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Review article

Affective disorders and risk of developing dementia: systematic review

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Background
Affective disorders are associated with cognitive disturbances but their role as risk factors for dementia is still not fully investigated.

Aims
To evaluate the risk of developing dementia in individuals with a history of affective disorder.

Method
We conducted a systematic review of case–control and cohort studies addressing the risk of developing dementia in people with affective disorders. To the best of our knowledge, this is the first systematic review that has included studies evaluating this risk specifically in people with bipolar disorder.

Results
Fifty-one studies were included. Most of the studies found an increased risk for developing dementia in individuals with depression. Greater frequency and severity of depressive episodes seem to increase this risk. The evidence is contradictory regarding whether there is a difference in risk in people with early- or late-onset depression. The few available risk estimates for dementia in people with bipolar disorder suggest an even higher risk than for those with depression.

Conclusions
Affective disorders appear to be associated with an increased risk of developing dementia, and one that is dependent on clinical and demographic variables. Depression may be both a prodrome and a risk factor for dementia. Future research should aim to elucidate the mechanisms that mediate these links.

Declaration of interest
None.

Dementia is a disabling clinical syndrome characterised by a progressive deterioration of cognition associated with impairment in activities of daily living.[1] It is on the increase in high-income countries and even more so in low- and middle-income countries.[2] At present, about 36 million people in the world live with dementia and this number will almost double in the next 20 years, thus imposing a great burden on patients, their families and society as a whole.[3] Because the current dementia treatments are still limited, a broad understanding of risk factors is essential for the prevention of these diseases.

Affective disorders are associated with cognitive disturbances that are not just limited to acute mood episodes. Even after major depression has remitted, patients show impairment in executive function and attention.[4] Similarly, euthymic individuals with bipolar disorder have deficits in verbal declarative memory and executive function.[5] Furthermore, structural brain abnormalities are found in people with affective disorders, including hippocampal atrophy in those with a history of depression[6,7] and white matter changes in individuals with bipolar or major depressive disorder, especially those with late-onset depression.[8] Regarding the autopsy of a patient with bipolar disorder, Kraepelin[9] wrote: 'The post-mortem showed widespread arterio-sclerosis of the blood vessels of the brain. This termination appears to be not altogether unusual in maniacal depressive insanity'. A wide gap prevailed between this observation made at the start of the twentieth century and the recent interest in affective disorders as risk factors for late-life dementia. A growing number of epidemiological studies have addressed this link, most of them focused on depression as a risk factor for Alzheimer's disease. In fact, two meta-analyses found that having a history of depression approximately doubled the probability of developing Alzheimer's disease[10] or dementia in general.[11] However, in the more recent meta-analysis[10] the results were calculated by pooling crude odds ratios from different studies. This may have led to some bias because important confounding factors such as age, gender and education were not generally accounted for. Furthermore, in order to calculate a pooled odds ratio from a group of homogeneous studies, strict selection criteria were used in these meta-analyses. This strategy may have excluded studies with relevant contributions to our understanding of the association between depression and dementia. Despite the aforementioned meta-analyses, this putative link is still the target of much controversy with the dispute over prodrome *v.* risk factor at the core. Byers & Yaffe[12] have recently revisited this subject. However, two issues may have limited their conclusions. They reviewed only studies published in 2000 or later, and the determinant criteria for including a study was relevance as judged by the authors.

In contrast to depression, and to the best of our knowledge, there are no published systematic reviews looking at bipolar disorder as a risk factor for dementia. We therefore conducted a thorough systematic review of longitudinal observational studies that evaluated affective disorders as potential risk factors for dementia. For this review we considered studies evaluating depression (major depression, minor depression or an increased level of depressive symptoms) and bipolar disorder (mania or hypomania). We considered dementia in general or specific subtypes of dementia (Alzheimer's disease, vascular dementia, frontotemporal dementias and dementia with Lewy bodies) as outcomes. By using appropriate search expressions and broadly defined criteria, we intended to consider a wide range of relevant studies. By doing so, we aimed to provide a more comprehensive perspective than the ones provided by previous reviews and meta-analyses.

Method

Data sources

We performed a systematic review using strategies recommended to retrieve aetiological studies (cohort and case–control studies).[13]

A first search block was constructed by using cohort studies OR risk OR [odds AND ratio*] OR [relative AND risk] OR case-control* OR [case-control studies] as search terms. This first block was intersected with a second block created using the following keywords: [dementia OR Alzheimer disease OR vascular dementia OR Frontotemporal dementia OR Frontotemporal lobar degeneration OR Lewy body disease OR Lewy body dementia] AND [depression OR depressive OR unipolar disorder OR mania OR bipolar disorder OR manic-depress*]. The correspondent Medical Subject Heading (MeSH) terms were used where available.

We used this strategy to undertake an electronic search of PubMed, PsycINFO and LILACS for references available up to June 2011. The publications found were reviewed by one of the authors (J.d.S.). The titles of identified references were reviewed and the ones highly unlikely to be relevant were disregarded. Next, the abstracts of the remaining articles were appraised. Relevant studies were read in full and their references were searched for suitable articles. Only peer-reviewed articles were considered and no language restrictions were applied. Authors were contacted by email when doubts regarding study design or presented data were hindering the decision whether to include them in the analysis.

Inclusion and exclusion criteria

Inclusion criteria were:

(a) study type: longitudinal studies either retrospective or prospective that evaluated the risk of developing dementia in people with affective disorders. Studies that compared the risk of developing dementia between different affective disorders (e.g. unipolar depression *v.* bipolar depression) were also included;

(b) participants: adults older than 18 years of age;

(c) outcome: any measure of risk (for example odds ratio, relative risk, hazard ratio) or results presented in a way that a crude odds ratio or relative risk could be calculated.

