Publication alert: A meta-analysis of prospective cohort studies that evaluated the association between depression and dementia revealed a 1.82 times increased risk of dementia among patients who had previously experienced or were experiencing depressive symptoms at the start of the study.

Tweet: A meta-analysis shows that past or present depression appears to nearly double the risk of developing dementia.

Depression as a Risk Factor for Dementia: A Meta-Analysis

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Dementia is a syndrome characterized by the deterioration of cognitive function beyond what is expected. The increased risk of developing this syndrome resulting from established modifiable risk factors, such as depressive episodes, is currently a subject of interest. The aim of this study was to review the scientific evidence that addresses the relationship between depression and dementia. A bibliographic search of the PubMed and PsycInfo databases for articles published over the past 20 years was conducted with the following medical subject heading (MeSH) terms: depression or depressive, dementia, and incidence or cohort studies. After articles meeting the inclusion criteria were selected, relevant moderating variables were grouped as sample characteristics, methodological characteristics, extrinsic characteristics, and outcome variables. The 26 selected studies resulted in a sample comprising 112,408 individuals. Statistical analysis revealed a pooled relative risk for the development of dementia of 1.88 (95% CI=1.53–2.31). The primary variables evaluated were the diagnostic methods for depression and dementia and the presence of depression. Other variables, such as mean age, methodological quality of each study, follow-up time, and publication year, were also evaluated. Only age was clinically not significant. No relevant publication bias or alterations in the results were found when accounting for the quality of the studies. It is recommended that new moderating variables are evaluated or that existing variables are reformulated in future studies.

Alzheimer's Disease, Dementia, Depression, Meta-Analysis, Risk Ratio

Dementia affects several cognitive domains and represents a decline that is severe enough to compromise personal and social functioning and, in many cases, to manifest behavioral and psychological symptoms (1). Epidemiological studies have confirmed that age is the main risk factor for the development of dementia, and the incidence practically doubles every 5 years after age 65 (2). According to the World Health Organization (WHO) (3), the appearance of approximately 30 million new cases every year will lead to an estimated 152 million cases of dementia by the year 2050. The impact will be of such importance that the WHO already recognizes dementia as a public health priority.

Because age is and will always be an unchangeable risk factor, studies on dementia incidence have focused on possible modifiable risk factors, such as diabetes, obesity, hypertension, hearing loss, depression, and tobacco and alcohol consumption, or potential protective factors, including physical activity, diet, intellectual activity, and social interaction. A reduction in risk of dementia of up to 40% has been attributed to these factors (4). With a focus on depression as a modifiable risk factor for dementia, numerous studies have suggested that depressive symptoms are an independent risk factor for the subsequent development of dementia. For example, a recent meta-analysis showed a clinically relevant association between depression and an increased risk of dementia and Alzheimer's disease, with a potential impact larger than that of other known risk factors (5). The analysis suggested that 8.6% of all new cases of dementia and 10.8% of new cases of Alzheimer's disease could be attributed to depression.

The link between depression and dementia is a complex, concerning issue that remains unclear. One problem is the difficulty in making an accurate diagnosis of dementia. With regard to the complexity of the relationship, functional MRI studies have revealed three

neural circuits involved in the association between depression and dementia: the default mode network, the executive control network, and the salience network (6). Changes in these circuits can be identified before the onset of cognitive impairment. Other studies have proposed that the relationship between depression and dementia may arise from chronic stress and inflammation generating vascular and neuronal damage that leads to or exacerbates depressive symptoms that in turn contribute to the subsequent development of dementia (7). Finally, a biomarker that is generating great interest is amyloid. Amyloid deposition has classically been associated with cognitive impairment; interestingly, studies have found that [^{18}F]-florbetapir binding values (a measure of amyloid deposition) in specific brain regions are higher among patients with late-life major depression than among comparison subjects (8). The lack of well-accepted biomarkers for dementia and depression results in high levels of diagnostic subjectivity (9).

Another point to consider is the way in which depression is diagnosed, because the symptoms that characterize depression are common to numerous conditions. For example, depression and apathy share important key symptoms, and apathy is one of the most prevalent behavioral and psychological symptoms of dementia (10). This fact may lead to diagnostic uncertainty, and although the nosological position of apathy as a syndrome separate from depression remains debatable (11), the differentiation between the two syndromes presents serious difficulties that may confound the study of risk factors.

