Review

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Does depression increase the risk of dementia? Updated meta-analysis of prospective studies

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Background. Our primary aim was to conduct an update meta-analysis of prospective studies investigating the association between depression and dementia risk.

Methods. We searched Pubmed database to identify all relevant papers published from January 2014 to March 2019. Prospective studies with a minimum follow-up period of 1 year, baseline depression assessment, absence of dementia or mild cognitive impairment at baseline were selected. We calculated pooled relative risks (RR), with a random effect model, as well as compute population attributable fraction (PAF) of dementia due to depression.

Results. Eight cohorts were included. A statistically significant association between depression and dementia risk, with a pooled RR of 1.63 (95% CI: 1.30-2.04), and a PAF of 9.0% (95% CI: 4.5%-14.1%), were found.

Conclusions. Depression is associated with an increased risk of dementia in this meta-analysis.

Keywords: Dementia, Depression, Risk Factor, Meta-Analysis

Actas Esp Psiquiatr 2020;48(4):169-80

¿La depresión aumenta el riesgo de demencia? Meta-análisis actualizado de estudios prospectivos

Objetivo. Realizar un meta-análisis actualizado de estudios prospectivos que evalúen la asociación entre la depresión y el riesgo de demencia.

Metodología. Se realizó una búsqueda bibliográfica en Pubmed para identificar estudios publicados desde enero de 2014 hasta marzo del 2019. Se seleccionaron estudios prospectivos con seguimiento mínimo de 1 año; evaluación de la depresión y ausencia de demencia y deterioro cognitivo leve (DCL) al inicio del estudio. Calculamos el riesgo relativo combinado (RR) mediante un modelo de efectos aleatorios, y la fracción de demencia poblacional atribuible (FAP) a la depresión.

Resultados. Ocho cohortes fueron incluidas. Obtuvimos una asociación estadísticamente significativa entre la depresión y el riesgo de demencia, con un RR global de 1,63 (IC 95%: 1,30-2,04), y una FAP de 9,0% (IC 95%: 4,5%-14,1%).

Conclusiones. La depresión se asocia con un aumento de riesgo de demencia en este meta-análisis.

Palabras clave: Demencia, Depresión, Factor de riesgo, Meta-análisis

INTRODUCTION

Global prevalence of depression is estimated to be around 4.4%, increasing with age. Thus, depression has been estimated to affect approximately 7% of the people over 60 years of age[1]. The impact of depression on disability-adjusted life years is greater when compared to any other mental disorder[2].

Dementia prevalence increases exponentially as of the age of 65 and it is likely that, as a result of population aging and increased life expectancy, dementia cases will increase in the coming decades[3]. Depression and dementia often occur simultaneously. However, the relationship between them remains unclear.

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A systematic review of depression as a risk factor for dementia was conducted in the 2014 *World Alzheimer Report*[4]. A total of 12 longitudinal studies were selected, and eight of these were part of a meta-analysis that also included studies from a previous meta-analysis[5]. The mean follow-up was 5 years (range: 2-17 years). The main result was that subjects with depressive symptoms at baseline had a two-fold increased risk of dementia at follow-up (OR: 1.97, 95% CI [1.67, 2.32]). No significant differences were found when analysis was stratified by length of follow-up but the association between depression and incident dementia tended to be weaker as the length of follow-up was longer. This result is consistent with the findings reported by Mirza et al.[6] They performed various statistical analyses for different follow-up intervals and found an increased risk of dementia in people with depression when follow-up periods were short or intermediate (duration up to 10 years), but without any apparent effect on longer follow-ups.

However, these meta-analyses[4,5] have methodological limitations, such as heterogeneity in classifying cases and non-cases of depression and a combination of results based on different diagnostic instruments, using both continuous measures of depressive symptomatology and categorical classifications[7].

Attempting to minimize these limitations, Cherbuin et al.[7] conducted a meta-analysis, including prospective longitudinal studies, with independent analyses using different specific cut-off points of validated instruments for depression diagnosis, such as the CES-D (Centre of Epidemiological Studies Depression Scale). In this study, clinically relevant depression was associated with an 80-100% increased risk of dementia, whereas mild depression was associated with an approximately 60-70% higher risk.