Exclusion criteria were:

(a) studies that did not describe the method for diagnosing dementia or depression;

(b) studies that did not specify the method of quantifying depressive symptoms in the cases where a continuous measure was used;

(c) longitudinal studies specifically addressing samples of people with cognitive impairment or subjective memory impairment at baseline.

Study quality and data extraction

The quality of studies was assessed using the Newcastle–Ottawa quality assessment scale.[14] This instrument was developed to assess the quality of both cohort and case–control studies and it is centred on three main categories: (a) selection of groups; (b) comparability of the groups; and (c) assessment of exposure in case–control studies or outcome of interest in cohort studies (online Tables DS1 and DS2). The studies were scored by one of the authors (J.d.S.) and a sample of these was cross-rated by another author (M.G.-P.) to improve reliability.

Study details, including country where it was conducted, type of study (case–control or cohort study), dementia and depression diagnostic criteria, sample size and study outcomes, were extracted using a standardised form. If available, adjusted measures of risk were collected, together with an indication of the variables that were controlled for. Otherwise, crude measures of risk were retrieved or calculated from the results. Information regarding clinical and demographic characteristics that influenced the risk of developing dementia was also collected.

Reporting study results

Starting with the studies that focused on depression, we report the risk estimates of developing dementia with a 95% confidence interval and address clinical and demographic characteristics that seem to modulate the magnitude of this risk (gender, number of depressive episodes, severity of depression, age at depression onset and apolipoprotein E (APOE) status). Finally, we describe the few studies evaluating the risk of developing dementia in people with bipolar disorder and report their outcome risk measure with a 95% confidence interval. Forest plots were rendered using MatLa R2010a (The MathWorks, Natick, USA, www.mathworks.com; Mac version). A custom code was used and it is available on request from the authors.

Results

The electronic search provided 4109 publications for analysis, of which a total of 51 publications met the inclusion criteria.[15–65] Of these, all had information regarding depression and the risk of developing dementia, but only five studies presented data in relation to this risk in bipolar disorder[19,26,27,38,41] (Fig. 1). The quality assessment of the publications included is summarised in Tables DS1 and DS2.

Depression as a risk factor for late-life dementia

Although the majority of published studies to date highlight an increased risk of late-life dementia in people with a previous diagnosis of depression,[15,17–26,33,35,37,38,40,42,44,45,47-54,57–60,62–65] approximately a quarter of the studies did not show a statistical significant increase in this risk (online Tables DS3 and DS4, Figs 2–4).[16,28,30–32,34,39,43,46,55,56,61] A protective effect of depression was only described in one study.[36] This isolated finding might

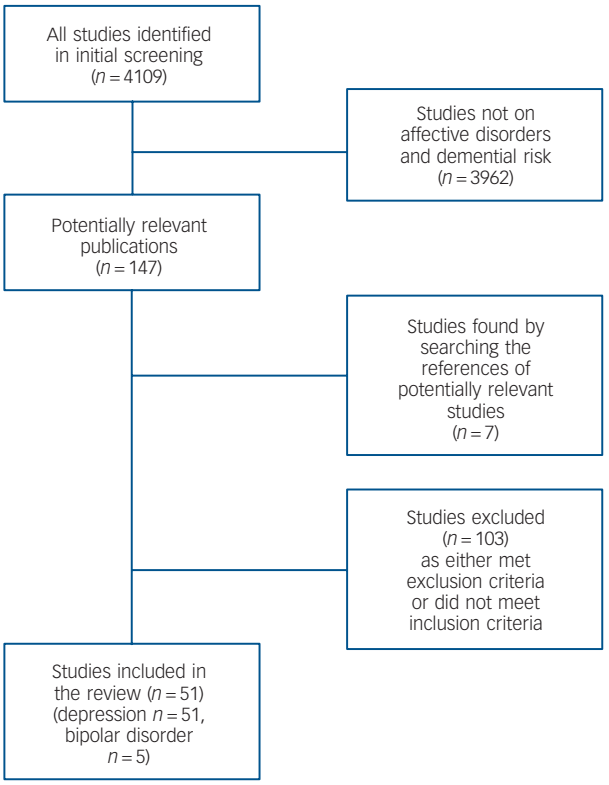

Fig. 1 Flow chart of literature search and study selection.

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be explained by the use of controls from populations with a high prevalence of depression (caregivers and elderly people living in nursing homes).[36]

There were only four studies providing results specifically with vascular dementia as an outcome.[33,50,62,64] Two of these studies reported a statistically significant risk of developing this type of dementia in patients with depression.[33,64] Lenoir *et al*[64] found a significant risk for vascular dementia but not for Alzheimer's disease, while Irie *et al*[50] found exactly the opposite using the same method to define depression.[66] In this last study the sample was exclusively composed of men, which may have contributed to these contradictory results. Only one study reported the effect of depression on the risk of developing mixed dementia, showing an increased risk for this subtype of dementia (hazard ratio (HR) = 2.8, 95% CI 1.5–5.1).[50] No study reported depression as a risk for developing dementia with Lewy bodies or frontotemporal dementia.

Risk of dementia according to the characteristics of depression: frequency, duration, severity and onset

Greater severity of depressive symptoms at baseline was associated with a higher risk of developing dementia[60] and Alzheimer's disease.[35,44,50,51,60] Moreover, a large case register-based cohort study in Denmark showed that the number of depressive episodes leading to admission increased the risk of being readmitted with a diagnosis of dementia. However, the difference was only significant when individuals with one depressive episode were compared with people who had more than four episodes (HR = 6.16, CI 95% 1.39–27.22).[41] Similarly, in a community cohort with a long follow-up period (median 23.6 years), Dotson *et al*[59] reported a dose–response relationship between the number of what they called 'episodes of elevated depressive symptoms' and the risk of developing dementia. Nonetheless, one study[44] found that participant-reported duration of depression was not predictive of Alzheimer's disease (OR = 1.01, 95% CI 0.88–1.15) or dementia (OR = 1.04, 95% CI 0.97–1.11). In this study, however, it was not clear what was measured with this self-report (for example either total duration of depressive episodes, or duration of present or last episode).

