Highlights

- Anxiety is associated with a 29% increased in the risk of dementia.
- This meta-analysis includes the latest prospective cohort studies.
- Treating or preventing anxiety may help to reduce the incidence of dementia.

Title: Anxiety and the risk of dementia: Systematic review and meta-analysis of prospective cohort studies

Running Title: Anxiety and risk of dementia: A meta-analysis

Authors: Javier Santabárbara (PhD) [a,b,c], Darren M. Lipnicki (PhD) [d], Beatriz Villagrasa (MD) [e], Elena Lobo (PhD)[a,b,c], Raul Lopez-Anton (PhD)[b,c,f*].

Affiliations:

[a] Departamento de Medicina Preventiva y Salud Pública, Universidad de Zaragoza, C/Domingo Miral s/n, 50009 Zaragoza, Spain.

[b] Instituto de Investigación Sanitaria de Aragón (IIS Aragón), Zaragoza, Spain

[c] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Ministry of Science and Innovation, Madrid, Spain

[d] Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales Medicine, Randwick, Australia.

[e] Servicio de Psiquiatría, Hospital Clínico Universitario, Avda. San Juan Bosco 15, 50009 Zaragoza, Spain.

[f] Departamento de Psicología y Sociología, Universidad de Zaragoza, C/Doctor Cerrada 1-5, 50009 Zaragoza, Spain.

***Corresponding and reprints author:**

Dr. Raul Lopez-Anton

Universidad de Zaragoza
Departamento de Psicología y Sociología
Calle Doctor Cerrada 1-5,
50009 Zaragoza, Spain
Tel/fax.: +34 976 55 11 67
E-mail: rlanton@unizar.es

~~WORD COUNT:~~
~~Abstract: 148 words~~
~~Text: 2840 words~~
~~References: 47~~
~~Figures: 2~~
~~Tables: 3~~

ABSTRACT

Objectives: Anxiety is postulated ~~as a potentially~~to be modifiable risk factor for dementia. Our primary aim was to conduct a meta-analysis of community-based cohort studies that investigated the association between anxiety and dementia.

Design: We identified relevant, high~~-~~-quality papers published ~~until~~ up to January 2018 by searching Pub~~m~~Med and Web of Science. Prospective cohort studies reporting relative risks (RRs) for the association between anxiety and dementia, adjusted at least for age, were considered eligible. Study-specific RRs were combined ~~by~~ using a random-effects model.

Results: Six prospective cohorts (reported in 5 studies), with a total of 10,414 participants, were included in the meta-analysis. The pooled RR of 1.29 (95% CI: 1.01–1.66) indicated a significant association between anxiety and dementia.

Conclusion: Anxiety significantly increases the risk of dementia. However, further research is needed to determine the extent to which anxiety is a cause of dementia rather than a prodrome or marker.

KEYWORDS: Meta-Analysis; Dementia; Anxiety; Risk Factor; Older People

~~Highliths~~

~~- Anxiety is associated with a 29% increased risk of dementia.~~

~~- We included in the Meta-analyses the latest prospective cohort studies.~~

~~- If anxiety is considered a cause, treating or preventing anxiety may help to reduce the incidence of dementia.~~

INTRODUCTION

Dementia has devastating effects not only for affected individuals, but also for their families and society. Since late-life dementia cannot be treated, there is an urgent public health priority for effective strategies that reduce the risk and delay the onset of dementia [1]. The development of risk reduction programs requires identification of related risk factors, and reliable estimations of the magnitude of their effects. Systematic reviews and meta-analyses are the optimal approaches to achieve this objective [2].

Interest in a relationship between anxiety and dementia has grown in recent years due to the high prevalence of anxiety in older populations (ranging from 5% to 21%), and its association with poorer cognitive performance, even after controlling for depression [3].

A recent meta-analysis (MA) found that anxiety may accelerate progression to dementia in individuals with mild cognitive impairment (MCI) [4] or preclinical Alzheimer's disease (AD) [5,6]. Some studies of cognitively healthy populations have reported that anxiety, as well as depression, is an early predictor of cognitive decline, and associated with more rapid progression towards dementia, but the data are inconclusive [7,8]. Further, while a previous MA of epidemiological studies reported that anxiety may be associated with an increased risk for dementia, especially with anxiety that emerges in late life [9], the study included and did not separate between samples of cognitively healthy individuals and those with MCI. Thus, whether anxiety is either or both an independent or mediating risk factor for dementia in cognitively normal populations remains unknown. Establishing this has implications for the development of strategies targeting dementia [9], and is best done with a systematic review of cohort studies [10].

The aims of our study were to systematically review the literature on anxiety as a risk factor for dementia, and conduct a MA of well-designed prospective epidemiological studies in community-based samples of older adults.

METHODS

We followed the MOOSE guidelines for reporting a MA of observational Studies in Epidemiology [11] (Supplementary Table S1).

Search strategy

Our search for all prospective cohort studies investigating an association between anxiety and dementia risk was undertaken in January 2018 on PubMed and Web of Science by 2 researchers (BV and RLA) independently. Two other researchers (JS and EL) reviewed a random sample of 10% of the studies to assess agreement on inclusion and exclusion criteria and to approve the studies meeting the final eligibility.

In brief, the search strategy was (anxiety AND dementia AND old AND (cohort studies OR incidence)) using both medical subject headings and free text. Studies were limited to the English language. The PubMed search strategy is available in Supplementary Table S2. In addition, the reference lists of selected publications were also screened for potentially eligible studies. Authors of studies were contacted directly when insufficient data were available in articles meeting the inclusion criteria.

Study selection

Studies selected for analysis had to meet the following requirements: (1) identification of baseline anxiety 'caseness' (dichotomous variable); (2) study design was a community-based prospective cohort; (3) investigate the association between anxiety and overall dementia incidence; (4) absence of dementia in the baseline assessment; and (5) included a summary estimate (relative risk, odds ratio or hazard ratio) with reported confidence intervals, adjusted for at least age (most important risk facor for dementia).

Studies that focused on MCI samples, as well as review articles and meta-analyses, were excluded. Studies not reporting original, published peer-reviewed results were also excluded to ensure only high quality research was included in the analyses.

Data Extraction

Two reviewers (JS and EL) independently extracted data for the included studies. We used a predesigned data extraction form to obtain information on country, sample size, number of prevalent cases of anxiety, number of incident cases of

dementia, percentage of females, average age, scale used to measure anxiety, dementia assessment and clinical criteria, covariates adjusted for in the analysis, adjusted RR estimates, and duration of follow-up.