According to the limitations pointed out by Cherbuin et al.[7], and to homogenize results based on a clinically significant diagnosis of depression, our team conducted a systematic review with meta-analysis[8] that included published prospective cohort studies of the association between depression assessed using GMS-AGECAT (Geriatric Mental State-Automated Geriatric Examination for Computer Assissted Taxonomy) criteria[9]. Results of this meta-analysis indicate that individuals with clinically significant depression have a 54 and 50% higher risk of overall dementia and Alzheimer's Disease (AD) in evolution, respectively, with a population fraction of dementia of 8.6% and 10.8% attributable to depression, respectively. According to a subsequent meta-analysis carried out by our research team[10], risk of AD for clinically significant depression doubled (RR: 2.01; 95% CI [1.70, 2.39]) when standardized clinical criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification Diseases (ICD) were added to the GMS-AGECAT criteria, raising the population attributable fraction to 16.3%.

Nevertheless, a growing number of studies have been published in the few last years that assess the association between depression, measured by validated instruments and scales, and the risk of dementia. We consider it pertinent to update the available evidence to elucidate the nature of this relationship.

METHODS

This meta-analysis followed the PRISMA[11] guidelines for conducting and reporting systematic reviews and meta-analyses.

Search strategy

A search of the PubMed database, which provides wide coverage of biomedical publications worldwide, was performed with the following strategy: [Depression AND Dementia AND (Cohort studies OR incidence)], limiting the search to the period between January 2014 and March 2019, due to the existence of a previous review covering a former period[7].

Study selection

After reviewing the references, studies were selected for data extraction and analysis based on the following criteria: 1) Longitudinal design with a follow-up of at least 1 year; 2) Diagnosis of depression at the beginning of the study or before it; 3) Absence of cognitive impairment at beginning of the study (dementia or mild cognitive impairment); 4) Investigation of the association between depression and overall dementia; 5) Including summary measures such as relative risk (RR), hazard ratio (HR) or subdistribution hazard ratio (SHR) with their corresponding confidence intervals and adjusted at least by age. Meta-analyses, systematic or narrative reviews were excluded.

Evaluation of the methodological quality

For the assessment of methodological quality, the Newcastle-Ottawa Scale (NOS)[12], specific for cohort studies, was used to evaluate the risk of bias of each study selected for inclusion in the meta-analysis. This is a nine-point scale that performs a qualitative assessment across three categories: sample selection, comparability, and outcomes. Scores of

0-3, 4-6, and 7-9 were assigned for studies of low, moderate, and high methodological quality, respectively.

Data extraction

The following data were extracted from the studies that were finally selected: country where the study was conducted, sample size of the study, mean age of participants and percentage of women, number of prevalent cases of depression, number of incident cases of dementia, scale used to measure or define depression, criteria for identifying cases of dementia, covariates adjusted for in the analysis, length of follow-up and adjusted measures of association (RR, HR or SHR). Where data were not available, the authors were contacted to try to obtain them.

Meta-analysis

All analyses were carried out using STATA software (version 10.0; College Station, TX, USA). All reported p-values were two-tailed, with a significance level of 0.05, unless otherwise indicated.

Effect size

We used Relative Risk (RR) as a measure of common association between the selected studies, considering HR an SHR as equivalent, as has been shown for rare events such as dementia[13,14]. For each study included in the meta-analysis, we extracted the reported risk measure for dementia and its 95% confidence interval (CI), prioritizing those from the models with the highest level of adjustment in relation to socio-demographic and medical covariates. Subsequently, this risk measure was transformed logarithmically, and its standard error was calculated from the 95% CI.

Statistical model

Afterward, all studies were grouped into an overall risk measure using a random-effects model[15], which is more appropriate than fixed-effect models when the number of studies included in the meta-analysis is low (<10)[16].

Cohen´s *d* statistic was calculated to document differences in the risk of dementia according to depression exposure. This coefficient measures the magnitude of the effect when the differences found do not reach statistical significance. The magnitude of the effect was classified as "small" (0.2), "moderate" (0.5), or "large" (0.8)[14].

Heterogeneity analysis

Cochran´s *Q* was used to describe heterogeneity between studies, as well as the calculation of the I^2 statistic with its 95% CI, as recommended when the number of studies is small[17]. If the *p*-value was below 0.10 on the *Q*-test and/or the I^2 index was greater than 75%, the pooled analysis was considered as significantly heterogeneus[18].