Previous research has produced some consistent findings. The age when depression appears and its subsequent course have been studied as factors associated with the subsequent development of dementia. Numerous studies show differences in the incidence of dementia, depending on whether depression is established in early adulthood or in late

adulthood (>65 years old); these studies generally show a greater association if the syndrome is established in late adulthood (12, 13). However, the results often differ. For example, a longitudinal study of 16,608 adults, who were screened for 6 years or until the onset of incident dementia, revealed no differences in dementia incidence based on whether depression was established in adulthood or late life (the cutoff was 65 years old). The lack of differences in the incidence of dementia were attributed to evolution of the depressive syndrome. There was no greater risk of dementia among patients whose depression was limited to early adulthood and among those with late-onset depression if the depressive symptoms were controlled (14). The investigators recommended expanding this field of research to assess how the treatment of a depressive syndrome may prevent dementia.

In the present meta-analysis, we aimed to explore, simplify, and update our present-day understanding of whether depression is a risk factor for dementia based on research findings. Therefore, we did not consider different types of dementia or different symptomatic or neuropsychological domains affected, but rather, we considered dementia and depression as syndromes themselves. Because we could not answer this question by means of a review of randomized trials and because we aimed to calculate differences in the incidence of a disorder, the most suitable type of studies for our analysis were those that involved prospective cohorts. Furthermore, following Cochrane recommendations (15), randomized studies were excluded, because the recommendation is to not combine randomized with nonrandomized studies.

Methods

We conducted a systematic review and a meta-analysis following the Cochrane Handbook for Systematic Reviews (15) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The protocol was documented before the database search to reduce the risk of confounding factors in a meta-analysis of nonrandomized trials.

Data Search and Sources

We conducted a search for potentially relevant studies in the electronic bibliographic databases PubMed and PsycInfo, considering that these two databases provide an adequate coverage of neuropsychological publications worldwide. We included the following search term: ((Depression [MeSH Terms]) OR (Depressive [MeSH Terms])) AND (Dementia [MeSH Terms]) AND ((incidence [MeSH Terms]) OR (cohort studies [MeSH Terms])). We selected articles published between January 2000 and December 2022 that were written in English or Spanish, and we contacted authors to provide full-text articles when necessary.

Study Selection

In accordance with our inclusion criteria, we selected prospective, longitudinal, nonrandomized, population-based studies that incorporated a follow-up period of more than 1 year. The studies included were those with samples comprising patients who presented with a diagnosis of depression as a syndrome before or at the start of the study and who showed no cognitive impairment at the beginning of the study. The studies had to

explain the diagnostic methods, including details of the criteria or method used to diagnose cognitive impairment as a syndrome. Finally, the studies had to report the association between depression and dementia in the form of a risk ratio (hazard ratio) or relative risk with its 95% confidence interval. Systematic reviews and meta-analyses were excluded.

Data Extraction, Moderator Variables, and Quality Assessment

We performed a full-text review of each study selected, and we recorded the crude hazard risk (and 95% confidence intervals) and the moderating variables. We grouped the moderating variables as sample characteristics (sample size, country, average age of participants, and gender), methodological characteristics (presence or absence of depression at the beginning of the study, diagnostic method for depression, diagnostic method for dementia, and follow-up time), extrinsic characteristics (methodological quality of the study and year of the study), and outcome variables (type of risk measure, results, and 95% confidence intervals).

Diagnostic methods were grouped into two categories: scales versus clinical criteria. To assess the quality of the cohort studies, we used the Newcastle-Ottawa Scale (NOS) (16), with 5 years as the time limit for the diagnosis of dementia (which we considered a sufficient time frame for the appearance of possible cognitive deterioration associated with the depressive syndrome), and we allowed a maximum loss of 25% of participants across the follow-up period (considering the time frames used in previous studies and the average age of the samples included in the analysis). The NOS is specific for cohort studies, and its use enabled us to assess the quality of the methodology and the risk of bias of each study

individually. NOS scores were coded as a variable for subsequent analyses as a moderator variable.

Statistical Analysis

Analyses were conducted with STATA, version 17.0, with a significance threshold set at $p<0.05$. Complementary analyses were conducted with Comprehensive Meta-Analysis, version 3.3.