Quality assessment

Study quality was assessed with the Newcastle-Ottawa scale (NOS) for cohort studies [12]. The NOS is a nine-point scale to assess the quality of nonrandomized studies with its design and content. It measures exposure (0–4 points), the comparability of cohorts (0–2 points), and the identification of the outcome and adequacy of follow-up (0–3 points). We assigned scores of 0–3, 4–6, and 7–9 to indicate low, moderate, and high quality studies, respectively. Two researchers (JS and EL) assessed the quality of all included studies. When discrepancy in scoring was present, a third researcher take a final decission (RLA).

Reliability

A fifth reviewer (DML) blinded to the primary reviewers' (BV, RLA, JS and EL) decisions checked the article selection, data extraction, and risk of bias assessment stages of the review. Any disagreement was resolved by consensus among all reviewers.

Statistical methodology

We used relative risks (RRs) as the common measure of association across studies, and considered hazard ratios (HRs) and odds ratios (ORs) as equivalents, as considered appropriate when the outcome condition is relatively rare (prevalence < 15%) [13]. We preferentially pooled risk estimates from fully adjusted models.

We conducted a random-effects model that allows for HRs and ORs to be incorporated into the same MA, as well as accounting for heterogeneity between studies [14].

The Hedges Q statistic was used to describe heterogeneity (statistical significance was set at $p< 0.10$). Additionally, to quantify heterogeneity we report the I^2 statistic [15,16], with its 95% confidence interval, as recommended when the number of studies is small [17,18]. We assigned low heterogeneity for I^2 values between 25%-50%, moderate for 50%-75%, and high for $\geq$ 75% [16]. We performed subgroup and meta-regression analyses [19] to explore sources of the heterogeneity expected in meta-analyses of observational studies [20].

A sensitivity analysis was performed to assess the influence of each individual study on the overall results, by omitting studies in turn one by one.

With fewer than 10 studies in our MA, the funnel plot could be misleading [21] and the Begg and Egger's test has low power to distinguish publication bias [22]. We

thus assessed publication bias using the classic fail-safe N value [23]. The fail-safe value determines the number of studies with null findings that would be necessary to produce a nonsignificant overall effect size. Using Rosenthal's recommendation [24], a value of 5K+10, where K is the number of observed studies, was used as the cutoff for an unlikely number of studies. If a publication bias in the pooled estimate was identified, we adjusted the overall RR with the 'trim and fill' method for the presence of publication bias [25].

All statistical analyses were performed with STATA statistical software (version 10.0; College Station, TX, USA), and p values are reported as two-sided, with 0.05 accepted as statistically significant except where otherwise indicated.

RESULTS

Study selection

Figure 1 presents the results of the literature search and study selection process. The primary search yielded 3,546 potential records, of which 887 duplicate articles were removed. A further 2,605 articles were excluded as their title/abstract did not meet the selection criteria. The full-text of the 54 remaining articles was read, after which 49 were excluded and 5 were included in the final review of this report.

[Insert Figure 1 around here]

Description of included studies

The 5 included articles were published between 2009 and 2017 [26-30]. They reported on 6 prospective cohorts (2 from de Bruijn et al. [26]), with a total of 10,414 participants.

Study details are presented in Table 1. Three studies were conducted in Europe [26,27,30]; and the others in the United States [28] and Mexico [29]. Four studies featured both women and men [26,27,29], 1 only women [28], and 1 only men [30].

The studies differed in the scales used to classify anxiety, with DSM-IV (Diagnostic and Statistical Manual of Mental Disorders [31]) criteria used instead of a scale for de Bruijn et al. (sample II). [26] The criteria for dementia was more uniform, and based on the DSM.

The duration of follow-up ranged from 3 to 28 years, with a median follow-up of 13 years (IQR: 4.5-19.7).

The level of adjustment for covariates differed across studies, and we used the risk estimates from the most fully adjusted models in estimating the pooled RR. Additionally, wherever possible, RRs from cognitively healthy participants were

used [30]. The adjusted RR varied between 0.81 (95% CI: 0.50-1.31) [26] and 1.77 (95% CI: 0.31-10.24) [30].

[Insert Table 1 around here]

Risk of bias assessment

Quality assessments for the cohort studies are shown in Table 2. Three studies had a quality score of 7-9, indicating a low risk of bias [26,27,29], whereas the two studies that only reported on one gender did not represent the broader population and had a quality score of 5-6, indicating a medium risk of bias [28,30].

[Insert Table 2 around here]

Meta-analysis of dementia incidence

Individual study estimates as well as the overall estimate for incident dementia according to anxiety status are shown in Figure 2. Four RR estimates were above unity (significant in 3 cohorts) and two were below unity (non-significant), resulting in a pooled RR of 1.29 (95% CI: 1.01-1.66). Therefore, compared with the reference group (non-anxiety), anxiety was associated with a statistically significant 29% higher dementia risk.

Modest heterogeneity was detected among the studies (I^2 = 47.5%; 95% CI: 0% – 79%; p = 0.094). Sensitivity analyses that excluded each study in turn showed moderate robustness, since the overall combined RR did not change substantially, with a range from 1.21 (95% CI: 0.99-1.47) to 1.41 (95% CI: 1.16-1.72), and I^2 varied from 32.9% to 42.3%. This clearly shows no major impact of any single study on the overall combined, and statistically significant RR (Supplementary Figure S1).

[Insert Figure 2 around here]

Subgroup and meta-regression analyses

Table 3 presents the results of subgroup analyses. Compared to individuals without anxiety, those with anxiety had an increased risk of dementia irrespective of the cohort's percentage of females, mean age at baseline, duration of follow-up, study location, quality, adjustment for depression or cardiovascular risk factors.

[Insert Table 3 around here]

Risk of publication bias

Visual inspection of the funnel plot (Supplementary Figure S2) could suggest some degree of publication bias. However, the fail-safe N was 13, below the tolerance level for an unlikely number of nonsignificant studies (40). Furthermore, adjustment for publication bias had a marginal effect on the risk estimate when a 'trim and fill' method was applied (RR: 1.28; 95% CI: 1.01-1.62) (Supplementary

Figure S3), with the new risk ratio estimate remaining statistically significant (p = 0.037).

DISCUSSION

Main findings

The present meta-analysis (MA) quantitatively assessed the association between anxiety and dementia risk in older adults. Across 6 cohorts, individuals with anxiety showed a statistically significant 29% increased risk of dementia compared to individuals without anxiety. Further, a subgroup analysis suggested that anxiety was a risk factor for dementia independent from depression.