Sensitivity analysis

A sensitivity analysis was performed to assess whether the magnitude of the summary effect was biased by the effect of any individual study. This analysis was performed by excluding studies one by one and comparing the magnitude of the resulting overall effect (*leave-one-out method*).

Evaluation of publication bias

The publication bias was determined by the Orwin "fail-safe" N statistics[19], because a funnel plot can be misleading with less than 10 studies[20], and the Begg and Egger tests have little discriminatory power (statistical power)[21]. This method determines the number of studies with null results (RR=1) that would need to be incorporated into our meta-analysis to obtain a magnitude of the overall effect that is non significant.

Meta-regression

Univariate meta-regression analyses were carried out to identify potential sources of heterogeneity across the studies included in the overall relative risk estimation, examining mean baseline age, percentage of women, duration of follow-up variables, and methodological quality.

Population Attributable Fraction (PAF)

The population proportion of dementia attributable to depression was estimated by calculating PAF[22], defined as the proportion of dementia risk that would have been avoided if the exposure (depression, in this particular case) had been eliminated, assuming a causal relationship between depression and dementia risk and non-biased estimations. To estimate the PAF, the following calculation was made[23]: [p*(RR-1)/(1+p*(RR-1)]*100, where "RR" represents the pooled relative risk (obtained from our meta-analysis) of dementia associated with depression and "p" represents the proportion of subjects exposed to depression (calculated by combining the prevalences of the included studies using a

meta-analysis with a random-effects model). The CI for PAF was calculated using the substitution method[24].

RESULTS

Search strategy

A total of 1521 references were obtained in the initial search. After reading the title and the abstract, 41 articles were selected for full-text reading. Once read, 8 articles met the inclusion criteria. Of the 33 excluded articles, 6 were reviews, 13 did not provide measures of association, 1 contained data duplicated in another study, 6 did not analyze risk of overall dementia (focused on subtypes), 2 did not include the diagnosis of depression at the beginning of the study, and 5 used non-community samples. (Figure 1).

Characteristics of the included studies

Table 1 summarizes the characteristics of the included studies. The 8 selected studies included a total of 2,476,454 individuals, most of the studies comprised populations over 50 years of age, except for that of Singh-Manoux et al.[25], which had an age range at the start of the study of 35-55 years. Thus, of the rest, the average age range was between 58.5[26] and 78.3 years[27]. All the studies included populations of both sexes, except for the study by Almeida et al.[28], which only included males.

The selected population in the studies was based on samples of the general population. The place of origin of these samples included a wide range of countries: United Kingdom[25, 29], United States[27], Mexico[30], Japan[31], Australia[28], Taiwan[32], and Denmark[26]. The average follow-up time ranged from 2[31] to 27 years[25].

Regarding the instruments used for depression diagnosis, 3 studies were based on the Geriatric Depression Scale-15 (GDS-15)[27,28,31], 2 studies used the Center for Epidemiological Studies-Depression scale (CES-D)[25,29], one study used the Neuropsychiatric Inventory Questionnaire (NPI-Q)[30] item of depression, and the remaining 2 studies were based on the diagnostic criteria of the International Classification of Diseases (ICD), using population records[26, 32]. Only 1 study used continuous measures[27] for depression diagnosis and the rest uses categorical measures. It should be noted that, although some studies used the same symptom scale to measure depression as a categorical variable, the cut-off points that define the presence of depression differed among them (table1).

In the cases of overall dementia diagnosis, most studies used international standardized criteria: ICD-10[25,26,28,31], ICD-9[32], or DSM-VI[27,30]. One study used a questionnaire based on symptoms referred by the informant (Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE)[29].

Concerning the results (Table 1), apart from one study[25], the rest found a significant association between depression and dementia risk, despite the variability in the covariates included in the analyses, the diagnostic instruments for depression, and the follow-up period. It is noteworthy that, unlike the rest of the studies included, the only one that did not find a significant association between the diagnosis of depression and the incidence of dementia at follow-up[25] was based on young adult population at the beginning of the study (35-55 years) and it had an average follow-up period of 27 years. However, when the authors performed a sub-analysis for the association between depression and dementia in the last 11 years of follow-up, when individuals in the cohort were 70 years old on average, they found a significant association between the two variables, with an increase in risk of dementia more than double for subjects who met criteria for depression (CES-D>16).