Hazard ratios were used to calculate the risk of developing dementia; we used this value as an adequate effect-size index to assess the role of contextual factors as covariates that represent an increased risk of the effect (dichotomous variable) in a study of cohorts. We log-transformed the risk measure and calculated the standard error with a 95% confidence interval to normalize the distribution and stabilize the variance. The results are reported with a forest plot.

Heterogeneity Analysis

Given the expected heterogeneity among studies, it seemed appropriate to use a random-effects model (DerSimonian-Laird method) for the global analysis of effect size, because the Cochrane manual allows this model to be used with nonrandomized trials that incorporate dichotomous variables. We assessed heterogeneity across studies with Cochrane's Q statistic ($p<0.05$ suggests significant heterogeneity) and the I^2 statistic.

Analysis of Moderator Variables

We performed analyses to identify potential sources of heterogeneity across the studies included in the overall risk estimate. Subgroup analyses were performed with the qualitative moderating variables: the diagnostic methods for depression and dementia and the presence of depression at the beginning of the study. We also performed a univariate meta-regression to examine the following quantitative variables: mean age, percentage of female participants, follow-up duration, publication year, and methodological quality (NOS scores).

Publication Bias Evaluation

We analyzed publication bias that could have affected the results by using the Rosenthal criterion as a cutoff point to evaluate our results and by visual inspection of the funnel plot (17) after applying the Duval and Tweedie trim-and-fill method (18).

Sensitivity Analysis

A sensitivity analysis was conducted by rerunning the analysis after excluding each study one by one, which removes the possible bias of a risk effect being overly influenced by any individual study and checks the stability of the results in terms of direction, effect magnitude, and statistical significance.

Results

Study Screening

We identified a total of 1,162 bibliographic references from the two databases, and 201 duplicate studies were discarded. A total of 259 studies were excluded because they did not meet the inclusion criteria, with the most frequent reason being that the study was not focused on the association between dementia and depression. Subsequently, 676 additional studies were excluded because they were not related to the question of interest. A total of 26 studies (6, 12, 19–42) were included in our meta-analysis (for further details, see the flow chart in the online supplement). The degree of overlap with similar meta-analyses was 11% (43), 18% (44), and 50% (5), which guarantees the originality of our results.

Study Characteristics

The 26 studies represented a total sample of 1,760,262 individuals. Demographic characteristics of the samples for each study are presented in Table 1tbl1. Most of the studies included patients older than age 65, with a mean age range from 56.1 to 83.8 years. Two studies included only female participants, and the remaining studies included both sexes. The target population of the primary studies we analyzed corresponded to the general population, with the United States being the country in which most studies were conducted. The mean follow-up duration ranged from 3 to 17 years. However, it was not possible to extract this variable from all studies.

Most of the studies required the presence of depressive symptoms at the beginning of the study; however, seven studies included individuals who had a history of at least one depressive episode in the past that was similar to that of patients from the group with depression at the start of the study. The prevailing diagnostic approach for both depression and dementia was the use of standardized clinical criteria (ICD-9 or ICD-10 and DSM-IV, DSM-IV-TR, or DSM-5). Other studies used assessment scales, such as the Center for Epidemiologic Studies Depression (CES-D) scale, the 17-item Hamilton Depression Rating Scale, or the structured interview for the diagnosis of dementia; in each case, a universal cutoff point was applied to make the variable dichotomous.

Regarding statistical analyses, all the studies estimated the risk measure by using Cox regression, and all of them found significant results except for two: a Spanish study (19), where a significant incidence was found only among individuals with severe depression, and a German study (12), where the investigators concluded that their results indicated that depression may be a prodrome and not a risk factor for cognitive impairment.

Global Effect of Depression as a Risk Factor for Dementia

Risk estimates were averaged across the 26 studies by using a forest plot (Figure 1 fig1). All hazard ratio estimates were larger than one and were statistically significant in all but two studies. The global estimate of the combined hazard ratio was 1.82 (95% CI=1.62–2.06, $p<0.05$). That is, patients with depression showed a 1.82 times higher risk of dementia compared with those who did not present with depression (or history of depression) at the beginning of the study.