Comparison with previous study

There appears to be only one previous systematic review and MA of the risk of dementia associated with anxiety in community-based population studies of older people [9]. The risk estimation found by that study (RR = 1.57) is twice as high as what we found. There are a number of reasons for this difference. We used more stringent inclusion criteria that focused specifically on cohort studies reporting risk ratios adjusted at least for age, given age is an established dementia risk factor [32]. Contrary to the previous MA, we excluded studies of MCI samples, because individuals with MCI and anxiety show an accelerated progression to dementia [4]. Excluding studies with pure MCI samples also makes our results more generalizable to the broader older population. In addition, we were able to include 3 studies published after the previous MA [27-29], and with these and the different selection criteria there was only one cohort in common (sample I from the Rotterdam study [26]). Compared to the previous MA, our set of cohorts had a younger age at baseline. Indeed, in our subgroup analysis (Table 3) only one study sample was aged 80+ [28], and it had a similar RR to the overall RR reported by Gulpers et al. [9]

Potential underlying biological mechanisms for the association between anxiety and dementia

Several hypotheses could help explain the increased risk of dementia associated with anxiety. Anxiety may promote negative neuroplasticity that decreases cognitive reserve across the life span [33]. Anxiety may also be involved in accelerated aging across multiple processes [34]. Further, there is growing evidence of an association between anxiety and CNS inflammatory changes [35] that are also characteristic of AD [36].

Strengths and limitations

Among the strengths of this study, our MA was of prospective cohort studies, which provide the strongest evidence of causal links between outcome and exposure [37]. Additionally, there are multiple reasons for having confidence in our findings: (1) cohort studies avoid the influence of recall and selection bias; (2) the risk of small study effects was minimized by including relatively large studies; (3) the follow-up period of each study was long enough for a sufficient number of incident dementia cases, and thus allow potential associations between anxiety and dementia to be observed; (4) the requirement for adjusted relative risk provided a more accurate estimation of effects.

This study also has several limitations. The cohorts we analyzed assessed anxiety using different scales, with one instead using clinical criteria [26], what cannot allow us to differentiate symptoms from anxiety disorders that could be considered different in terms of psychopathology, management and outcome. Two of the cohorts were comprised of only one gender. However, our results did not differ when these were excluded in sensitivity analyses. Our results may be influenced by differences in what studies adjusted for or did not adjust for in their analyses. de Bruijn et al. [26], that weight almost for 40% of the effects analysis, reported non-significant associations between neither anxiety disorder nor anxiety symptoms and dementia incidence in their two cohort. Nonetheless, they admitted that the 'generalizability of results to other populations was limited' because of the special characteristics of their sample. In addition, unlike other studies they adjusted for ApoE-ε4, a well-known biological marker of dementia risk, which presence could explain the non-significant association found. Finally, although there was some evidence of publication bias, the pooled relative risk corrected for publication bias was similar to the non-corrected value.

Clinical implications

The finding of a 29% increased risk of dementia for individuals with anxiety has significant clinical implications. Firstly, the diagnosis and assessment of late-life anxiety is especially challenging, as symptoms can be confused with some aspects of the normal ageing process (eg. fatigue, lack of concentration, and subjective memory loss), as well as with medical conditions and comorbid mental disorders, including depression [38]. Anxiety symptoms are much more prevalent among older individuals suffering from depression [39], and late-life depression has been associated with a two-fold increased risk of dementia [40]. "Some studies also report a higher risk of dementia associated with long-term use of benzodiazepines [41,42], which are estimated to be used by 15-20% of older individuals. Therefore,

since comorbidity between anxiety and depression is highly frequent, the association of anxiety and dementia could be hypothetically mediated by depression. However, five of the six cohorts in our study controlled for depression in their analyses yet still found an association between anxiety and dementia.

Secondly, from a clinical point of view, if anxiety is considered a predisposing factor for dementia rather than a prodrome [43], it could be important to know whether anxiolytics might reduce the risk of AD associated with anxiety; however, evidence seems inconclusive [44,45], mainly because early non-cognitive symptoms of dementia can be present many years before a dementia diagnosis and the length of follow-up in supporting studies are insufficient [46]. Nevertheless, this potential confusion factor in the relationship between anxiety and dementia is only addressed in two cohorts that controlled for medication use: benzodiazepines [27] and psychotropic drugs [28] and our data are inconclusive. Therefore, following Bocti et al. [46], we recommend carefully monitoring cognition of elder people who develop anxiety or treated with benzodiazepines. Thus, more research is needed to determine whether an effect of medication may moderate the association between anxiety and dementia.

Public health implications

Our finding of a 29% increased risk of dementia for individuals with anxiety is similar in size to other dementia risk factors such as education (HR = 1.27), but slightly lower than others such as ApoE-ε4 allele carriage (HR = 1.47) and depression (HR = 1.48) [47]. The comparable and considerable effect of anxiety we found supports the need for further research to determine the mechanisms by which anxiety may promote dementia, and to develop preventative strategies.

Conclusions

In conclusion, this meta-analysis of prospective cohort studies suggests that anxiety significantly increases the risk of dementia. Considering the high prevalence of anxiety in older populations worldwide, our results suggest that treating or preventing anxiety may help to reduce the incidence and prevalence of dementia, and the heavy burden that this condition brings. However, further research is needed to determine the extent to which anxiety is a cause of dementia rather than a prodrome or marker.

~~AKNOWLEDGEMENTS~~

~~Author~~ Contributorsions

Javier Santabárbara conceived and designed the study, assessed papers for inclusion in the study and rated them for quality, extracted data, performed the analyses, and contributed substantially to drafting the article and revising it critically for intellectual content.

Darren M. Lipnicki contributed substantially to drafting the article and revising it critically for intellectual content.

Beatriz Villagrasa conducted the literature search.

Elena Lobo assessed papers for inclusion in the study and rated them for quality, and extracted data.

Raul Lopez-Anton conceived and designed the study, conducted the literature search, and contributed substantially to drafting the article and revising it critically for intellectual content.

~~RLA and JS conceived and designed the study.~~

~~BV and RLA conducted the literature search.~~

~~JS and EL assessed manuscripts for inclusion in the study and rated them for quality. JS and EL extracted data.~~

~~JS performed analyses.~~

~~RLA, JS and DML contributed substantially to drafting the article and revising it critically for intellectual content.~~ All authors gave final approval to the submitted manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding ~~Sponsors role~~

There was no specific funding for this review.

Provenance and peer review

This article has undergone peer review.