Evaluation of the quality of studies

The risk of bias assessment of the studies included in the meta-analysis is shown in Table 2. Seven studies had high methodological quality and therefore a low risk of bias (7-9 points)[25-30,32], and one had an intermediate risk (6 points)[31], according to the Newcastle-Ottawa Scale (NOS) for cohort studies.

Estimation of the effect of depression on the risk of overall dementia

Individual study estimates, as well as the combined estimate for the incidence of overall dementia according to depression, are presented in Figure 2. All RR estimates were above 1 (significant in 6 cohorts), and the combined RR was 1.63 (95% CI [1.30, 2.03], $p<0.001$). This indicates that cases of depression had a 63% higher risk of dementia than those free of depression, which was statistically significant. This effect was also approximately "moderate" in magnitude (Cohen´s $d=0.4$).

Heterogeneity analysis and sensitivity analysis

The level of heterogeneity found between studies was high ($I^2=95.3\%$; 95% CI [93%, 97%]). However, our results seem moderately robust, as the exclusion of articles one by

Table 1 Characteristics and results of the studies included in the meta-analysis (n=8)

Study	Country	Sample size	Age (years), mean (SD)	Females, n (%)	Follow-up period(years), Mean (SD)/ median (IQR)	Instrument for depression diagnosis (cut-off point)	Instrument for dementia diagnosis	Incident cases of dementia, n (%)	Risk estimates (95% CI) (statistical analysis)	Covariates
Acosta et al.[30]	Mexico	n=1,355	73.2 (6.4)	1,144 (62.7)	3.0 (3.0-3.2)	NPI-Q	DSM-IV	129 (9.5)	RR=1.4 (1.0-2.0) (Poisson regression)	Age, sex, educational level, Mild cognitive impairment. Other psychiatric symptoms
Almeida et al.[28]	Australia	n=4,922	77.2 (3.7)	0 (0)	8.9 (NR)	GDS-15 (7+)	ICD-10	903 (18.3)	SHR=1.5 (1.2-2.0) (competing risk regression)	Age, stroke and diabetes history
Chen et al.[32]	Taiwan	n=4,237	65.4 (7.5)	2,744 (64.7)	Up to: 13	ICD-9 (Major depression)	ICD-9	322 (7.8)	HR=3.02 (2.46-3.70) (Cox regression)	Demographics* (urbanization, income). Psychiatric comorbidities (alcohol and other substances), medical comorbidities (hypertension, dyslipemia, diabetes, ischemic heart disease, cerebrovascular disease, COPD, head injury)
Ezzati et al.[27]	USA	n=1,219	78.3 (5.3)	756 (62.0)	4.4 (3.5)	GDS-15 (continuous)	DSM-IV	132 (10.8)	HR 1.11 (1.03-1.20) (1 GDS point increases) (Cox regression)	Age, sex, race, educational level and chronic medical conditions (hypertension, diabetes, stroke, ischemic heart disease, heart failure, Parkinson´s disease, rheumatoid arthritis, COPD)
Katon et al.[26]	Denmark	n=2,454,532	NR	1,268,002 (51.6)	5.6 (NR)	ICD-10 or antidepressant use.	ICD-10	59,663 (2.4)	HR=1.68 (1.64-1.71) (Cox regression)	Age, sex, period between both diagnosis (exc. 2 years), marital status, medical comorbidities (ischemic heart disease, heart failure, peripheral vascular disease, atrial fibrillation, cerebrovascular disease, head injury, COPD)

