# History of depression as a risk factor for dementia: an updated review

Anthony F. Jorm

**Objective:** This review updates an earlier meta-analysis of the data on history of depression as a risk factor for dementia. It also considers the available evidence on the hypotheses proposed to explain the association between history of depression and dementia.
**Method:** A meta-analysis was carried out on results from seven case-control and six prospective studies. A qualitative review was carried out on the evidence related to the hypotheses to explain the association.
**Results:** The meta-analysis found evidence to support an association from both case-control studies (estimated relative risk 2.01; 95% CI 1.16–3.50) and prospective studies (estimated relative risk 1.87; 95% CI 1.09–3.20). However, the evidence did not clearly support any one hypothesis explaining the association. The most likely contenders are: (i) depression can be an early prodrome of dementia, (ii) depression brings forward the clinical manifestation of dementing diseases, and (iii) depression leads to damage to the hippocampus through a glucocorticoid cascade.
**Conclusions:** The possibility that history of depression is a risk factor for dementia needs to be taken seriously and explanations of the association need to be further researched.
**Key words:** Alzheimer's disease, dementia, depression, risk factors, vascular dementia.

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This paper updates an earlier review on history of depression as a risk factor for dementia [1]. Since the publication of this review, a number of new studies have come out. These add further evidence that history of depression is a risk factor, and have implications for the plausibility of various hypotheses to explain the association.

## An up-dated meta-analysis

A Medline search up to the end of 2000 was carried out using the same specifications as used previously [1]. This search looked for case-control studies (in which people with dementia and controls are assessed retrospectively for a history of depression) and prospective studies (in which people with or without a history of depression are followed over time to see if they develop dementia). The search produced one additional case-control study and one additional prospective study. These have been added to the studies identified earlier and summarized in Tables 1 and 2. Meta-analyses using the graphical 'odd man out' technique [16] gave the summary estimates of relative risk shown at the bottom of each table. Prospective studies are methodologically superior to case-control studies, but the results from the two sorts of studies were consistent. From these meta-analyses, we can conclude that a history of depression approximately doubles the risk of developing dementia.

These findings raise the question of whether it is the risk of Alzheimer's disease, vascular dementia, or both, that is increased. Most of the case-control studies dealt with Alzheimer's disease specifically, whereas most of the prospective studies dealt with dementia in general. However, because in Western countries most cases of dementia are due to Alzheimer's disease, it is fair to conclude that risk of Alzheimer's disease is increased by a history of depression. Only one study has looked

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*Table 1. Case-control studies examining history of depression as a risk factor for dementia*

| Study | Diagnosis of cases | Estimate of relative risk (95% CI) |
|---|---|---|
| EURODEM [2] | Alzheimer's | 1.82 (1.16–2.86) |
| Speck *et al.* [3] | Alzheimer's | 1.8 (0.9–3.5) |
| Cooper & Holmes [4] | Dementia | 2.31 (1.16–4.62) |
| Wetherell *et al.* [5] | Alzheimer's | 4.00 (0.64–25.16) |
| Agbayewa [6] | Alzheimer's | 2.77 (0.61–12.54) |
| Steffens *et al.* [7] | Alzheimer's | 2.08 (1.22–3.52) |
| Zalsman *et al.* [8] | Dementia | 1.94 (0.98–3.84) |
| Summary estimate | – | 2.01 (1.16–3.50) |

*Table 2. Prospective studies examining history of depression as a risk factor for dementia*

| Study | Diagnosis of cases | Years of follow-up | Estimate of relative risk (95% CI) |
|---|---|---|---|
| Buntinx *et al.* [9] | Dementia | 1–10 | 2.38 (1.08–5.06) |
| Devanand *et al.* [10] | Dementia (mainly Alzheimer's) | 1–5 | 2.05 (1.16–3.62) |
| Henderson *et al.* [11] | Dementia | 3.6 | 0 (0–5.5) |
| Chen *et al.* [12] | Alzheimer's | 4 | 1.28 (0.51–3.20) |
| Palsson *et al.* [13] | Dementia | 3 | 1.5 (0.8–2.9) |
| Kessing *et al.* [14]* | Dementia | 21 | 13.7 (12.1– 15.4) |
| Geerlings *et al.* [15] | Alzheimer's | 3.2 | 2.21 (1.09–4.48) |
| Summary estimate[1] | – | – | 1.87 (1.09–3.20) |

*Kessing *et al.* [14] was an outlier and excluded from the summary estimate

specifically at whether history of depression increases risk of vascular dementia [17]. In a prospective study spanning 5 years, history of depression was found to increase the risk of developing vascular dementia by 2.41 times (95% CI 1.22–4.52). However, further analysis showed that the risk was highest in people who had a previous stroke, so that depression may simply be a marker of the effects of an earlier stroke. Whether depression per se increases risk of vascular dementia needs further research.