REFERENCES

[1] M. Prince, J. Jackson, World Alzheimer Report, (2014) https://www.alz.co.uk/research/WorldAlzheimerReport2014.pdf (14 February 2018).

[2] R. Harbour, J. Miller J, for the Scottish Intercollegiate Guidelines Network Grading Review Group, A new system for grading recommendations in evidence based guidelines, BMJ 323 (2001) 334-336.

[3] S.E. Starkstein, R. Jorge, G. Petracca, R.G. Robinson, The construct of generalized anxiety disorder in Alzheimer disease, Am J Geriatr Psychiatry 15 (2007) 42-49.

[4] X.X. Li, Z. Li, The impact of anxiety on the progression of mild cognitive impairment to dementia in Chinese and English data bases: a systematic review and meta-analysis, Int J Geriatr Psychiatry 33 (2018) 131-140.

[5] R.H. Pietrzak, Y.Y. Lim, A. Neumeister, D. Ames, K.A. Ellis, K. Harrington, et al., Amyloid-β, anxiety, and cognitive decline in preclinical Alzheimer disease: a multicenter, prospective cohort study, JAMA Psychiatry 72 (2015) 284-291.

[6] L. Mah, M.A. Binns, D.C. Steffens, Alzheimer's Disease Neuroimaging Initiative. Anxiety symptoms in amnestic mild cognitive impairment are associated with medial temporal atrophy and predict conversion to Alzheimer disease, Am J Geriatr Psychiatry 23 (2015) 466-476.

[7] S.J. Banks, R. Raman, F. He, D.P. Salmon, S. Ferris, P. Aisen, et al., The Alzheimer's Disease Cooperative Study Prevention Instrument Project: longitudinal outcome of behavioral measures as predictors of cognitive decline, Dement Geriatr Cogn Dis Extra 4 (2014) 509–516.

[8] S.A. Beaudreau, R. O'Hara, Late-life anxiety and cognitive impairment: a review, Am J Geriatr Psychiatry 16 (2008) 790–803.

[9] B. Gulpers, I. Ramakers, R. Hamel, S. köhler, R. Oude Voshaar, F. Verhey, Anxiety as a predictor for cognitive decline and dementia: a systematic review and meta-analysis, Am J Geriatr Psychiatry 24 (2016) 823–842.

[10] P.B. Burns, R.J. Rohrich, K.C. Chung, The levels of evidence and their role in evidence-based medicine, Plast Reconstr Surg, 128 (2011) 305-310.

[11] D.F. Stroup, J.A. Berlin, S.C. Morton, I. Olkin, G.D. Williamson, D. Rennie, et al., Metaanalysis of observational studies in epidemiology: a proposal for reporting, Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group, JAMA 283 (2000) 2008–2012.

[12] G.A. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, et al., The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, (2016) http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (21 February 2018).

[13] I. Shrier, R. Steele, Understanding the relationship between risks and odds ratios, Clin J Sport Med 16 (2006) 107–110.

[14] R. DerSimonian, N. Laird, Meta-analysis in clinical trials, Control Clin Trials, 7 (1986) 177–188.

[15] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat med, 21 (2002) 1539–1358.

[16] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman. Measuring inconsistency in meta-analyses. BMJ 327 (2003) 557-560.

[17] K. Thorlund, G. Imberger, B.C. Johnston, M. Walsh, T. Awad, L. Thabane, et al., Evolution of heterogeneity (I2) estimates and their 95% confidence intervals in large meta-analyses, PLoS One 7 (2012) e39471.

[18] P.T. von Hippel, The heterogeneity statistic I(2) can be biased in small meta-analyses, BMC Med Res Methodol, 15 (2015) 35.

[19] S.G. Thompson, J.P. Higgins, How should meta-regression analyses be undertaken and interpreted? Stat Med 21 (2002) 1559–1573.

[20] M. Egger, M. Schneider, G. Davey Smith, Spurious precision? Meta-analysis of observational studies, BMJ. 316 (1998):140-144.

[21] J. Lau, J.P. Ioannidis, N. Terrin, C.H. Schmid, I. Olkin, The case of the misleading funnel plot, BMJ 333 (2006) 597-600.

[22] J.A. Sterne, A.J. Sutton, J.P. Loannidis, N. Terrin, D.R. Jones, J. Lau J, et al, Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials, BMJ 343 (2011) d4002.

[23] R. Rosenthal, The “file drawer problem” and tolerance for null results, Psychol Bull 86 (1979) 638–641.

[24] R. Rosenthal, Meta-analytic procedures for social research, Sage Publications, Newbury Park, CA, 1991.

[25] S. Duval, R. Tweedie, Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis, Biometrics, 56 (2000) 455-463.

[26] R.F. de Bruijn, N. Direk, S.S. Mirza, A. Hofman, P.J. Koudstaad, H. Tiemier et al., Anxiety is not associated with the risk of dementia or cognitive decline: The Rotterdam Study, Am J Geriatr Psychiatry 22 (2014) 1382–1390.

[27]A.J. Petkus, C.A. Reynolds, J.L. Wetherell, W.S. Kremen, N.L. Pedersen, M. Gatz, Anxiety is associated with increased risk of dementia in older Swedish twins, Alzheimers Dement 12 (2016); 399-406.

[28] A.M. Kassem, M. Ganguli, K. Yaffe, J.T. Hanlon, O.L. Lopez, J.W. Wilson et al., Anxiety symptoms and risk of dementia and mild cognitive impairment in the oldest old women, Aging Ment Health 22 (2018); 474-482.

[29] I. Acosta, G. Borges, R. Aguirre-Hernandez, A.L. Sosa, M. Prince, 10/66 DEMENTIA RESEARCH GROUP, Neuropsychiatric symptoms as risk factors of

dementia in a Mexican population: A 10/66 Dementia Research Group study, Alzheimers Dement 14 (2018); 271–279.

[30] J. Gallacher, A. Bayer, M. Fish, J. Pickering, S. Pedro, F. Dunstan et al., Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study, Psychosom Med 7 (2009) 659-666.

[31] American Psychiatric Association (2000). Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association.

[32] A.F. Jorm, D. Jolley, The incidence of dementia: a meta-analysis, Neurology, 51 (1998) 728–733.

[33] D.E. Vance, A.J. Roberson, T.M. Mcguinness, P.L. Fazeli, How neuroplasticity and cognitive reserve protect cognitive functioning. J Psychosoc Nurs Ment Heal Serv 48 (2010) 23–30.

[34] G. Perna, G. Iannone, A. Alciati, D. Caldirola, Are anxiety disorders associated with accelerated aging? A focus on neuroprogression. Neural Plast (2016); 8457612.