Table 1 Continuation

Study	Country	Sample size	Age (years), mean (SD)	Females, n (%)	Follow-up period(years), Mean (SD)/ median (IQR)	Instrument for depression diagnosis (cut-off point)	Instrument for dementia diagnosis	Incident cases of dementia, n (%)	Risk estimates (95% CI) (statistical analysis)	Covariates
Kontori et al.[29]	UK	n=4,859	65.9 (9.4)	2,679 (55.1)	8.0 (NR)	8 item CES-D (4+)	16 item IQCODE	216 (4.4)	HR= 1.82 (1.13-2.95) (Cox regression)	Age, sex, educational level, marital status, purchasing power, cardiovascular comorbidity (ischemic heart disease, heart failure, arrhytmia, stroke), smoking and physical activity. Excludes subjects with metabolic syndrome (Hypertension, diabetes, obesity, dislipemia…)
Makizako et al.[31]	Japan	n = 3,663	71.5 (5.2)	1,933 (52.8)	Up to: 2	GDS-15 (6+)	ICD-10	72 (2.0)	HR= 2.41 (1.19-4.86) (Cox regression)	Age, sex, educational level. Excluded Mild Cognitive Impairtment
Singh-Manoux et al.[25]	UK	n=10,189	44.9 (6.0)	3,351 (33.0)	27 (NR)	GHQ-30 (5+) /20 item CES-D (16+)	ICD-10	322 (3.2)	HR=1.21 (0.95-1.54) (Cox regression)	Sociodemographic variables (age, sex, race, marital status, educational level, work activity) smoking, alcohol intake, physical activity, diabetes, cardiovascular diseases (stroke, ischemic heart disease), use of medication for cardiovascular disease or antidepressants

CES-D=Centre of Epidemiological Studies Depression Scale; ICD=International Classification Disease; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders 4th Ed; GDS=Geriatric Depression Scale; GHQ=General health questionnaire; IQCODE=ítem informant Questionnaireon Cognitive Decline in the elderly. NR=No reported.
*Case-matched controls by sex and age.

one in the sensitivity analysis did not substantially modify the pooled RR, which remained significant in a range that varied from 1.29 (95% CI [1.21, 1.37]) (when we excluded Katon et al.[26]) to 1.68 (95% CI [1.21, 1.37]) (when we excluded Ezzati et al.)[27] Then, no relevant impact of any of the individual studies on the combined overall RR was observed.

Publication bias

Visual inspection of the funnel plot (not shown) might suggest the presence of publication bias, although both the Egger test (p=0.723) and the Begg test (p=0.902) indicated an absent or minimal risk of bias in our analysis. However,