Age at onset of depression (early- and late-onset depression specifiers) has also been used to explore whether depressive illness is a real aetiological risk factor for dementia, an early clinical manifestation (prodrome) or a psychological reaction to the disease process.[20,22,24,26,29,31,37,44,50,53,54] Most of the studies evaluated only late-onset depression or late-life depression. Some also looked at early- and late-onset depression or late-life depression at the same time.[20,24,27,43,54,58] However, contradictory findings undermine a straightforward conclusion, with data supporting an increased risk only for late-onset depression,[24,58] early-onset depression alone[20,30,54] or both[37] (Fig. 5). In the latter study,[37] the authors went further and presented risk estimates depending on the interval (in years) between onset of depression and Alzheimer's disease onset. Although the risk of developing dementia was greater for people who had a first episode of depression a few years before the onset of cognitive impairment, the risk was also significantly increased for individuals with much earlier onset of depression (25 years before the onset of dementia).[37] However, the study had some limitations, the most obvious being the method for diagnosing depression (Table DS3).

Gender differences and risk of dementia in patients with late-life depression

Although gender differences were generally controlled for in most of the analysed studies, few publications evaluated separately the risk for women and men. In the PAQUID study, depressive symptoms at baseline increased the risk for developing Alzheimer's disease only in men (odds ratio (OR) = 3.7, 95% CI 1.7–7.9 for men and OR = 0.6, 95% CI 0.3–1.3 for women).[39] Likewise, Dal Forno *et al*[42] reported an increased risk of Alzheimer's disease only in males with increased depressive symptoms (OR = 1.06, 95% CI 1.04–1.09 for men, and OR = 0.99, 95% CI 0.95–1.02 for women). The results were similar

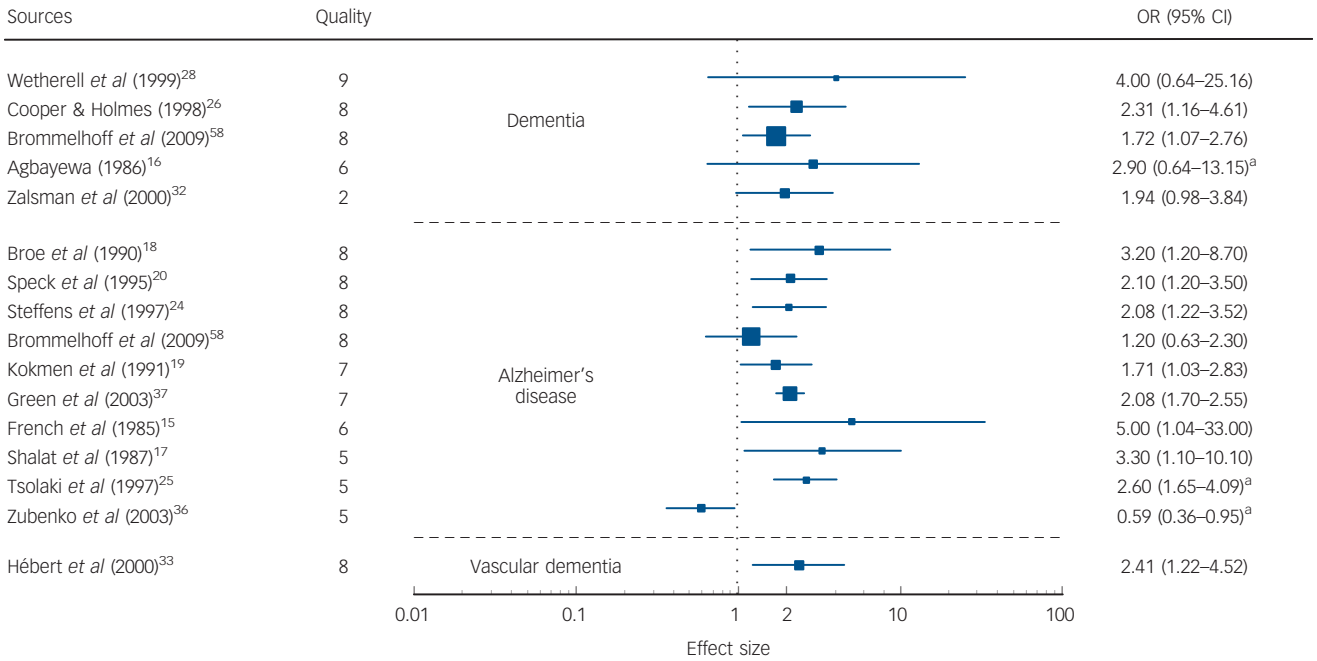

Fig. 2 Forest plot of case–control studies that evaluated depression as a risk factor for dementia, Alzheimer's disease or vascular dementia.

Studies are organised from high quality (top) to lower quality (bottom). OR, odds ratio. a. Crude odds ratio.