[35] S. Salim, G. Chugh, M. Asghar, Inflammation in Anxiety, Adv Protein Chem Struct Biol, 88 (2012) 1-25.

[36] A.C. Cuello, Early and Late CNS Inflammation in Alzheimer's Disease: Two Extremes of a Continuum?, Trends Pharmacol Sci, 38 (2017) 956-966.

[37] A. Kingston, C. Jagger, Review of methodologies of cohort studies of older people, Age Ageing, 1 (2017) 1-5.

[38] Z. Therrien, J. Hunsley, Assessment of anxiety in older adults: a systematic review of commonly used measures, Aging Ment Health 16 (2012) 1-16.

[39] A.W. Braam, J.R. Copeland, P.A. Delespaul, A.T. Beekman, A. Como A, M. Dewey M, et al., Depression, subthreshold depression and comorbid anxiety symptoms in older Europeans: results from the EURODEP concerted action, J Affect Disord 155 (2014) 266-72.

[40] N. Cherbuin, S. Kim, K.J. Anstey, Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis, BMJ 5 (2015) e008853.

[41] S. Billioti de Gage, Y. Moride, T. Ducruet, T. Kurth, H. Verdoux, M. Tournier, et al., Benzodiazepine use and risk of Alzheimer's disease: case-control study, BMJ 349 (2014) g5205.

[42] S.L. Gray, S. Dublin, O. Yu, R. Walker, M. Anderson, R.A. Hubbard et al., Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study, BMJ 352 (2016) i90.

[43] Z. Ismail, J. Gatchel, D.R. Bateman, R. Barcelos-Ferreira, M. Chantillon, J. Jaeger, et al., Affective and emotional dysregulation as pre-dementia risk markers:

exploring the mild behavioral impairment symptoms of depression, anxiety, irritability, and euphoria, Int Psychogeriatr 30 2018 185-196.

[44] S.L. Burke, J. O'Driscoll, A. Alcide, T. Li T, Moderating risk of Alzheimer's disease through the use of anxiolytic agents, Int J Geriatr Psychiatry 32 (2017) 1312-1321.

[45] S. Billioti de Gage, B. Bégaud, F. Bazin, H. Verdoux, J.F. Dartigues, K. Pérès, T. Kurth, A. Pariente. Benzodiazepine use and risk of dementia: prospective population based study. BMJ (2012) 345:e6231.

[46] C. Bocti, J. Roy-Desruisseaux, C.Hudon, P. Roberge. Benzodiazepine and dementia: a time for reflection. Maturitas 75 (2013) 105-106.

[47] K. Ritchie, I. Carrière, C.W. Ritchie, C. Berr, S. Artero, M.L. Ancelin, designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors, BMJ 341 (2010) c3885

FIGURES AND TABLES

Figure 1. Flowchart for identifying eligible studies.

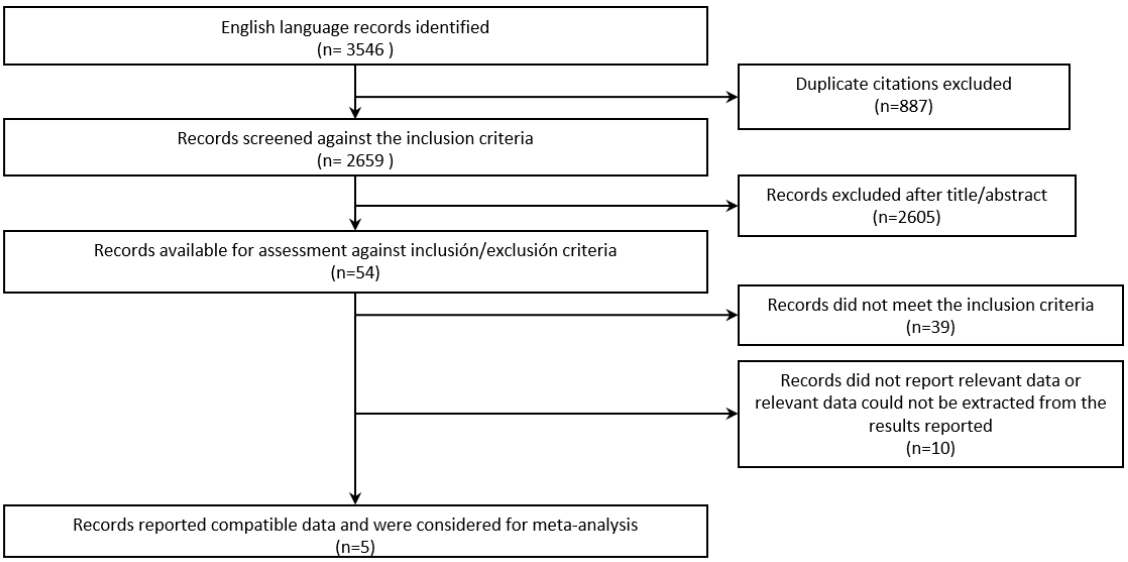


Figure 2. Forest plot showing combined estimates of anxiety status and risk of dementia