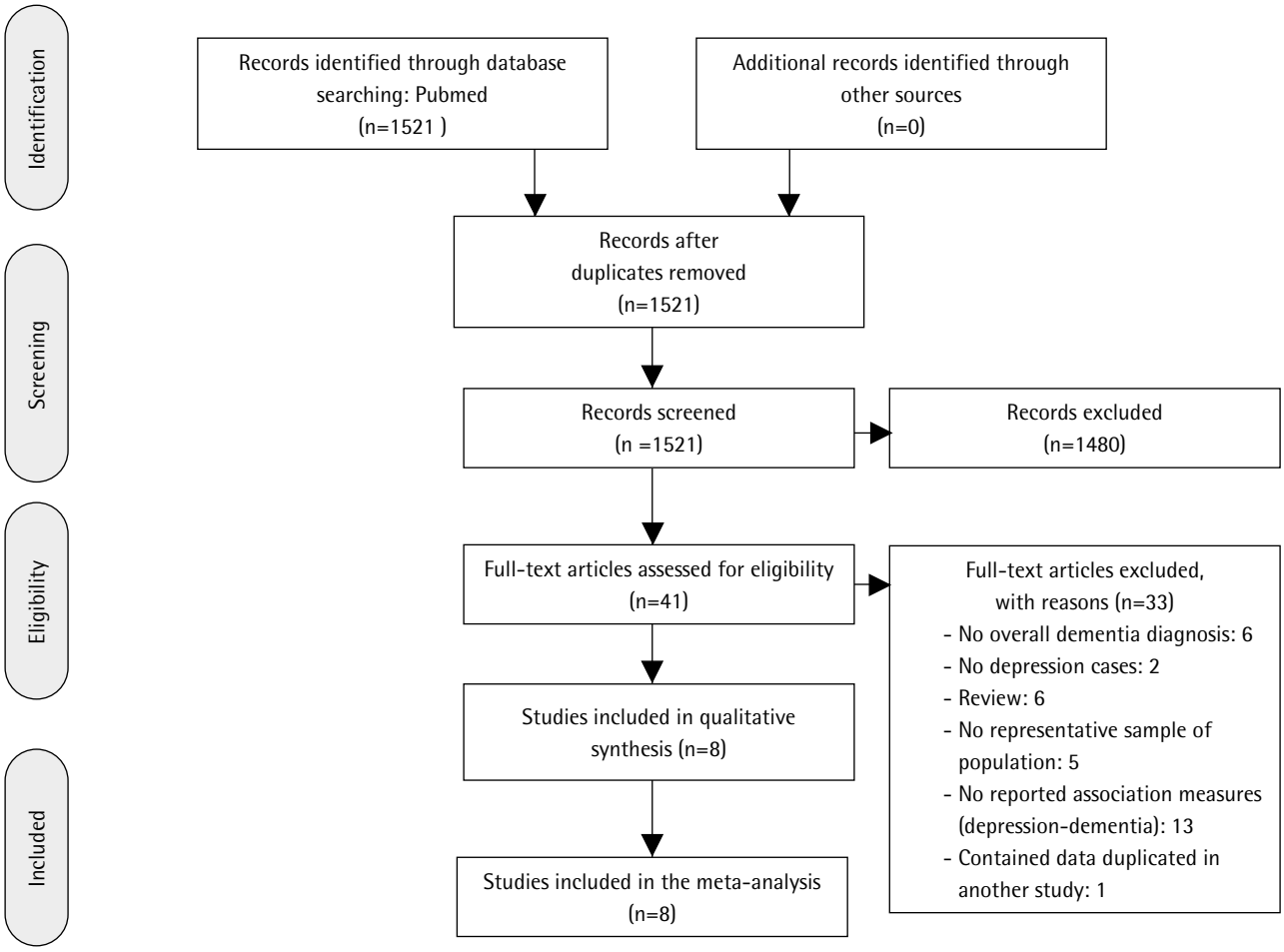

Figure 1 | *Flowchart*

the presence of publication bias should not be discarded, as the Orwin's N statistic was 8. That is, it would be necessary to include 8 articles with null results (RR=1) in our meta-analysis to obtain a nonsignificant magnitude of the overall effect.

Meta-regression

We investigated potential sources of heterogeneity among our studies using univariate meta-regression analysis (conducted on the natural logarithm of the RR, log (RR)). We found no statistically significant association with mean age, percentage of women, follow-up period, and methodological quality of the included studies with the risk of incident dementia.

Population Attributable Fraction

We estimated that the proportion of the population with depression was 15.8% (95% CI [9.6%, 22%]), giving a dementia PAF for depression of 9.0% (95% CI [4.5%, 14.1%]). Thus, assuming a causal relationship between depression and dementia cases and unbiased estimates, 9.0% of the dementia cases in the population would be attributable to depression.

Table 2 Newcastle-Ottawa Scale (NOS) qualityscore of the cohorts included in the meta-analysis (n=8)

Study	Selection				Comparability		Outcome			Overall quality score (Maximum=9)
	1	2	3	4	5A	5B	6	7	8	
Acosta et al.[30]	*	*	*	*	*	*	*	-	*	8
Almeida et al.[28]	-	*	*	*	-	*	*	*	*	7
Chen et al.[32]	*	*	*	*	*	*	*	*	-	8
Ezzati et al.[27]	*	*	*	*	*	*	*	*	-	8
Katon et al.[26]	*	*	*	*	*	*	*	*	-	8
Kontori et al.[29]	*	*	*	*	*	*	-	*	-	7
Makizako et al.[31]	-	*	*	*	*	*	*	-	-	6
Singh-Manoux et al.[25]	*	*	*	*	*	*	*	*	*	9

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: educational level, 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 (≥5 years) 8. Complete follow-up (all participants are accounted for or subjects lost to follow-up unlikely to introduce bias).