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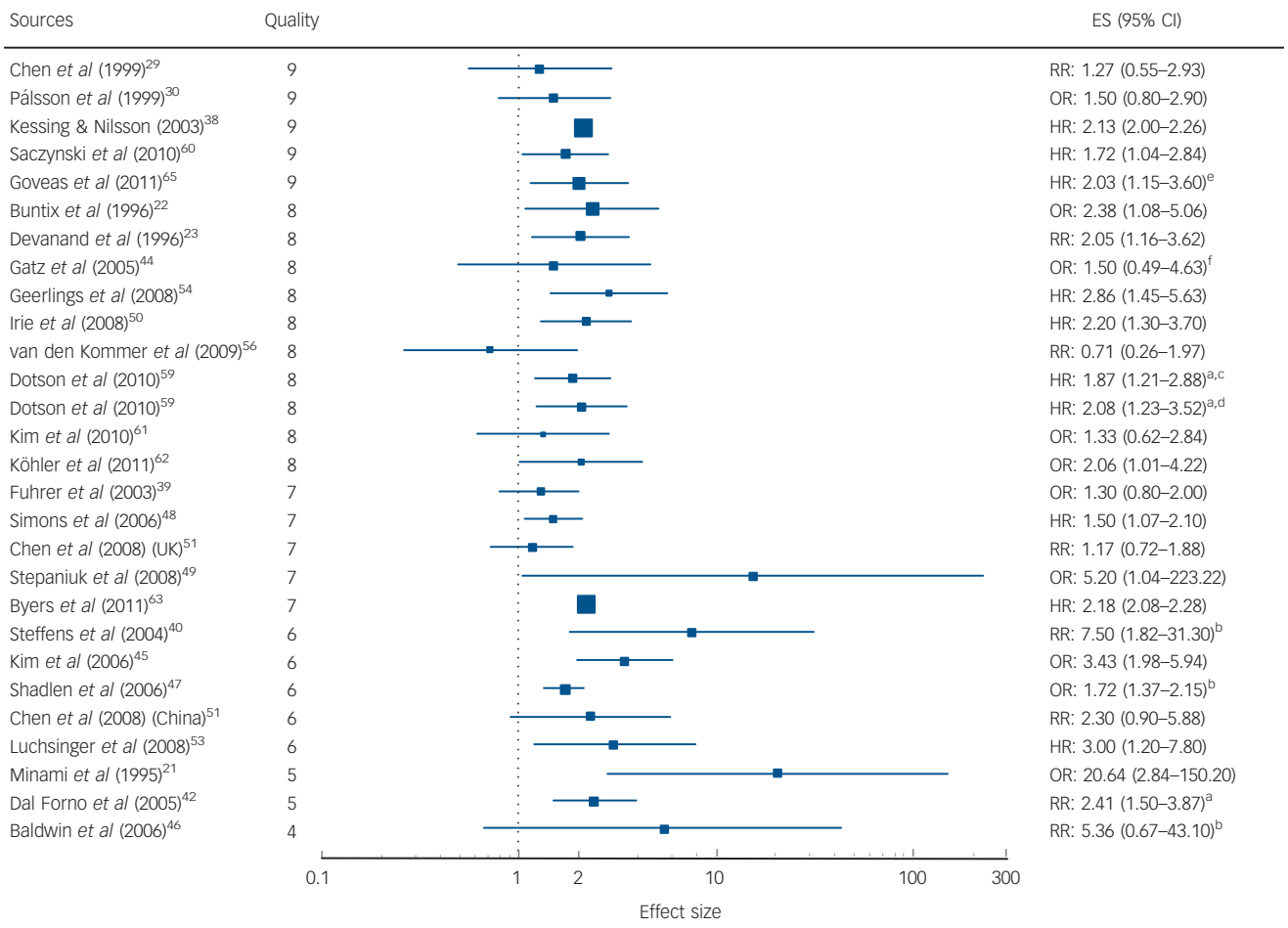

Fig. 3 Forest plot of cohort studies that evaluated depression as a risk factor for dementia.

Studies are organised from high quality (top) to lower quality (bottom). ES, effect size; RR, relative risk; OR, odds ratio. a. Samples may overlap. b. Crude odds ratio calculated from the results. c. Risk estimate for one depressive episode. d. Risk estimate for ⩾2 depressive episodes. e. Risk estimate for history of depression and depression at baseline. f. Risk estimate for late-life depression was also provided: OR 2.75 (1.04–7.24).

irrespective of whether dementia in general was considered or depression onset was limited to 4 or more years before Alzheimer's disease was diagnosed. Both these studies had a prospective design with a long follow-up period and both evaluated depression using the Center for Epidemiologic Studies Depression Scale (CES-D).[66]

However, in another cohort study,[48] only women with depression had a significantly higher risk for developing dementia (OR = 1.69, 95% CI 1.06–2.69 *v.* OR = 1.26, 95% CI 0.70–2.08) when more depressed participants (higher tertile) were compared with less depressed participants (lower tertile). Furthermore, in the Women's Health Initiative Memory study,[65] although depression at baseline was not associated with a higher risk of developing dementia, women with a history of depressive disorder had a higher risk of being diagnosed with probable dementia during the follow-up. In another study, depression and the *APOE* ε4 allele were shown to interact and increase the risk for developing dementia (OR = 5.85, 95% CI 1.77–19.38).[61] Again, this was statistically significant in men but not in women.

Risk of dementia and interaction between depression and APOE ε4

Some studies evaluated the interaction between depression and APOE status. They found that, irrespective of APOE status, the risk of developing dementia is increased in patients with a history of depression.[24,50,52,53,60] When present together, depression and the *APOE* ε4 allele interacted to greatly increase the risk of developing dementia.[24,50,57,60] Interestingly, this was shown even when depression was not an independent risk factor for dementia.[61] Other studies seem to contradict these results. Devanand *et al*[23] found that when controlling for *APOE* ε4 status, depression was still associated with higher risk of dementia, but this association was no longer statistically significant (relative risk (RR) = 2.82, 95% CI, 0.93–8.6, $P = 0.07$). The data on *APOE* ε4 status was only available for less than a third of the sample. Also in disagreement with the previously cited studies, Lenoir *et al*[64] did not find an increased risk in *APOE* ε4 carriers with depression at baseline.