Heterogeneity and Sensitivity Analyses

Heterogeneity across studies was larger than 45% (I^2=95.33%, Q=534.78; p<0.05). Therefore, moderator analyses were needed to explore different sources of potential variability underlying the pooled average of the hazard ratios. The robustness of our findings was evaluated by testing the influence of each study with the leave-one-out cross-validation method, and we did not find a relevant impact of any individual study on the combined relative risk. The overall estimate was 1.82, and the sensitivity analyses resulted in values that ranged from 1.78 (95% CI=1.58–2.01, p<0.05), when the study by Burke et al. (20) was excluded, up to 1.87 (95% CI=1.65–2.12, p<0.05), when the study by Heser et al. (12) was excluded.

Subgroup Analysis of Heterogeneity

We analyzed possible sources of heterogeneity from qualitative moderators by means of subgroup analyses. We included the diagnostic methods for depression and dementia and the presence or absence of depression at the beginning of the study as moderator variables. These results were not significant. There was a tendency toward less heterogeneity when all studies were compared with the group of studies that did not require the presence of depression at the beginning of the study. In this comparison, we also found a lower, but not significantly lower, combined relative risk (relative risk=1.64, 95% CI=1.35–2.01; p<0.05).

Meta-Regression

We found significant results when evaluating possible sources of heterogeneity with a meta-regression analysis using mean age at the beginning of the study (Table 2tbl2). No

statistically significant effects were found when using percentage of female participants, methodological quality, and year of publication as factors, nor did we find a clinically significant association with mean age at the beginning of the study ($b=-0.03$, $p<0.05$). Regarding the year of publication, a cumulative heterogeneity analysis showed that the results of studies have become increasingly similar in recent years.

Publication Bias

We analyzed the funnel plot by applying the trim-and-fill method (Figure 2fig2); the analysis suggested that there may have been a small publication bias, given the absence of published studies with a small sample size on the left side of the graph. The Rosenthal criterion, which establishes a minimum number of unpublished studies (5k+10) (in our case, the result would be 140), and the nonsignificant results of the Egger's test ($p=0.001$) provided additional evidence of the presence of publication bias. The trim-and-fill method estimated a total of nine missing studies (existing but not published), and it was estimated that the impact of these studies on the combined relative risk would be moderate, moving from a risk of 1.82 (described above) toward a relative risk of 1.50 (95% CI=1.35–1.68, $p<0.05$).

Discussion

In this meta-analysis, we evaluated the global impact of the presence of depression on the subsequent development of dementia. Our results point toward a 1.82 times higher risk of dementia among patients who had experienced or were experiencing a depressive episode at the start of the study. Although our results showed a significant pooled relative risk for the development of dementia, we could not explain the large degree of heterogeneity among the different effect sizes; there was only a small correlation regarding age, which was the only clinically nonsignificant variable. Furthermore, we found no relevant issues when assessing the quality of the studies or publication bias.

Depression as a Cause or Consequence of Dementia

The results of our study indicate an increase in the relative risk of dementia among patients who experience or have experienced a depressive syndrome. Our results are in line with those of previous studies reporting an increased relative risk of 1.85 (95% CI=1.67–2.04, $p<0.001$) for all causes of dementia (45) and, as reported by Santabárbara et al. (5), a combined relative risk of 1.63 (95% CI=1.30–2.04, $p<0.01$). Santabárbara et al. also found a high degree of heterogeneity in their results that, as in our analysis, did not detract from the robustness of the analysis, based on the results of the leave–one-out cross-validation method. However, these results can only lead us to postulate a possible causal relationship, which brings us back to our initial question of whether depression is the cause or a consequence of dementia. In a systematic review, Wiels et al. (46) concluded that this question is not yet answered; they found that depression was noted as a risk factor in seven studies and as a prodromal symptom in 10. Some studies provide evidence that could

support both possibilities, showing changes in white matter that could indicate shared risk factors or a shared pattern of neuronal damage (47). For example, there are studies showing that sustained exposure to proinflammatory cytokines characteristic of aging could alter microglial function, which may lead to compromised activity of the enzymes responsible for amyloid metabolism (48), a peptide that has been reported to be associated with depressive symptoms in some studies (e.g., 8). Other studies have revealed other common pathophysiological pathways, such as astrocytic dysfunction, which appears to be related to the progression of depressive symptoms in Alzheimer's disease (49). In any case, common pathophysiological mechanisms are conceivable (chronic inflammation, glucocorticoid-related toxicity, neuronal dysregulation, etc.). For this reason, some investigators suggest that the presence of depression should be quantified with a scale, rather than classified as dichotomous data (i.e., presence versus absence), because if there was a common relationship, a "dose-response" would be expected (46). flushleft