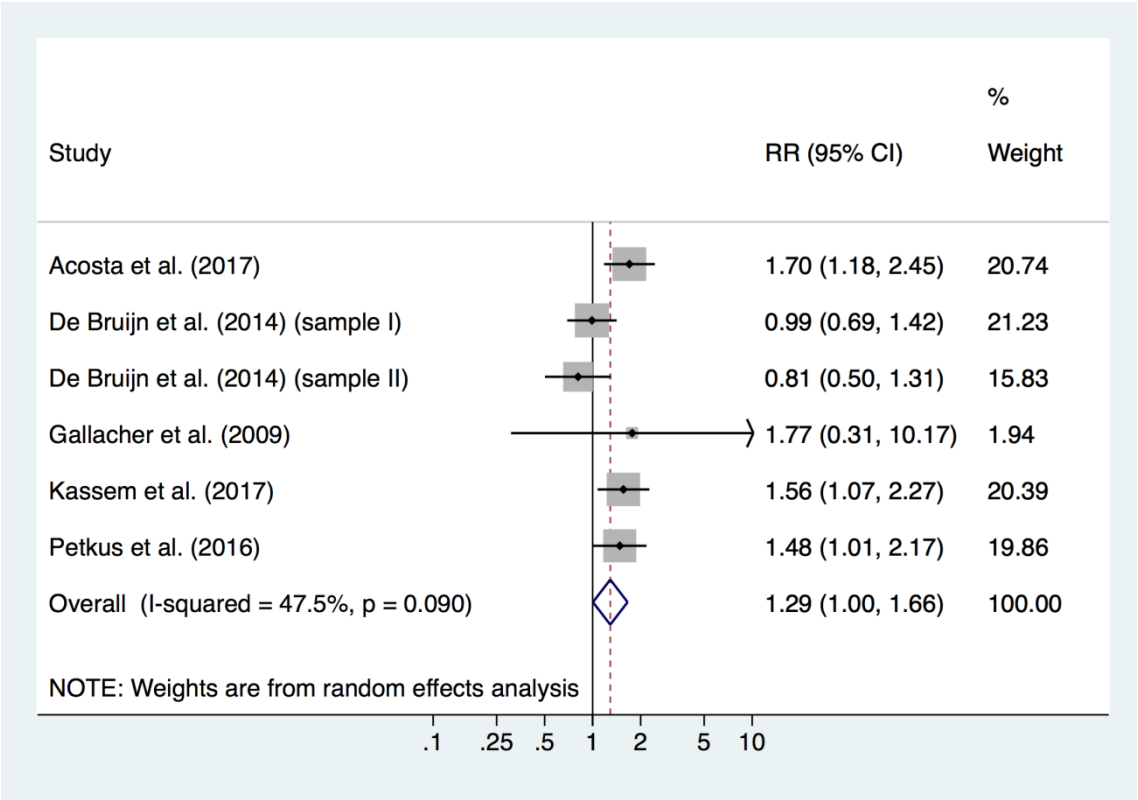


Table 1. Characteristics of studies included in the meta-analysis.

Authors, year (no. of participants)	Country	Study name	Year(s) baseline conducted	Follow-up period (years)	Age at baseline (years), mean (SD)	Females, n (%)	Drop-outs, n (%)	Anxiety measure	Dementia criteria (no. of incident cases)	Risk estimates (95% CI)	Statistical methods	Covariates
Acosta et al., 2017 (n=1355) [29]	Mexico	10/66 Dementia Research Group Study	2003-2006	3	73.6 (6.4)	1144 (62.7)	468 (25.7)	NPI-Q	DSM-IV (129)	Relative risk (RR): 1.7 (1.2-2.5)	Poisson regression	Age, sex, education, MCI, delusions, hallucinations, depression, and aberrant motor behaviour
de Bruijn et al., 2014 (sample I) (n=2708) [26]	The Netherlands	The Rotterdam Study	1993-1995	17	68.6 (8.5)	1495 (55.2)	225 (7.4)	HADS	DSM-III-R (358)	Hazard Ratio (HR): 0.99 (0.69 – 1.41)	Cox proportional hazards regression	Age, sex, educational level (low), ApoE-ε4 and depressive symptoms.
de Bruijn et al., 2014 (sample II) (n=3079) [26]	The Netherlands	The Rotterdam Study	2002-2004	9	75.5 (6.2)	1810 (59.1)	66 (2.0)	DSM-IV	DSM-III-R (248)	Hazard Ratio (HR): 0.81 (0.50-1.30)	Cox proportional hazards regression	Age, sex, educational level (low), ApoE-ε4 and depressive disorder.
Gallacher et al., 2009 (n=755) [30]	United Kingdom	Caerphilly Prospective Study (CaPS)	1983-1988	17	NR (NR)	0 (0)	NR	STAI	DSM-IV (NR)	Odds ratio (OR): 1.77 (0.31-10.2)	Logistic regression	Age, Vascular risk factors, GHQ and NART
Kassem et al., 2017 (n=1425) [28]	USA	Study of Osteoporotic Fractures (SOF)	2002-2004	5	82.8 (3.1)	1425 (100)	NR	GAS	DSM-IV (233)	Odds ratio (OR): 1.56 (1.07-2.26)	Logistic regression	Age, education, marital status, health behaviours, medical history, psychotropic medications, depression, poor sleep.

Petkus et al., 2015 (n=1082) [27]	Sweden	Swedish Apdoption Twin Study of Aging (SATSA)	1984	28	60.8 (11.1)	612 (56.6)	NR	STAI	DSM-III, DSM-IV (172)	Hazard Ratio (HR): 1.48 (1.01–2.18)	Cox mixed effects proportional hazards regression	Age, sex, education, physical illness, depression (average and symptoms),benzodiazepines, neuroticism.

Abbreviations in the table: ApoE: Apolipoprotein E; DSM- III: Diagnostic and Statistical Manual, Third Edition; DSM- IV: Diagnostic and Statistical Manual, Fourth Edition; GAS: Geriatric Anxiety Scale; GHQ: General health questionnaire; HADS: Hospital Anxiety and Depression Scale; HR: Hazard Ratio; MCI: Mild Cognitive Impairment; NART: National adult reading test; NPI-Q: Neuropsychiatric Inventory Questionnaire; NR: not reported; OR: Odds Ratio; RR: Relative Risk; SD: Standard deviation; STAI: State-Trait Anxiety Inventory; y.:years

Table 2. Quality assessment of studies in the meta-analysis using the Newcastle-Ottawa scale (NOS).

Authors, year	Selection				Comparability		Outcome			Overall Quality Score (Maximum = 9)
	1	2	3	4	5A	5B	6	7	8	
Acosta et al., 2018 (29)	*	*	*	*	*	*	*	-	-	7
de Bruijn et al., 2014 (sample I) (26)	*	*	*	*	*	*	*	*	*	9
de Bruijn et al., 2014 (sample II) (26)	*	*	*	*	*	*	*	-	*	8
Gallacher et al., 2009 (30)	-	*	*	*	-	-	*	*	*	6
Kassem et al., 2017 (28)	-	*	*	*	-	-	*	-	*	5
Petkus et al., 2015 (27)	*	*	*	*	*	*	*	*	-	8

NOS items: 1. Truly representative of the exposed cohort. 2. Non-exposed participants from same community as exposed participants 3. Ascertainment of exposure (Secured records or structured interview) 4. Demonstration that outcome of interest was not present at start of study (only incident cases of dementia). 5. Comparability of cohorts on the basis of the design or analysis (5A. Study controls for age and sex 5B. Study controls for any additional factor: education attainment, depression, physical inactivity, diabetes, obesity, smoking or hypertension) 6. Quality of outcome assessment (Independent blind assessment or record linkage) 7. Follow-up long enough for dementia to occur (≥ 10 years) 8. Complete follow-up (all participants are accounted for or subjects lost to follow-up unlikely to introduce bias).