Bipolar disorder as a risk factor for dementia

Bipolar disorder has also been evaluated as a putative risk for dementia,[19,26,27,38,41] albeit much less so than depression (online Table DS5). Risk estimates are higher here than in most studies evaluating depression. Three of these studies[27,38,41] reported results that achieved statistical significance. In one of these studies, people with one episode of bipolar disorder had a higher risk of developing dementia than individuals with one episode of unipolar depressive disorder (Fig. 6).[41] In this same study, using as a reference patients with only one episode of bipolar disorder, the risk was higher only for those with four episodes or more. However, this result did not achieve statistical significance.

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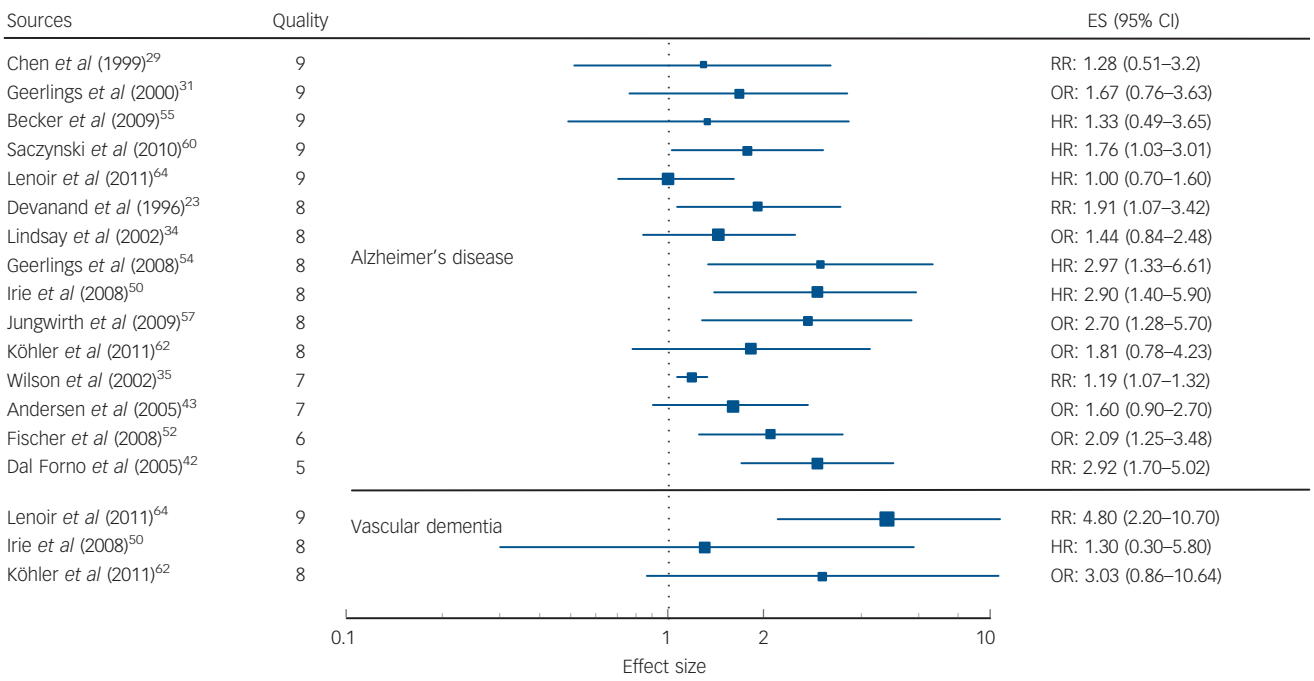

Fig. 4 Forest plot of cohort studies that evaluated depression as a risk factor for Alzheimer's disease or vascular dementia.

Studies are organised from high quality (top) to lower quality (bottom). ES, effect size; RR, relative risk; OR, odds ratio; HR, hazard ratio.