Along these lines, Verdelho et al. (50) used the Geriatric Depression Scale and showed that the severity of depressive symptoms predicted subsequent cognitive performance on scales such as the Mini-Mental State Examination and the cognitive subscale of the Vascular Dementia Assessment Scale, regardless of confounding factors. One of the studies included in our analysis mentioned this issue as well. Gracia-García et al. (19) did not find significant results on the overall relationship between depression and dementia, although this relationship was statistically and clinically significant when data from only those patients with a diagnosis of severe depression were analyzed (relative risk=4.30, 95% CI=1.39–13.33; $p<0.05$). The magnitude of the relative risk was markedly higher than the combined relative risk found in our meta-analysis or in other studies discussed here. Other

studies have also suggested a probable association of the severity of depressive symptoms with the risk of dementia (51), and therefore we recommend further research along these lines.

Another issue to consider when investigating the direction of the depression-dementia relationship is the type of dementia. Most of the studies we included in our analysis examined all-cause dementia. However, many studies focus on the two most common types of dementia: Alzheimer's disease and vascular dementia. These two types of dementia present different pathophysiological mechanisms. Therefore, if we want to consider the depressive syndrome as a prodrome of any type of dementia, we must rethink the pathophysiological explanation that we provide. Differences in the relationship have been identified for each type of dementia, as noted in several reviews. For example, Diniz et al. (45) found that, among patients with late-onset depression, the risk of vascular dementia (relative risk=2.52; 95% CI=1.77–3.59, $p<0.001$) was significantly higher than the risk of Alzheimer's disease (relative risk=1.65; 95% CI=1.42–1.92, $p<0.001$) ($p=0.03$). Although our analyses did not focus on this aspect, it would be interesting to analyze these two entities separately in future studies and meta-analyses.

Moderator Variables and the Depression-Dementia Relationship

We did not find significant results in our meta-analysis when analyzing moderator variables, which is consistent with previous studies (5, 44). However, Cherbuin et al. (44) found statistically significant moderating effects on the relationship between the risk of dementia and depression, when the latter was measured as a continuous variable

(quantified with the CES-D scale). In particular, variables such as dropout rate, percentage of females, average age, and quality of the study accounted for up to 46% of the unexplained variance.

However, some studies, two of which were included in the present analysis, have considered gender as a possible moderator to the extent of including only female patients. For example, Goveas et al. (26) included only female patients on the basis of a possible hormonal influence among postmenopausal women. They found significant results for the global effect of depression on the risk of dementia, and this effect was essentially unaltered when variables such as hormone replacement therapy were included in the model. Another study included in our analysis, conducted by Neergaard et al. (36), addressed the same hormonal influence and obtained similar results. However, the investigators found some significant moderator variables, such as obesity in late life, to be protective factors for dementia; when compared with normal-weight women, those who were overweight had a decreased risk of dementia. Other studies, which were excluded in our meta-analysis, described specific associations related to sex when the focus was on different aspects of the depressive spectrum. For example, depressive effects are predominant among women and somatic symptoms are apparent in both sexes (52).

In the Spanish meta-analysis conducted by Santabárbara et al (5), the investigators noted the possible influence of the diagnostic method (i.e., the use of scales versus clinical criteria) as a possible source of heterogeneity. Our results do not support this hypothesis because no differences were found in terms of heterogeneity, nor were important differences found in terms of combined relative risk when we divided the studies according to the diagnostic method; this finding is in line with the results reported by Diniz et al. (45), who did not find significant differences when they divided their sample into two groups

based on diagnostic approach (patients diagnosed with the CES-D scale and those who were not).

However, conflicting results have been reported in other studies. A recent meta-analysis found that the use of diagnostic criteria for depression results in greater consistency and significant findings compared with the use of symptom scales (53). The investigators described differences in the cutoff points used for these scales that explained up to 53% of the variability. They also mentioned that the larger effect size may have been related to the inclusion of studies that diagnosed depression by using clinical criteria, which could factor into the comparison of our results with those of Santabárbara et al. (5). Similarly, Cherbuin et al. (44) found differences in the relative risks based on the cutoff point used on the CES-D scale. These differences could simply be methodological, or, as noted in the study, the difference may indicate the severity of the condition and therefore imply that greater relative risk of dementia denotes greater severity of the depressive condition. If this is true, the findings could indicate a possible relationship between dementia and "dose-dependent" depression.

