to increase the risk of cognitive progression in SCD. However, anxiety and SCD-related worry confers an increased risk of clinical progression to MCI or dementia in individuals with SCD. This may be a symptom of incipient dementia or underpinned by the dysregulation of the HPA axis and increased levels of AD pathology. Future studies should focus on assessing if psychological interventions aimed at reducing anxiety can also reduce the risk of progression in individuals with SCD.

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Studies identified through search of Medline (n=1047)

Studies identified through search of Pubmed (n=1539)

Studies identified through search of PsycINFO (n=929)

Studies identified through search of Embase (n=2726)

Studies identified through search of Web of Science (n=406)

Studies identified through database searches (n=6647)

Duplicates removed(n=2222)

Unique studies screened on title and abstract after duplicates removed (n=4425)

Articles excluded on title and abstract (n=4233)

Full text studies assessed for eligibility (n=192)

Full-text studies excluded
Type of population (n=11)
Not in English (n=2)
Type of publication (n=59)
Type of study design (n= 10)
Type of exposure (n=59)
Type of outcome (n=26)
Overlapping cohorts (n=13)

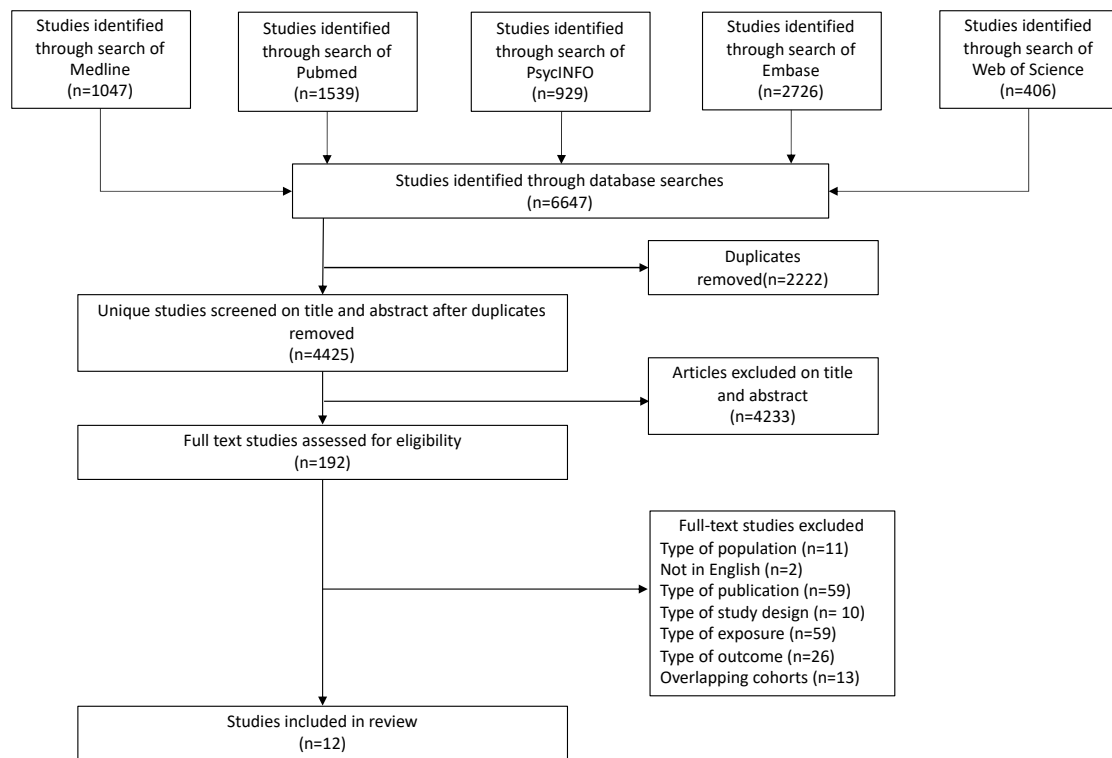Studies included in review (n=12)

Figure 1 Flow diagram of study selection

Table 1 Characteristics of included studies

Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses of interest	Population	Age mean (SD), range (years)	Woman (%)	SCD assessment	Assessment of affective symptoms	Outcome Assessment	Adjustment for covariates	Statistic reported	Effect size	95%CI
Bessi et al., 2018	Italy	1990	2.0-27.2	109	Self-referred consecutive patients at the Cognitive Disorders Centre	64.6 (7.03)	67.9	SCD was defined as present if participants perceived decline in cognitive capacity in > 4 out of 5 activities related to memory in everyday life	HDRS	MCI	None	Mean and standard deviation	MCI SMD=-0.07	-0.46 – 0.31
Fernández-Blázquez et al., 2016	Spain	NR	10.7-22.4	53	Cognitively intact community-dwelling individuals between 70-85years	74.14 (3.86)	62.0	Cognitive concerns were coded according to the SCD-I guidelines	GDS STAI	MCI	None	Mean and standard deviation	GDS: SMD=0.46 STAI -S SMD=0.36	-0.24 – 1.15 -0.34 – 1.05

Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses of interest	Population	Age mean (SD), range (years)	Woman (%)	SCD assessment	Assessment of affective symptoms	Outcome Assessment	Adjustment for covariates	Statistic reported	Effect size	95%CI
Hong et al., 2015	South Korea	2005-2013	0.5-4.7	129	Consecutive participants recruited from 31 dementia clinics in South Korea	65.9 (8.17)	78.3	Single question: 'Do you feel your memory is impaired?'	Korean version of the Neuropsychiatric Inventory (depression sub index)	Combined MCI and dementia	None	Mean and standard deviation	SMD=-0.65	-1.07 – -0.23
Jessen et al., 2010	Germany	2003-2004	1.5-3	1201	Participants aged 75+ recruited via GP surgeries	79.6 (3.7)	62.4	Single question: 'Do you feel like your memory is becoming worse?'	GDS	MCI	None	Mean and standard deviation	SMD > .0001	-0.16 – .001
Kim et al., 2006	South Korea	2000	2.4	135	Community dwelling residents aged 65+ in national residents registration lists	71.3 (5.2)	53.9	SCD was assessed from response to a series of questions from the GMSS. This rates the presence and severity of memory difficulties, recent forgetfulness of names, placed objects and efforts to	GMSS depression	Dementia	Age, education, sex	OR	SCD without depression versus no SCD OR=2.71	1.36 – 5.38

Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses of interest	Population	Age mean (SD), range (years)	Woman (%)	SCD assessment	Assessment of affective symptoms	Outcome Assessment	Adjustment for covariates	Statistic reported	Effect size	95%CI
								remember things. SCD was present as a score >3					SCD with depression versus no SCD OR=1.17	0.24 – 4.67
Liew 2019	USA	2005-2018	4.4	2605	Participants recruited from Alzheimer's disease centers in the US	72 (66-78)	65.3	Single question: 'have you noticed a decline in memory relative to previously attained abilities?'	GDS	Combined MCI and dementia	Age, sex, ethnicity, education, family history of dementia, current smoking, diabetes mellites, hypertension, hyperlipidaemia and MMSE	HR	SCD without depression: HR =2.0 SCD with depression: HR= 2.8	1.8–2.2 2.4–3.4
Liew 2020	USA	2005 - 2019	4.5	3809	Participants recruited from Alzheimer's disease	71 (65-77)	65.5	Single question: 'have you noticed a decline in memory relative to previously attained abilities?'	Anxiety symptoms were evaluated with a single question based on whether the	Combined MCI and dementia	Age, sex, ethnicity, years of education, APOE e4 status, current smoking,	HR	Anxiety versus no anxiety or SCD HR = 1.49	1.1–1.8

Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses of interest	Population	Age mean (SD), range (years)	Woman (%)	SCD assessment	Assessment of affective symptoms	Outcome Assessment	Adjustment for covariates	Statistic reported	Effect size	95%CI
					centers in the US				participants have experienced "any signs of nervousness such as shortness of breath, sighing, being unable to relax, or feeling excessively tense		hypertension, hyperlipidaemia, diabetes mellitus		SCD only versus no anxiety or SCD HR = 1.90	1.7 – 2.1
													Anxiety and SCD versus no anxiety or SCD HR =2.40	1.9 – 2.9
Luck et al., 2020	Germany	2003/4	13.5	440	Participants aged 75+ recruited via GP surgeries	79.7 (3.6)	65.1	Single question: 'do you feel like your memory is becoming worse?'	SCD-related worry: 'yes' versus 'no'	Dementia	Age, mortality	HR	SCD without worries versus no SCD HR=1.19	0.98 – 1.44

Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses of interest	Population	Age mean (SD), range (years)	Woman (%)	SCD assessment	Assessment of affective symptoms	Outcome Assessment	Adjustment for covariates	Statistic reported	Effect size	95%CI
													SCD with worries versus no SCD HR=1.99	1.64 – 2.42
Mazzeo et al., 2019	Italy	1994-2016	5.0-25.3	150	Patients referred to the Cognitive Disorders Hospital in Florence	61.3	69.3	SCD was defined as present if participants perceived decline in cognitive capacity in > 4 out of 5 activities related to memory in everyday life	HRDS	Dementia	None	Mean and standard deviation	SMD=0.07	-0.39 – 0.54
Reisberg et al., 2010	USA	1984-1997	6.8	166	Community dwelling individuals recruited into a longitudinal study of aging	65.7 (8.9)	65.0	SCD assessed using the Global Deterioration Scale for age-associated cognitive decline and dementia	HDRS	Combined MCI and dementia	None	Mean and standard deviation	SMD=0.16	-0.17 – 0.47