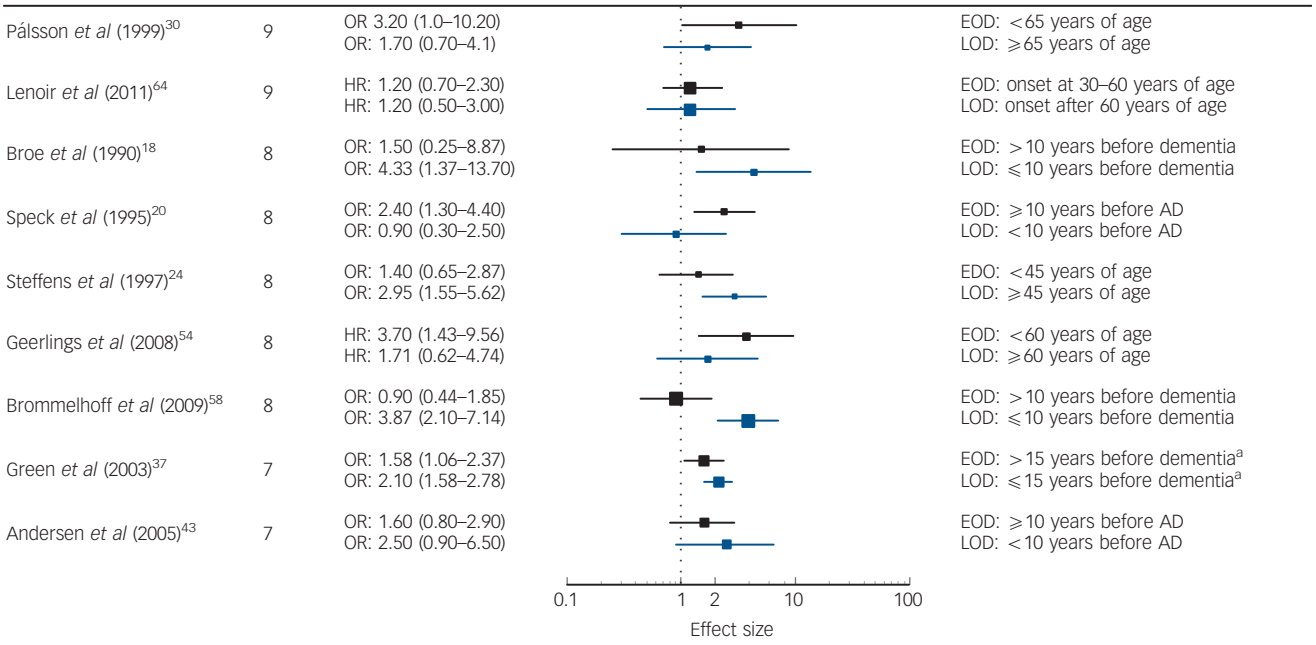

Fig. 5 Forest plot of studies that evaluated risk of dementia associated with both early- and late-onset depression.

Studies are organised from high quality (top) to lower quality (bottom). ES, effect size; OR, odds ratio; HR, hazard ratio; EOD, early-onset depression; LOD, late-onset depression; AD, Alzheimer's disease.
a. This study evaluated the risk associated with LOD and EOD using different cut-offs for the interval in years between depression onset and Alzheimer's disease onset (1 to 25 years). The ORs for the 15 year cut-off is shown here.

Discussion

In the present review we address the evidence for affective disorders as risk factors for dementia. Current research has been insufficient to fully clarify the links between depression or bipolar disorder and the later development of dementia. However, the data reviewed here may add to our understanding of some issues that have been raised.

Is depression a prodrome or a risk factor for dementia?

The notion that depression may be a prodrome for dementia has been put forward in a number of publications.[29,67,68] For example, depression increases the probability of conversion from mild cognitive impairment to dementia.[69] This has been recently supported by research with peripheral biomarkers. Elderly patients with depression but without cardiovascular disorders exhibit a similar profile to that reported in patients with Alzheimer's

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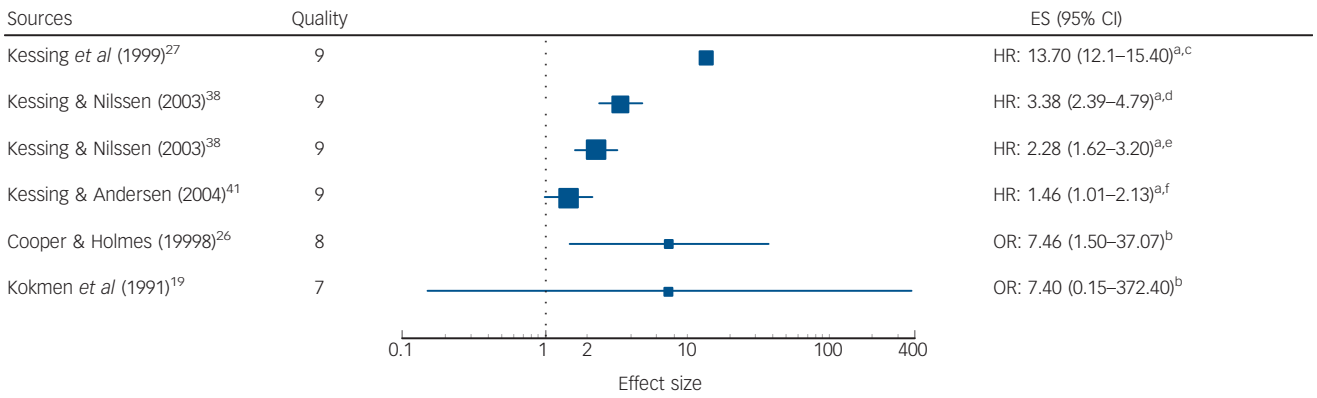

Fig. 6 Forest plot of studies that evaluated bipolar disorder as a risk factor for dementia or Alzheimer's disease.

Studies are organised from high quality (top) to lower quality (bottom). ES, effect size; HR, hazard ratio; OR, odds ratio. a. Samples may overlap. b. Peto odds ratio was calculated because none of the controls presented with the outcome. c. Unipolar disorder and bipolar disorder *v.* general population. d. Bipolar disorder *v.* osteoarthritis. e. Bipolar disorder *v.* diabetes. f. Bipolar disorder *v.* unipolar disorder.

disease:[70] a decreased plasma concentration of amyloid (Aβ) peptide Aβ42 with a corresponding increase in the Aβ40/Aβ42 ratio.[71]

However, several of the studies included in our review show that the risk of developing dementia is not limited to late-life depression.[20,30,37,54] In fact, a previous meta-analysis[10] found that the interval between diagnosis of depression and Alzheimer's disease was positively correlated with an increased risk of developing Alzheimer's disease. Furthermore, many of the prospective studies presented in our review controlled for cognitive scores at baseline and in several of them depression was still found to be significantly associated with a higher risk of developing dementia.[23,31,39,54]

It has also been argued that depression is linked with a higher risk of developing dementia because it is a frequent reaction to the emotional losses associated with cognitive decline. In this regard, Wilson *et al*[72] re-analysed the data of a cohort used to study depressive symptoms and the risk of developing mild cognitive impairment or Alzheimer's disease and could not find an increase in depressive symptoms during the preclinical phase of Alzheimer's disease. This suggests that the association between depressive symptoms and the latter development of Alzheimer's disease is not due to reactive issues.