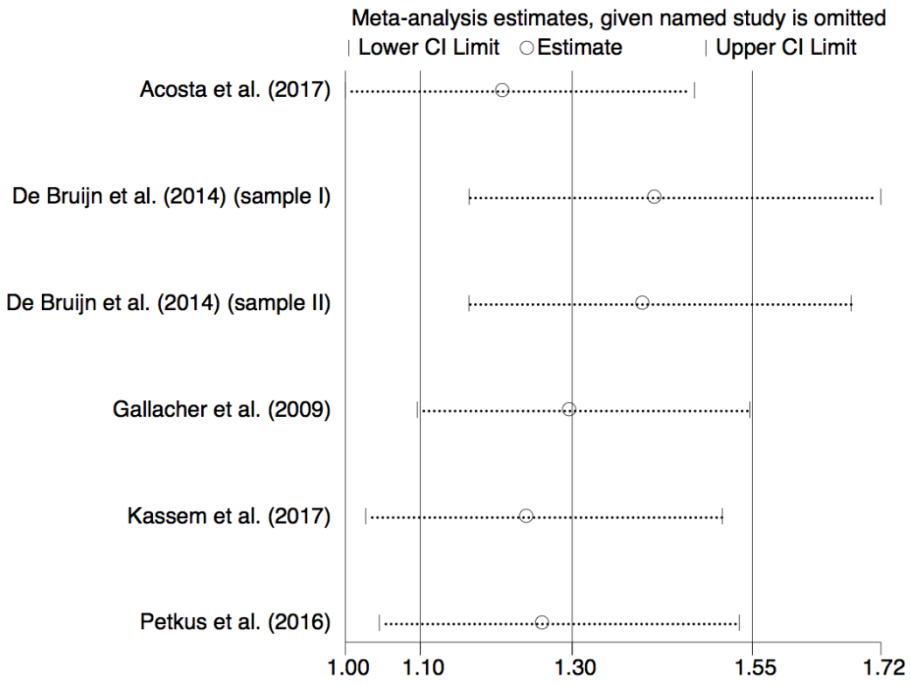
Table 3. Overall risk ratios of the association between anxiety and dementia risk according to study characteristics

		Association		Heterogeneity	
Subgroup	**Number of cohorts**	**Relative risk (95% CI)**	**p ***	**I^2(%) (95% CI)**	**p**
Mean age at baseline (years)					
< 80	5	1.23 (0.91 – 1.66)	0.538	52.3 (0 - 82)	0.078
≥ 80	1	1.56 (1.07 – 2.26)		N.A.	N.A.
Sex (% female)					
<50	1	1.77 (0.31-10.24)	0.751	N.A.	N.A.
≥50	5	1.28 (0.98 - 1.67)		57.5 (0 - 84)	0.052
Geographical region					
America	2	1.63 (1.25 – 2.12)	0.126	0	0.748
Europe	4	1.10 (0.81 - 1.48)		33 (0 - 76)	0.214
Sample size					
< 2000	4	1.58 (1.28 – 1.96)	0.041	0 (0 - 85)	0.963
≥ 2000	2	0.92 (0.69 – 1.23)		0	0.510
Mean of follow-up (years)					
< 10	3	1.32 (0.87 – 2.01)	0.816	68.9 (0 - 91)	0.040
≥ 10	3	1.21 (0.89 – 1.65)		18.2 (0 - 91)	0.295
Quality rating					
Medium (< 7)	2	1.57 (1.09 – 2.26)	0.479	0	0.890
High (≥ 7)	4	1.21 (0.87 – 1.68)		63.5 (0 - 88)	0.042
Adjustments for counfunders					
Depression					
No	1	1.77 (0.31-10.24)	0.751	N.A.	N.A.
Yes	5	1.28 (0.98 - 1.67)		57.5 (0 - 84)	0.052
ApoE ε4 carrier status					
No	4	1.58 (1.28 – 1.96)	0.041	0 (0 - 85)	0.963
Yes	2	0.92 (0.69 – 1.23)		0	0.510
Vascular risk factors					
No	2	1.57 (1.09 – 2.26)	0.479	0	0.890
Yes	4	1.21 (0.87 – 1.68)		63.5 (0 - 88)	0.042
Anxiety assessment					
Diagnostic criteria	1	0.81 (0.50 – 1.30)	0.154	N.A.	N.A.
Scales or questionaries	5	1.40 (1.13 – 1.74)		22.5 (0 - 68)	0.271

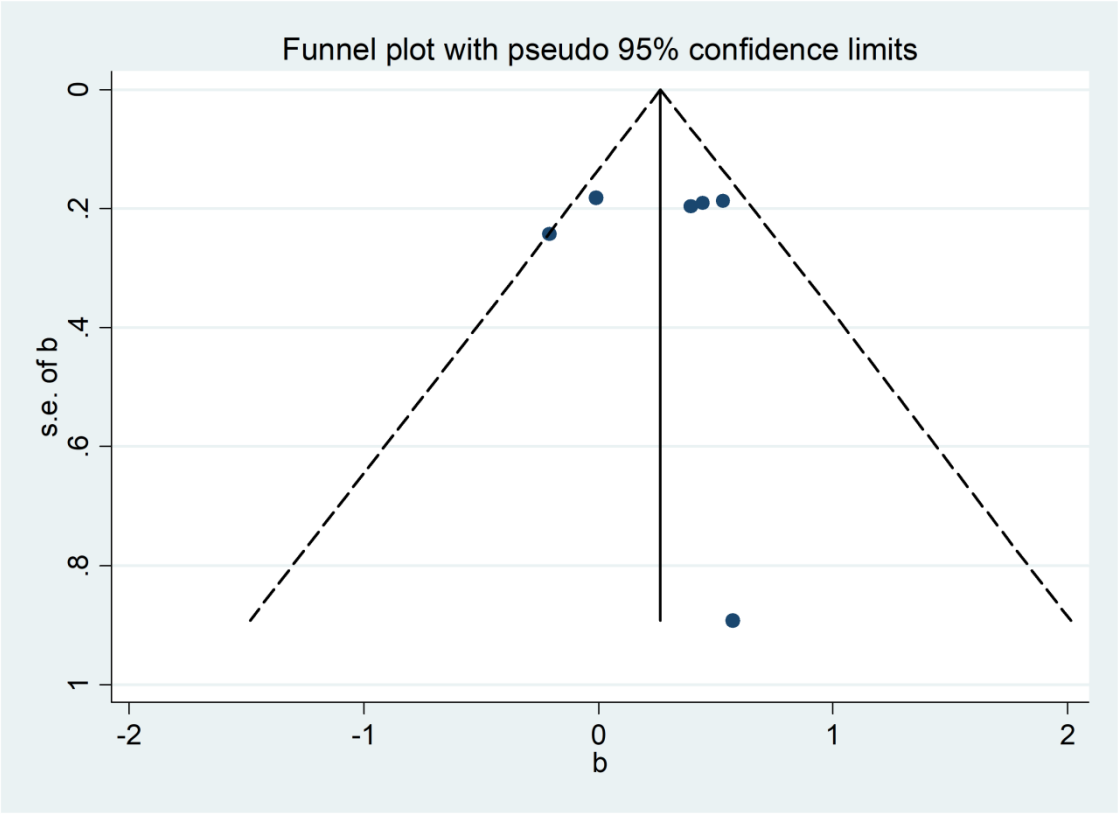
*P value obtained from univariate meta-regression.