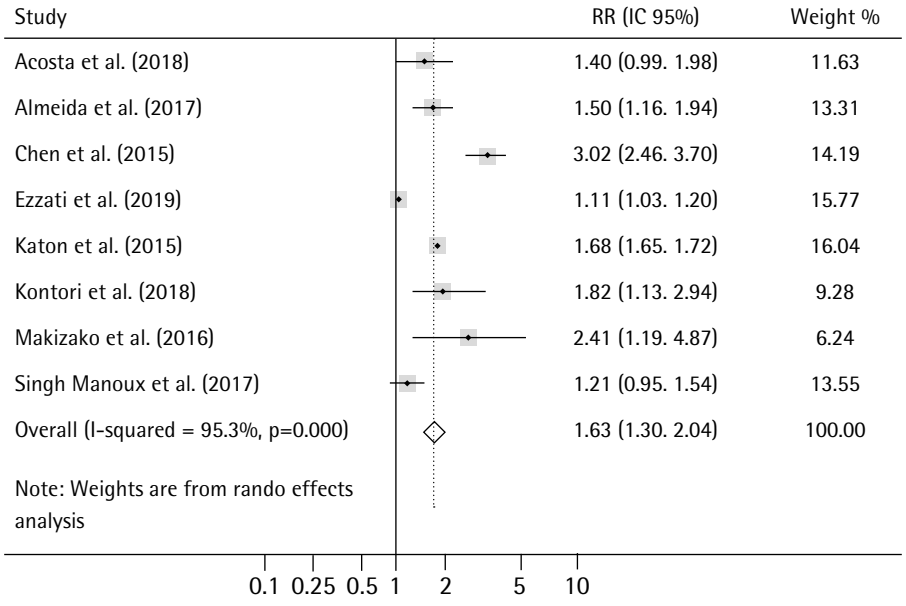

Figure 2 *Forest plot*

Table 3 Results of the univariate meta-regression of the log (RR)

Covariate	b	95% CI	p
Age (10 years increase)*	0.001	(-0.378; 0.380)	0.994
Female (10% increase)	0.039	(-0.115; 0.193)	0.558
Follow-up (1 year increase)	-0.004	(-0.047; 0.039)	0.830
Methodological quality (1 point increase)	-0.159	(-0.567; 0.247)	0.374

b=regression coefficient; CI= confidence interval; p=p value.
*Excluding Chen et al.[32]

DISCUSSION

The aim of this meta-analysis was to update the available evidence about the risk of dementia associated with depression. Based on the results of eight longitudinal studies, we found a 63% increase in the risk of overall dementia among older people with depression compared to participants without depression, suggesting that 9% of incident cases of overall dementia could be attributed to depression.

Firstly, it should be noted that there are methodological differences between the different studies (sample sizes, diagnostic methods, follow-up periods, variables by which the effect is adjusted...). However, the significant association between depression and dementia is sustained in practically all of them, and it is necessary to underline some points.

Previous meta-analyses of the relationship between depression and overall dementia have tried to minimize the heterogeneity of the included studies by analyzing separately those that used a clinically significant diagnosis of depression[7,8]. Nevertheless, the present work includes heterogeneous studies regarding the diagnosis of depression, ranging from studies that evaluate a single item of depression[30] to studies that use standardized clinical criteria[26]. Although dementia diagnosis is more homogeneous among different studies, one study based the diagnosis of dementia on a screening scale[29]. However, although methodological differences between the studies may have contributed to their heterogeneity, it is interesting that we continue to find a statistically significant association between depression and the risk of overall dementia, with less strength than that reported by Cherbuin[7], but similar to that reported in our previous work[8] for clinically significant depression.

Some studies examined the risk of dementia in individuals with a history of depression before the beginning of the study. Thus, Almeida et al.[28]found no increased risk of dementia for individuals who reported having suffered depression before. However, studies that collect a previous history of depression based on population records, following standardized diagnostic criteria[26,32] found a significant increase in dementia risk for subjects with previous depression, at follow-up intervals of up to 12 years.

Differences in the length of the average follow-up and how some authors found differences in their results depending on this variable should also be noted. In the study by Almeida et al.[28], when stratifying the analyses by follow-up intervals, the relationship between depression and dementia was only significant in the first 5-years of follow-up and it was more relevant in the case of the elderly over 85. These authors suggested that depression is probably an incipient marker of dementia, rather than a risk factor. The same conclusion was reached by Sigh-Manoux et al.[25], who carried out the longest follow-up period, including middle-aged adults at the beginning of the study. These authors only found a significant increase in the risk of dementia for individuals with depression in the last 11 years of follow-up, when the study subjects had an average age of 70. Both studies used symptom scales for the diagnosis of depression. In the case of studies that used international standardized criteria for depression diagnosis[26,32], the authors concluded that although the risk of dementia decreases with the time interval since the diagnosis of depression, from 3[32] and even 6[26] years, it remains double and statistically significant. These results would support the hypothesis of depression as a risk factor of dementia. In this regard, Ezzati et al.[27] found that the increase in dementia risk with the GDS score for depression was significant only in the long term, as of 3 years of follow-up. These results seem inconsistent with the hypothesis of depression as a prodromal symptom, according to which an increase in association could be expected the shorter the interval between depression and dementia.