As well as studies examining depression as a risk factor for depression, there are prospective studies looking at whether depression symptom scores predict subsequent decline on cognitive tests. The earlier review summarized four of these studies, with only one of them showing a significant association [1]. Since then, two other studies of this type have been published. One study found that depressive symptoms predicted cognitive decline in men but not in women [18], whereas the other found an effect in people with a higher level of education but not in those with a lower level [15]. Unfortunately, it is not possible to carry out a meta-analysis of these results because of the diverse ways in which they have been reported. However, it can be concluded that, while there are more significant results than expected by chance, the findings are far from consistent.

## Specific depressive symptoms predicting dementia

In addition to the above studies on history of depression as a risk factor for dementia or cognitive decline, two studies have looked at individual depressive symptoms as risk factors. One prospective study assessed depressive symptoms and then followed up participants over 3 years [19]. Those who developed Alzheimer's disease were more likely to have 'motivational symptoms' of depression at baseline, but not 'mood symptoms'. These motivational symptoms were lack of interest, loss of energy and concentration difficulties. A second prospective study following participants over an average of 3.2 years found that subjective slowing of thinking and depressed mood were the only symptoms to predict subsequent Alzheimer's disease, but these associations were only found in those with a higher level of education [20]. The results of these two studies are not entirely compatible. While subjective slowing of thinking might be a 'motivational symptom', depressed mood clearly is

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not. It is therefore uncertain from the limited evidence available whether a specific pattern of depressive symptoms is associated with subsequent dementia.

## Six hypotheses explaining the association

The meta-analysis results lead to the conclusion that depression is likely to be a risk factor. In the previous review, six hypotheses to explain the association were put forward. Since then, some additional evidence has appeared with implications for the viability of some of these hypotheses.

### Depression treatments are a risk factor for dementia

Depression could appear to be a risk factor for dementia if treatments used for depression such as antidepressants, benzodiazepines and electroconvulsive therapy (ECT) led to increased risk. However, the earlier review found little support for this hypothesis and there is no new evidence to alter this conclusion.

### Depression and dementia share common risk factors

Depression and dementia could also appear to be linked if they shared common risk factors. However, the commonly acknowledged risk factors for depression show little overlap with those for Alzheimer's disease and vascular dementia. The only exception is that preexisting vascular disease is associated with increased risk of vascular dementia and may also increase risk of depression, since depression is more common in people with disabling physical diseases of any type.

### Depression is a prodrome of dementia

There are clinical observations that people initially diagnosed with depression progress on to clear dementia. These observations suggest that depression may be a prodrome in some cases of dementia. The hypothesis of depression as a prodrome is most compatible with studies in which depression occurs close in time to the onset of dementia. However, because the pathological changes of dementing diseases can begin decades before dementia onset [21], it is also conceivable that depression could be a very early prodromal feature. Two possible mechanisms by which depression could be a prodrome have been proposed: one involving Alzheimer's disease and the other vascular dementia.

If depression was a prodrome of Alzheimer's disease, we might expect that older people who are depressed will tend to have more subclinical Alzheimer neuropathology. However, this does not appear to be the case [22]. Nevertheless, it is still possible that depression could be a prodrome in a minority of cases of Alzheimer's disease. A possible mechanism involves loss of noradrenergic neurones, which is a variable feature of Alzheimer's disease and is associated with comorbid depression [23]. However, for noradrenergic neuronal loss to account for prodromal depression, it would need to be an early neuropathological change in Alzheimer's disease, whereas it is most likely to be found in the later stages of dementia [24].

A second possibility is that depression is a prodrome of vascular dementia. It has been proposed that some cases of depression in old age are due to cerebrovascular disease and that this disease may not be clinically evident when the depression first appears [25]. Supporting evidence comes from MRI studies on depression in old age which show a higher prevalence of white matter changes thought to reflect cerebrovascular disease [26]. These lesions also tend to be associated with cognitive impairments [26] and one prospective study found that depressed patients with white matter changes were more likely to progress to vascular dementia [27]. While these findings support the possibility that depression could be a prodrome of vascular dementia, a difficulty is that the epidemiological evidence is more consistent with depression as a risk factor for Alzheimer's disease. However, there is now some evidence that vascular factors may have a role in Alzheimer's disease as well [28].

### Depression occurs as an early reaction to cognitive decline

Another hypothesis is that people with dementing diseases show early insight into their failing capacities and react to this loss with depression [29]. Most studies do in fact find that people who complain of poor memory or cognitive decline are more likely to develop dementia, although the predictive power of such complaints is weak [30–34]. There is also much evidence showing a strong relationship between cognitive complaints and depressive symptoms, although much of this association is probably due to depression leading to a negative evaluation of cognitive performance rather than to an awareness of cognitive decline leading to depression [34].

The key prediction of this hypothesis is that depression should no longer be a risk factor once the effect of cognitive complaints is statistically controlled. One prospective study did find that the association of depressive symptoms with subsequent dementia disappeared once cognitive complaints were statistically controlled, but subjects with clinical depression were unfortunately excluded from the analysis [33]. More recently, the

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hypothesis was properly tested in two prospective studies and the effect of depression as a risk factor was found to persist even when complaints were statistically controlled [25]. If confirmed by other research, these results would rule out the hypothesis that depression occurs as an early reaction to cognitive decline.