Finally, it should be noted that although age did not prove to be a clinically significant moderator variable in the present meta-analysis, it is one of the most studied factors when the relationship between depression and dementia is evaluated. One of the studies included in our analysis that did not yield significant overall results found a significant relative risk of 5.48 (95% CI=2.41–12.46, $p<0.001$) when the analysis focused on very-late-onset depression (depression established after age 70) (12). In fact, numerous studies mentioned late-onset depression (established after age 65) as the type of depression that is most closely related to dementia (12, 13, 32, 41). A recent review highlighted that long-term

prospective cohort investigations in the preclinical phase of dementia are rare (13). This review concluded that early-onset late-life depression, defined as depression beginning before age 60, increases the chances of developing dementia among predisposed individuals, whereas late-onset depression appears to be prodromal and a clear accelerating factor of cognitive decline.

Publication Bias in Depression and Dementia Studies

Finally, it should be noted that we found publication bias in our meta-analysis similar to that found in other meta-analyses, which have reported a safety number between 43 and 132 (44). Other studies, however, did not find publication bias, such as the Spanish study by Santabárbara et al. (5), in which the Egger's and Begg's tests were not statistically significant. We suggest that there is an evolution toward an improvement of this bias over time, possibly related to the growing interest in investigating the modifiable risk factors for dementia, and we believe that limiting our search to only two databases may have biased our results.

It is noticeable that most of the studies included in our analysis were conducted in the United States, possibly because it is one of the countries expecting an increase in the incidence of this pathology in the future. The U.S. Centers for Disease Control and Prevention currently predicts that the prevalence of the disease in the United States may increase to 13.9 million people, almost 3.3% of the population, by the year 2060. Regardless, it is evident that the interest in research on the development and the treatment of dementia is growing, and any results, either positive or negative, are important for our further understanding of the possible mechanisms that could help slow its progression.

Limitations

This study has several limitations, given that both depression and dementia have been considered to be separate syndromes. During our evaluation, we found that the different types of dementia, as well as the severity and age at onset of depression, are widely studied factors that seem likely to have an important impact. In addition, our search was potentially too restrictive, which prevents us from drawing robust conclusions. We recommend that future studies analyze these variables more superficially and separately.

Conclusions

The relationship between depression and dementia is a growing concern. However, the nature of this relationship is complex and raises many questions that, to date, have not been answered, including questions about the nature of the two pathologies themselves. Given the importance of both pathologies and the epidemiological impact they present, as well as the methodological difficulties posed by the study of uncontrollable variables, it is essential to conduct additional research on both conditions, together and separately, and on the moderating factors that could help to broaden our understanding of this complex relationship.

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FIGURE 1. Risk estimates of developing dementia among participants with or without depression across 26 prospective cohort studies.

FIGURE 2. Assessment of publication bias in prospective cohort studies evaluating the association between depression and dementia[a]

[a] Estimated ϕ_{DL}=estimate of between-study variance based on the DerSimonian-Laird estimator.

TABLE 1. Study and sample characteristics of the included studies (N=26) evaluating the association between depression and dementia[a]