Here is where the main controversy lies concerning the studied issue, as dementia is an illness with a long latency period, and it is difficult to discriminate whether depression is a risk factor or a prodrome of dementia. The results of this work, consistent with meta-analyses of previously published longitudinal studies[7,8], find a statistically significant association between depression and dementia risk. As depression continues to be significantly associated with the diagnosis of dementia in follow-up periods exceeding 10 years[25,26,32] in individuals without cognitive impairment at the beginning of the study, this suggests that depression cannot be exclusively a prodromal symptom of dementia. Furthermore, if depression were a prodromal symptom of dementia, a stronger association between them could be found in studies assessing non-specific depressive symptoms; however, consis-

tent with the results of Cherbuin et al.[7], the study that found a greater degree of association between depression and dementia in our meta-analysis used a specific and standardized diagnosis of depression[26].

These criteria would support the hypothesis of depression as a risk factor. Depressive symptomatology, and especially clinically significant depression, could be related to the pathological mechanisms involved in neurodegeneration, and could precede by years the first symptoms of cognitive impairment, in which case we could refer to a common etiopathogenic basis of the two disorders.

When studying depression as a possible risk factor of dementia, it is important to consider the time throughout life when it happens, as well as the time from the depressive episode to the onset of dementia. The result, in this regard, again highlights the existing controversy. Some studies have reported that depression in early adulthood predisposes to the development of dementia, increasing the risk by 2 to 5 times[33]. Additionally, this meta-analysis[33] found a direct and significant association with the time interval between the diagnosis of depression and incident dementia. Subsequent longitudinal studies with long follow-up periods[34] have found a significant risk of dementia associated with depression, which would support the hypothesis of depression as a risk factor of dementia.

The association between depression and dementia may depend on the age of onset of the first depressive episode[35]. Depression that appears in youth is associated with greater chronicity, poorer psychosocial functioning and quality of life, and more genetic factors[36,37]. Thus, people who have been exposed to more depressive episodes may repeatedly activate steroid levels, leading to permanent damage to the hippocampal area[37-39]. On the other hand, some studies suggest that depression may favor the deposit of beta-amyloid and the formation of neurofibrillary tangles[40]. In recent years, there is growing evidence of the association between depression and markers of inflammation, as well as the association between neuroinflammation and beta-amyloid load[41]. Depression also constitutes a risk factor for myocardial infarction or stroke[42,43], factors which in turn predispose to the development of dementia[44].

One of the strengths of this study is that, as a systematic review and meta-analysis of all available studies of depression and overall dementia risk, it is more powerful in detecting an effect than any of the individual studies included. The present study is robust, as it includes a selection of prospective studies that avoid the influence of memory and selection bias. In addition, the inclusion of large sample-size studies reduces the risk of the effects of small studies, and we obtain a significant number of incident cases. Also, each included study had a sufficiently long follow-up period (minimum of one year) to observe the potential association between depression and the risk of dementia. Hence, given that case-control or cross-sectional studies were excluded from this analysis, the exclusive use of cohort studies provides greater evidence in establishing the cause-and-effect relationship according to the causality criteria proposed by Hill[45]. Moreover, the combined RRs were consistent in the influence analysis. Likewise, the use of the random effects model in our analyses takes into account the heterogeneity between studies.

This study has several limitations. First, the meta-analysis contains a limited number of effect magnitudes, and this may affect the power of the test used. However, some research has shown that meta-analyses of a few studies will still be able to provide important information[46]. In this sense, we used the I^2 confidence interval for the assessment of heterogeneity instead of only the Q contrast, which is recommended in meta-analyses of few individual studies[47].

CONCLUSIONS

Longitudinal studies examining the relationship between depression and dementia consistently find that participants with depression are at greater risk of developing dementia in their course of life. Previously published meta-analyses and the one carried out in this paper, which includes studies published in recent years, support these results. To elucidate whether depression is a modifiable risk factor of dementia, studies should be conducted to investigate whether effective treatment of depression has a preventive effect on the risk of dementia.

CONFLICT OF INTEREST

BV has received payment from Janssen for travel and subscriptions to attend a scientific meeting. PGG has received fees from Jansen and Servier, and payment of travel and subscription expenses to attend scientific meetings from Esteve, Servier, Nutricion Médica and Pfizer. The authors have no conflict of interest to declare in relation to this work.

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