## Depression brings forward the clinical manifestations of dementing diseases

Alzheimer's disease and vascular dementia can be viewed as parts of a continuous pathological spectrum involving various degrees of neuronal loss. There may be a long preclinical phase, with clinically evident dementia occurring once some threshold of neuronal loss is reached. Thus, risk factors for dementia may affect either the rate of neuronal loss or the point where the threshold is reached [35]. It has been hypothesized that individuals who have a larger brain reserve may be better able to compensate for neuronal loss and so manifest dementia at a later stage of pathology [36]. This hypothesis explains findings that individuals who are better educated, more intelligent and with larger brains may have a lower risk of Alzheimer's disease, because all these factors are indicators of brain reserve.

The same hypothesis can be extended to account for depression as a risk factor for dementia. Depression may not affect the pathological processes involved in Alzheimer's disease or vascular dementia, but rather the threshold for manifesting dementia. Depression is well known to involve significant cognitive deficits [37]. These may cumulate with those caused by dementing diseases to bring forward the clinical manifestation of dementia. Depression also involves motivational deficits which may add to those caused by a dementing disease. Such cumulative effects might also be seen in individuals who have a history of depression, but are not currently clinically depressed, because remitted depression is associated with residual cognitive deficits [38].

The key prediction of this hypothesis is that depression will be related to earlier diagnosis and should be a stronger risk factor in studies based on clinical series. Furthermore, individuals with dementia and a history of depression should have less brain pathology when they reach the threshold of clinical recognition. These predictions remain to be tested.

## Depression leads to damage to the hippocampus through a glucocorticoid cascade

Sapolsky and colleagues [39] have put forward a 'glucocorticoid cascade' hypothesis which provides a potential link between depression and dementia. According to this hypothesis, the brain stimulates the adrenal cortex to secrete glucocorticoids in response to stressors. Glucocorticoid secretion prepares the body for coping with the stressor by increasing circulating energy substrates. There are receptors in the hippocampus which detect the increased level of glucocorticoids and inhibit their further secretion. Although secretion of glucocorticoids helps to cope with stressors, prolonged secretion has ill effects, including toxic effects on the hippocampus. With ageing, there is loss of glucocorticoid receptors in the hippocampus. This loss leads to impaired feedback inhibition of glucocorticoid secretion and further damage to the hippocampus, setting off a cascade effect.

Most of the evidence to support this hypothesis has come from animal studies. However, there has been some work on humans. Lupien *et al*. [40] measured cortisol levels in elderly people over a five-year period and related this to memory performance and hippocampal volume. They found that people with high and rising cortisol levels over the five years had poorer memory performance and greater hippocampal atrophy.

Although the participants in this study did not have either clinical depression or dementia, implications have been drawn for an association of depression with dementia [41]. Hypersecretion of cortisol and nonsuppression in the dexamethasone suppression test have been reported as more common in both depression and dementia. Furthermore, atrophy of the hippocampus is one of the early brain changes in Alzheimer's disease [42] and has also been observed in some depressed patients [43]. These observations have led to the proposal that depression and dementia represent two different time points along a continuum of disease induced by the hypothalamic-pituitary-adrenal (HPA) axis [41]. Depression is hypothesized to lead to increased cortisol levels and prolonged exposure to cortisol leads to hippocampal atrophy and cognitive deficits. When the hippocampal atrophy is severe enough, the person will qualify for a diagnosis of dementia. Unfortunately, there is little evidence directly testing this hypothesis and what evidence does exist is not entirely supportive. No association has been reported between HPA axis disregulation and hippocampal atrophy in depressed patients [44,45]. Only one small study has followed up depressed patients with and without hippocampal atrophy over time. This study found that atrophy did not predict either dementia or cognitive decline over a two-year period [46].

In summary, there are correlational data linking depression, cortisol hypersecretion, hippocampal atrophy and dementia, although the predicted correlations are not always found. However, a direct causal pathway from depression and cortisol hypersecretion to hippocampal atrophy and dementia has not been demonstrated and requires further research.

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## Conclusion

The accumulated evidence reinforces the earlier conclusion [1] that depression is a likely risk factor for dementia in general and for Alzheimer's disease specifically. The association with vascular dementia requires more investigation before a conclusion can be reached. Of the six hypotheses to explain the association, three appear to be the most plausible: (i) depression can be an early prodrome of dementia, (ii) depression brings forward the clinical manifestation of dementing diseases, and (iii) depression leads to damage to the hippocampus through a glucocorticoid cascade. These hypotheses are not mutually exclusive and more than one could be correct.

If depression is a risk factor for dementia, this raises the issue of whether preventive action can be taken. However, treating depression is unlikely to be preventive under most of the hypotheses considered. Only the hypothesis of hippocampal damage through a glucocorticoid cascade predicts a preventive effect of depression treatment.

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