No unequivocal evidence connects late-onset depression with Alzheimer's disease-like pathology. Therefore, although Alzheimer's disease pathology can start to build up very early in life,[73] it seems far-fetched to claim that early-life depression is already a manifestation of these neuropathological changes. Furthermore, even in the presence of increased Alzheimer's disease pathological changes in elderly patients with depression, other explanations besides the prodrome theory are valid. For example Rapp *et al*[74] found that people with Alzheimer's disease and a history of depression showed higher plaque and tangle formation within the hippocampus, as compared with those with Alzheimer's disease without a lifetime history of depression. Thus, it can be argued that depression may build on Alzheimer's disease pathology, inducing higher lesion burden. Given these contradictory results, it seems that the risk of developing dementia associated with depressive disorders is not exclusively explained by the prodrome hypothesis.

Contrary to late-life depression, the association between early-life depression and dementia risk is more difficult to study. It poses greater methodological challenges such as recall bias, retrospective definition of cases or the necessity for a longer follow-up period. In a recent review, Byers & Yaffe[12] concluded that early-life depression is a consistent risk factor for dementia but that the results regarding late-life depression were conflicting. Our review does not completely support this perspective. For instance, the results from studies that evaluated both early- and late-life depression as risk factors for dementia are not consistent (Fig. 5). This may be explained by methodological differences, especially divergences with regard to the definition of age at onset of late-onset depression. We cannot exclude the possibility that both early- and late-onset depression are related to an increased risk of developing dementia.

Is there a gender gap?

The results of studies evaluating both genders independently were surprising and raise important research questions. If depression is a risk factor for males and not females, then causal pathways that offer no logical explanation for observed gender differences should be discarded.[39] On the other hand, it is known that women tend to recognise non-specific feelings of distress as an emotional problem more promptly than men. Thus, males in these studies may in fact be a group of men with depressive symptoms severe enough to be self-reported.[42] This may lead to a dilution of the risk in women and an overestimation in men, since, as previously discussed, the risk increases with increased severity of depression at baseline.[35,44,50] Nonetheless, results supporting a gender gap were not consistent. Furthermore, most studies reported that depression was an independent risk factor for dementia while adjusting for gender.[21,23,44,48,53,54,60,62,64] It may be that studies that found differences between men and women were the only ones to report the results separately for both genders. In fact, the authors of a previous systematic review on depression and risk of Alzheimer's disease reported that the risk for each gender was only shown separately in those studies that found differences in risk between men and women.[10]

Is bipolar disorder a risk factor for dementia?

Most of the studies included in this review did not address bipolar disorder as a potential risk factor for dementia. On the other hand, the large majority of studies that considered depression were poorly controlled for bipolar disorder. Thus, some individuals with bipolar depression might have been included in the analyses, probably more so in studies considering early-onset depression. Although the depressive episodes are generally predominant in relation to the mania/hypomania episodes in bipolar disorder,[75]

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the disorder itself is substantially different from unipolar disorder and bipolar depression has different characteristics when compared with unipolar depression.[76] Thus, one cannot extrapolate from the data regarding depression to encompass bipolar disorder.

Nevertheless, almost all studies that analysed bipolar disorder as a risk factor for dementia consistently found a higher risk in these patients.[19,26,27,38,41] Most of these studies used a methodology based on case registers[19,26,27,38,41] and 2 studies compared individuals with bipolar depression either to people with somatic disorders or to those with other psychiatric disorders.[38,41] This may occasionally lead to bias. For example, people with osteoarthritis are usually medicated with anti-inflammatory drugs, found to be a protective factor for dementia in several studies.[77] Therefore, this may result in an over-estimation of the risk associated with bipolar disorder. However, an increased hazard ratio when comparing individuals with bipolar disorder to people with diabetes is a robust finding, since diabetes is a well-documented risk factor for Alzheimer's disease and vascular dementia.[78]

Another source of bias is the fact that people with bipolar disorder are known to the psychiatric services and this may lead to an increased probability of being admitted throughout one's lifespan, and eventually being diagnosed with dementia in advancing years. However, the opposite could also be argued. It is common in clinical practice to delay a diagnosis of dementia in people with a psychiatric history because behavioural changes and cognitive impairments are wrongly attributed to the psychiatric disorder or to psychopharmacological treatments.

Pathophysiological mechanisms linking depression to the development of dementia

Two major hypotheses have been put forward to explain the association of late-onset depression with a greater risk of developing dementia: (a) depression is associated with the development of dementia because it is a reaction to an early stage of the cognitive decline; and (b) depression is a prodrome of dementia. Both hypotheses do not concern depression as a causal determinant for dementia. However, these two hypotheses do not fully explain the data presented above, because a higher risk has been described even for patients who had depression several years before dementia's onset.[20,30,37,54] Thus, a complex interaction of determinants seems more probable than a single and simple aetiological mechanism.

It may be that depression and dementia share common aetiological factors.[11] For example, inflammation, vascular changes and vascular risk factors have been implicated in both disorders. In this regard, recent studies have controlled for vascular risk factors and vascular disease when evaluating the risk of developing Alzheimer's disease in patients with depression[53,60,62–65] (Table DS4). Nevertheless, in all of these studies, depression still remained an independent risk factor for Alzheimer's disease. The results of some of the studies reviewed suggest yet another mechanism by reporting a synergistic effect between depression and the *APOE* ε4 allele.[24,50,57,60]

An additional hypothesis is that affective disorders lower the threshold for the clinical manifestation of dementia. The results of this review tend to support this, demonstrating a non-specific increase in the risk of developing dementia (Alzheimer's disease, vascular dementia and dementia in general). Glucocorticoid neurotoxicity may be a plausible underlying mechanism,[79–81] although longitudinal data derived from human studies is still scarce.[54,82] Psychosocial factors such as disrupted social interactions and lower lifetime achievements of people with affective disorders, by leading to a lower cognitive reserve, may also decrease the threshold for dementia. However, these remain to be explored. Other mechanisms have been proposed to explain this link but an extensive discussion of pathophysiological mechanisms is outside the scope of this paper (for a comprehensive review see Duman[83]).

