

Depression and dementia: Preventable and overlooked.

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The Lancet meta-analyses

- ☀ This commission chose the seven studies included by Stafford and colleagues with a 10–14-year follow-up compared with people without depression.
- ☀ Stafford analysis: Used three databases and 33 studies that dealt with depression alone with sample sizes from 212 to 3,341,010 (Swedish cohort study from 1964 to 2016).
- ☀ Commission also included a Swedish nationwide study of 41727 twins, with an 18-year follow-up.

The research itself and problems

- ☀ The Lancet report acknowledges many methodological difficulties across the studies examined
- ☀ Study designs
- ☀ Large sample sizes and longitudinal data
- ☀ Still great confidence with findings of the Commission

Lancet

☀ But the trend is becoming clear(er):
there is an undeniable bi-directional
relationship between depression and
dementia.



Lancet

☀ Mechanisms linking depression to dementia are unknown

☀ Suggest:

- Reduced self-care and social contact
- Oversecretion of cortisol leading to hippocampal atrophy or inflammatory response

How was depression measured?

- ☀ Not clearly explained in some studies
- ☀ Researchers generally tried to satisfy DSM/ICD diagnostic criteria but not always
- ☀ A variety of instruments used (GMS, AGE-CAT, GDS, CES-D, self-report, Europe Depression scale, Anxiety and Depression Index, Hospital Anxiety and Depression Scale, SCL-90)

DSM-V criteria

- ☼ DSM: Five or more of the following for a two week period and a change from previous functioning:
 - ☼ Depressed mood most of the day, nearly every day
 - ☼ Loss of interest/pleasure
 - ☼ Weight gain or loss
 - ☼ Insomnia or hypersomnia
 - ☼ Psychomotor agitation/retardation
 - ☼ Fatigue or loss of energy nearly every day
 - ☼ Feelings of worthlessness or excessive or inappropriate guilt
 - ☼ Diminished ability to think or concentrate (may be observed by others)
 - ☼ Recurrent thoughts of death (not fear of dying), suicidal ideation without a plan, or an attempt
- ☼ Symptoms must cause clinically significant distress or impairment in social, occupational or other areas of functioning.
- ☼ Episode is not attributable to a substance or other medical condition
- ☼ Not better explained by schizoaffective disorder, schizophrenia and others
- ☼ No manic or hypomanic episodes

ICD -10 criteria

- ▶ **Involves 10 symptoms.**
- ▶ **Three of these for at least two weeks:**
 - ☼ persistent sadness or low mood; and/or
 - ☼ loss of interests or pleasure
 - ☼ fatigue or low energy

These seven symptoms determine severity:

- ☼ disturbed sleep
- ☼ poor concentration or indecisiveness
- ☼ low self-confidence
- ☼ poor or increased appetite
- ☼ suicidal thoughts or acts
- ☼ agitation or slowing of movements
- ☼ guilt or self-blame

The 10 symptoms then define the degree of depression:

- **Not depressed** (fewer than four symptoms)
- **Mild depression** (four symptoms)
- **Moderate depression** (five to six symptoms)
- **Severe depression** (seven or more symptoms, with/without psychotic symptoms)
- Symptoms should be present for a month or more and every symptom should be present for most of every day

Lancet quick summary

☀ *In the 2020 Lancet Commission, we concluded based on published studies that the link between depression and dementia was probably bidirectional and that, in the years before dementia presentation, depression can be:*

- *a symptom of evolving dementia*
- *a reaction to cognitive impairment*
- *or a cause of cognitive impairment.*

☀ *We also noted that few studies had considered whether risk of dementia was affected by treatment for depression (p. 581).*

The (long) prodrome before dementia

- ☀ Neuropathological changes (amyloid β , tau accumulation)
- ☀ May initially have only few cognitive changes
- ☀ Changes in behaviour and health can occur long before dementia onset so potential risks identified in the few years before dementia onset could be true causal effect or reverse causation, or the link could be bidirectional

In the context of depression:

- ☀ Overall the studies suggest *that depression increases the risk of dementia at all adult ages.*
- ☀ In late life this association is caused by pre-clinical dementia
- ☀ The Lancet Commission classify depression *as a mid-life risk factor.*
- ☀ Genetics? Twin studies suggest no significant genetic risk or early life environment although more than 8 years education appears to be protective.

UK biobank study (not perfect)

- ☀ 354,313 participants
- ☀ 50 – 70 years old
- ☀ Median 11.9 year follow up
- ☀ Dx of depression (n=46280) significantly higher risk of developing dementia
- ☀ Significantly less likely if treated by either pharmacotherapy, psychotherapy or combination
- ☀ Those who remitted did not have a higher risk of dementia than those without depression.

Stafford et al., 2022

- ☀ Meta analysis 33 studies on depression
- ☀ Depression associated with increased risk of all-cause dementia
- ☀ Did not find significant differences between VaD and AD
- ☀ The association with dementia was strongest in the first 6 months after depression diagnosis then decreased rapidly but persisted for over 20 years
- ☀ The association was strongest in the 10 years before dementia diagnosis compared with >10 years prior
- ☀ Dose response data (severity of depression) was mixed
- ☀ One study found strongest association with people who had failed at least two ADT trials

Mirza et al. 2013

- ☀ Followed 4393 people for 13.7 years
- ☀ Depression as risk factor or prodrome
- ☀ Associations strongest for short follow up time and attenuated with longer times
- ☀ Late onset depressive symptoms preceding dementia could be a reactive phenomenon to cognitive decline, or,
- ☀ Late onset symptoms may represent a prodrome of dementia where prodrome is defined
- ☀ More pronounced in men

Edo et al. 2013 - Mild cognitive impairment (MCI)

- ☀ n = 2160
- ☀ Study makes the point that MCI and depressive symptoms have long noted to have an association with dementia
- ☀ Vascular factors have been linked to late-life depression, and cerebrovascular disease might be an important contributor to MCI, dementia, and depression in late life.
- ☀ Participants with dementia were depressed twice as often as were those without dementia and this association was stronger for VaD compared with AD.

Mild cognitive impairment (MCI)

- ☀ Found that progression from MCI to dementia was stronger for VaD compared with AD.
- ☀ Study suggests that depression develops with the transition from normal cognition to dementia.
- ☀ Suggests that the importance of cerebrovascular risk factor and depression (hence VaD connection)
- ☀ Did not find any association between apathy and increased risk of MCI to dementia.

Takeaway points

- ☀ The presence of mood disturbance is a significant risk factor with regard to development of dementia
- ☀ Treatment of depression appears to be preferable rather than ignored
- ☀ Overlap of MCI and depression symptoms should be considered
- ☀ The subtlety of the prodromal phase of dementia remains a clinical challenge

Main references

- ▶ 1. Livingston, G. Huntley, J. Liu, K. et al. (2024). Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *The Lancet*, Vol. 404, 572-628. Published Online July 31, 2024. [https://doi.org/10.1016/S0140-6736\(24\)01296-0](https://doi.org/10.1016/S0140-6736(24)01296-0)
- ▶ 2. Stafford J, Chung WT, Sommerlad A, Kirkbride JB, Howard R. Psychiatric disorders and risk of subsequent dementia: systematic review and meta-analysis of longitudinal studies. *Int J Geriatr Psychiatry* 2022; **37**: 375.