First author and year (reference)	Country	Number of participants	Mean age (years)	Female (%)	Depression diagnostic method	Dementia diagnostic method	Hazard ratio	95% CI
Boyle 2010 (21)	United States	470	74.49	63.19	Diagnostic criteria	MADRS	3.68	2.1–6.42
Brewster 2021 (22)	United States	8,529	73.9	63.5	GDS	Diagnostic criteria	1.29	1.03–1.62
Burke 2018 (20)	United States	12,083	71.05	65.09	Diagnostic criteria	NINCDS-ADRDA	2.72	2.15–3.43
Chen 2015 (23)	Taiwan	1,946	65.45	65.4	Diagnostic criteria	Diagnostic criteria	3.02	2.46–3.70
Gallagher 2018 (24)	United States	2,655	70.1	72.9	Diagnostic criteria	NINCDS-ADRDA	1.48	1.23–1.77
Gilsanz 2019 (25)	United States	3,742	56.1	41.2	Diagnostic criteria	Diagnostic criteria	1.98	1.30–3.01
Goveas 2011 (26)	United States	6,376	69.9	100	Diagnostic criteria	Diagnostic criteria	2.03	1.15–3.60
Gracia-García 2015 (19)	Spain	3,864	73.5	79.4	GMS-AGECAT	NINCDS-ADRDA	1.82	0.97–3.42
Heser 2013 (12)	Germany	2,663	82.52	69.2	CIDI	Diagnostic criteria	0.92	0.62–1.37
Katon 2015 (27)	United States	19,239	58.8	49	PHQ	Diagnostic criteria	2.02	1.73–2.35
Katon 2010 (28)	United States	3,837	63.2	47.9	PHQ	Diagnostic criteria	2.69	1.77–4.07
Kim 2021 (6)	United States	10,739	70.7	74.8	Diagnostic criteria	NINCDS-ADRDA	2.0	1.5–1.5; 2.6
Kontari 2019 (29)	United Kingdom	4,859	65.9	55.1	CES-D	IQCODE	2.68	1.70–1.70; 4.25
Korhonen 2022 (30)	Finland	1,616,321	68.9	56	Diagnostic criteria	Diagnostic criteria	1.27	1.23–1.31
Lenoir 2011 (31)	France	7,989	74	61	MINI	Diagnostic criteria	1.5	1.2–2.2
Li 2011 (32)	United States	3,410	75.8	67.2	CES-D	NINCDS-ADRDA	1.71	1.37–2.13

Luchsinger 2008 (33)	United States	526	78.1	67.7	HAM-D	Diagnostic criteria	3.4	1.5–8.1
Luppa 2013 (34)	Germany	1,265	83.8	83.6	SCID	SIDAM	1.03	1.01–1.05
Mirza 2014 (35)	Netherlands	4,393	72.7	59.2	CES-D	Diagnostic criteria	1.38	1.06–1.80
Neergaard 2016 (36)	Denmark	5,512	75.1	100	Antecedents	Diagnostic criteria	1.75	1.32–2.34
Oh 2021 (37)	Korea	4,456	N/A	N/A	Diagnostic criteria	Diagnostic criteria	3	1.56–5.85
Ou 2019 (38)	Taiwan	15,944	65.7	15.32	Diagnostic criteria	Diagnostic criteria	1.32	1.13–1.54
Saczynski 2010 (39)	United States	949	79	63.6	CES-D	NINCDS-ADRDA	1.72	1.04–2.84
Singh-Manoux 2017 (40)	United Kingdom	10,189	60	33	CES-D	Diagnostic criteria	1.72	1.21–2.44
van Uden 2016 (41)	Netherlands	496	65.6	43.1	CES-D	Diagnostic criteria	2.7	1.4–5.2
Wu 2022 (42)	United States	7,810	62.7	80.5	CES-D	Langa-Kabeto-Weir algorithm	2.82	2.17–3.67

[a] CES-D=Center for Epidemiologic Studies Depression scale; CIDI=Composite International Diagnostic Interview; GDS=Geriatric Depression Scale; GMS-AGECAT=Geriatric Mental State–Automated Geriatric Examination for Computer Assisted Taxonomy; HAM-D=17-item Hamilton Rating Scale for Depression; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; MADRS=Montgomery-Åsberg Depression Rating Scale; MINI=Mini-Mental State Examination; NINCDS-ADRDA=National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; PHQ=Patient Health Questionnaire; SCID=Structured Clinical Interview for DSM Disorders; SIDAM=structured interview for the diagnosis of dementia of the Alzheimer type, multi-infarct dementia and dementias of other etiology according to ICD-10 and DSM-III-R.

TABLE 2. Meta-regression results across 26 prospective cohort studies analyzing the association between depression and dementia

Covariate	Regression coefficient	95% CI	p
Age (years)	−0.04	−0.06, −0.01	0.01
Percentage of females	0.002	−0.007, 0.013	0.62
Methodological quality	−0.18	−0.48, 0.12	0.24
Year of publication	−0.03	−0.08, 0.02	0.25
Follow-up time	0.00	−0.047, −0.047	0.98