SUPPLEMENTAL INFORMATION.

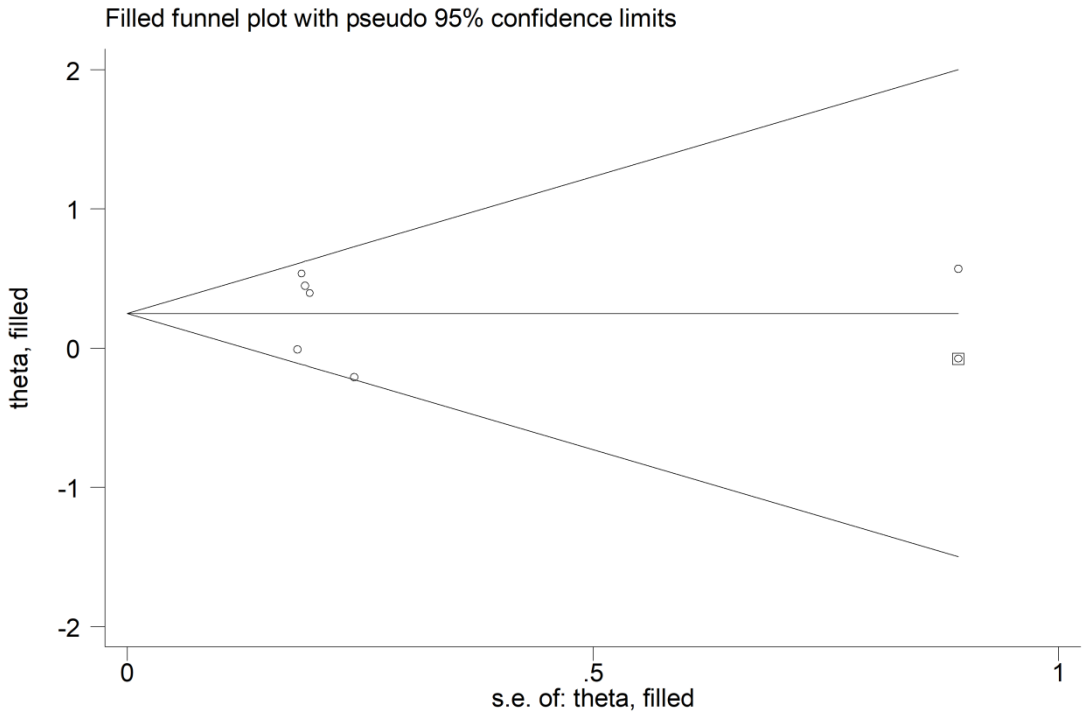
Supplementary Figure S1. The results of sensitivity analysis.



Supplementary Figure S2. The funnel plot of meta-analysis.



Supplementary Figure S3. Filled funnel plot of meta-analysis.



Supplementary Table S1. MOOSE Checklist for Meta-analyses of Observational Studies.

Items	Page #	Comments
TITLE Identify the study as a meta-analysis (or systematic review)	1	
ABSTRACT Use the journal's structured format	2	
INTRODUCTION		
· The clinical problem	3	
· The hypothesis	3	
· A statement of objectives that includes the study population, the condition of interest, the exposure or intervention, and the outcome(s) considered	4	
SOURCES		
· Qualifications of searchers (eg, librarians and investigators)	4	1 psychiatrist, 1 psychology
· Search strategy, including time period included in the synthesis and keywords	4	Supplementary Table 2
· Effort to include all available studies, including contact with authors	4	
· Databases and registries searched	4	Supplementary Table 2
· Search software used, name and version, including special features used (eg, explosion)	-	
· Use of hand searching (eg, reference lists of obtained articles)	4	
· List of citations located and those excluded, including justification	-	
· Method of addressing articles published in languages other than English	-	
· Method of handling abstracts and unpublished studies	4	
· Description of any contact with authors	-	
STUDY SELECTION		
· Types of study designs considered	4	Prospective cohorts
· Relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	4	
· Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5	
· Documentation of how data were classified and coded (eg, multiple raters, blinding, etc)	5	
· Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	5	
· Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	6	Meta-regressions, subgroup analysis
· Assessment of heterogeneity	6	Yes
· Statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	5,6	
RESULTS		
· A graph summarizing individual study estimates and the overall estimate	Figure 2	

· A table giving descriptive information for each included study	Table 1, and Table 2	
· Results of sensitivity testing (eg, subgroup analysis)	Table 3	+ Supplementary Figure 1
· Indication of statistical uncertainty of findings	6-8	
DISCUSSION		
· Strengths and weaknesses	9-10	
· Potential biases in the review process (eg, publication bias)	10	Funnel plot (Supplementary Figure 2 and Figure 3) (publicacion bias)
· Justification for exclusion (eg, exclusion of non–English-language citations)	-	
· Assessment of quality of included studies	10	Table 2
· Consideration of alternative explanations for observed results	9	
· Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	11	
· Guidelines for future research	11	
· Disclosure of funding source	12	

Supplementary Table S2. Pubmed search strategy

("anxiety disorders"[Mesh] OR "anxiety"[mesh terms] OR "anxiety"[tw] OR “neuropsychiatric symptoms” [tw]) AND (“dementia” [Mesh] OR “dementia” [tw] OR dementing) AND ("cohort studies"[Mesh] OR "epidemiologic study"[tw] OR "epidemiologic studies"[tw] OR cohort*[tw] OR longitudinal[tw] OR prospective*[tw] OR “risk” [tw] OR “incidence” [Mesh]) AND (("0001/01/01"[PDAT] : "2018/01/19"[PDAT]) AND English[lang])

Conflict of interest

The authors declare that they have no conflict of interest.