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Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses of interest	Population	Age mean (SD), range (years)	Woman (%)	SCD assessment	Assessment of affective symptoms	Outcome Assessment	Adjustment for covariates	Statistic reported	Effect size	95%CI
Snitz et al., 2018	USA	NR	3.09 (2.95)	592	Population cohort participants aged 65+ were recruited from voter registration	78.32 (7.32)	59.8	16-item questionnaire	SCD-related worry: 'yes' versus 'no'	MCI	Age, sex, education	HR	SCD without worries versus no SCD HR=1.11	0.94 – 1.33
													SCD with worries versus no SCD HR=1.66	1.24 – 2.24
Yue et al., 2020	China	2011	7	76	Community based cohort	69.4 (7.0)	52.6	Self-report based on Jessen et al., (2014) criteria	GDS	MCI		Mean and standard deviation	SMD = -0.31	-0.79 – 0.18

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Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses of interest	Population	Age mean (SD), range (years)	Woman (%)	SCD assessment	Assessment of affective symptoms	Outcome Assessment	Adjustment for covariates	Statistic reported	Effect size	95%CI

NIA-AA: National Institute on Aging -Alzheimer's Association; NINCDS-ADRDA: National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; GDS: Geriatric Depression Scale; MCI: Mild Cognitive Impairment; SMD: Standardised Mean Difference; STAI -S: State Trait Anxiety Inventory -State; HR: Hazards Ratio; HDRS: Hamilton Depression Rating Scale; CES-D: Centre for Epidemiological Studies Depression; OR: Odds Ratio; GMSS: Geriatric Mental State Schedule; IQR: Interquartile Range
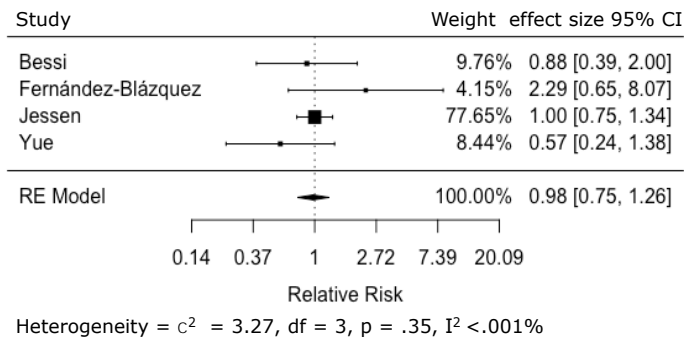
Study		Weight	effect size 95% CI
Bessi		9.76%	0.88 [0.39, 2.00]
Fernández-Blázquez		4.15%	2.29 [0.65, 8.07]
Jessen		77.65%	1.00 [0.75, 1.34]
Yue		8.44%	0.57 [0.24, 1.38]
RE Model		100.00%	0.98 [0.75, 1.26]

0.14   0.37   1   2.72   7.39   20.09

Relative Risk

Heterogeneity = c^2 = 3.27, df = 3, p = .35, I^2 <.001%

Figure 2. Forest plot of studies of depressive symptoms and risk of MCI

Study		Weight	effect size 95% CI
Kim		51.31%	0.43 [0.19, 0.96]
Mazzeo		48.69%	1.14 [0.49, 2.68]
RE Model		100.00%	0.69 [0.27, 1.79]

0.14   0.37   1   2.72

Relative Risk

Heterogeneity = c^2 = 2.66, df = 1, p = .10, I^2 = 62.35%
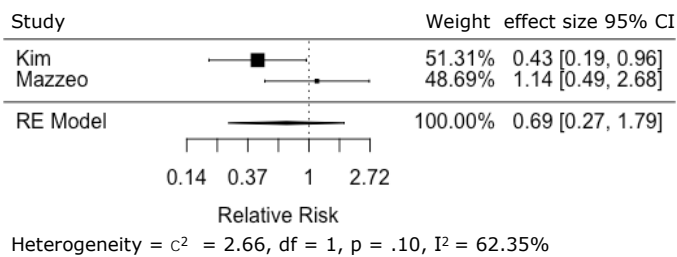
Figure 3. Forest plot of studies of depressive symptoms and risk of dementia

Study		Weight	effect size 95% CI
Fernández-Blázquez		1.43%	1.90 [0.54, 6.67]
Liew		46.37%	1.26 [1.14, 1.40]
Luck		9.30%	1.70 [1.08, 2.69]
Snitz		42.90%	1.50 [1.32, 1.69]
RE Model		100.00%	1.40 [1.20, 1.63]

0.37   1   2.72   7.39

Relative Risk

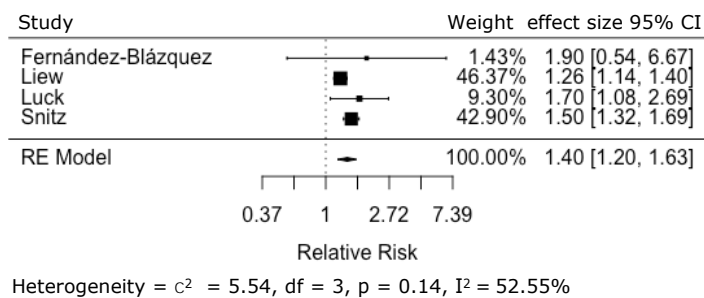Heterogeneity = c^2 = 5.54, df = 3, p = 0.14, I^2 = 52.55%

Figure 4. Forest plot of studies of anxiety or SCD-related worry and risk of MCI/dementia