Methodological issues and limitations

We used a wide range of search terms together with broadly defined criteria in order to avoid missing important evidence. This strategy enabled us to include a large number of studies. However, these studies were very heterogenous (for example different diagnosis criteria for dementia, different types of dementia, distinct methods for diagnosing depression and differences regarding the onset of depression). Because of this, we decided not to do a meta-analysis and, thus, we were not able to provide summary estimates of the risk of developing dementia in individuals with a history of affective disorders. Instead, we present a wider view of this topic, one that would have been lost if stricter and more homogenised criteria were applied. Nevertheless, to make the strength of the evidence easier to assess, we provided a broad assessment of the quality of each study and comprehensive extraction of data.

When analysing the list of studies retrieved, one can see that the earliest studies were mainly case–control studies in contrast to the most recent ones, which were predominantly cohort studies. The initial case–control studies struggled with recall bias and/or selection bias due to the need to establish retrospectively a diagnosis of depression.[15–20,24–26,28,32,33,36,37] Generally, the design of these studies relied on proxy informants or clinical records for depression diagnosis, since the patients had dementia. The major problem with using a proxy informant as the only source of information is that it is very difficult to have a reliable diagnosis based on current diagnostic criteria. Similarly, relying exclusively on clinical records could lead to selection bias. For example, people with a depressive illness have a greater probability of being referred to mental health services and thus an increased probability of being identified as having dementia and being included in the group of cases. In spite of this, good agreement has been found between case–control and cohort studies. Jorm[11] reported in his meta-analysis a summary risk estimate of 2.01 (95% CI 1.16–3.5) for the case–control studies and 1.87 (1.09–3.2) for cohort studies. Similar findings were also reported by Ownby *et al*[10] regarding depression and the risk of developing Alzheimer's disease, with an odds ratio of 2.03 (95% CI 1.73–2.38) for case–control studies and 1.90 (95% CI 1.55–2.33) for cohort studies with a combined result of 2.02 (95% CI 1.80–2.26).

Most epidemiological studies reviewed in this paper, as well as previous meta-analyses, showed an increased risk for dementia in individuals with affective disorders. However, publication bias has to be considered (i.e. a lower probability of negative results being published). In fact, in a previous meta-analysis[10] the funnel plot analysis did indicate that such bias existed in this type of publication. Even so, when the odds ratios were corrected for potential publication bias, there were no significant changes in the risk estimates.

Clinical implications

It was believed that in elderly people with so-called depressive pseudodementia, cognition and function could be entirely restored to normal if depression was treated. However, this concept has been progressively abandoned since cognitive dysfunction may not be totally reversed by antidepressant

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treatment and more than 40% of people with pseudodementia eventually develop dementia.[84,85] Our results support a link between affective disorders and the later development of dementia, especially in men[39,42,61] and in people with recurrent depressive disorder.[41,59] Therefore cognitive dysfunction in such patients should not be disregarded as a minor phenomenon. Clinical monitoring of cognition may be warranted, for at least a subset of patients.

Future research

Previous meta-analyses had not explored some important characteristics that may help in the understanding of the link between depression and dementia. Throughout the present review it has become apparent that the number of disease episodes, severity of depressive symptoms and patient gender are important modulators of the risk of developing dementia. This can help to guide basic research focused on understanding the mechanisms behind this link. Also, the data reviewed suggests that both hypotheses of affective disorders being a prodrome and a risk factor may be consistent. In fact, these hypotheses are not mutually exclusive and in one instance they were even supported by data from the same study.[37] This should be considered when delineating future research, because both early- and late-onset depression may increase the risk for developing dementia through different mechanisms.

Although the results regarding bipolar disorder are very interesting, the available evidence is still limited. Exploring bipolar disorder as a risk factor for dementia requires more complex methodologies than the ones used for depression. For example, given the lower prevalence of bipolar disorder, a larger sample size is needed. It is also important to control for different types of affective episodes, so that the weight of depressive and manic episodes can be properly evaluated. Similarly, care must be taken to control for treatment because mood stabilisers may be protective factors for dementia in people with bipolar disorder.[86–88] Thus, there is a need to refine methods in order to clarify this issue.

Given all the possible mechanisms that have been put forward to explain why depression leads to an increased risk of developing dementia, a multifactorial model seems almost inevitable. In fact, Butters *et al*[89] have proposed a multiple pathways model where cerebrovascular disease and glucocorticoid neurotoxicity associated with depression lower the brain reserve and interact with Alzheimer's disease neuropathology, thereby leading to the clinical manifestations of Alzheimer's disease. However, such models are still much more based on associative data then on evidence of causality. Thus, they must be seen more as a 'road map' for future epidemiological and experimental studies, and not as the actual explanation of the link between affective disorders and higher risk of developing dementia. Understanding this link could lead to a better comprehension of the pathophysiology of both depression and Alzheimer's disease, two of the most disabling diseases affecting humankind.

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EXTRA CONTENT ONLINE

100 words

Gambling

Sanju George

Long shrouded in conceptual and nosological ambiguity, gambling addiction is set to be classified under addictive disorders in DSM-5. Gambling addiction has a general population prevalence of approximately 1%. It cuts across age, gender, class and culture, and has a negative impact on the person's physical and psychological health, finances and family. Despite high comorbidity among those with psychiatric disorders, professionals' limited awareness leads to it going undetected. Simple screening tools aid early detection and brief psychological interventions are effective. Cognitive–behavioural therapies are the treatment of choice and although no drug is licensed for use, opioid antagonists show promise.

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