

**Citation:** Sun J et al. Association of Major Depressive Episodes With Stroke Risk in a Prospective Study of 0.5 Million Chinese Adults. *Stroke*. 2016;**47**:2203-8

**Author's declarative title:** Uncertain association between depression and stroke risk in Chinese mega-study

### **What is already known on this topic**

Depression may be a direct cause of stroke. Alternatively, an observed association between depression and stroke may be generated by indirect processes when depression is not the immediate cause. Depression, particularly if chronic or recurrent, could act as an upstream influence leading to increased stroke risk via intervening behaviours linked with low motivation such as smoking and lack of exercise. Further, a depression-stroke association could be spurious. A non-causal explanation likely accounted for findings from 24-year follow-up of the Whitehall II cohort.<sup>1</sup> Depressive symptoms were linked robustly to incidence of major acute coronary events, but the association with stroke was limited to the five-year period after psychological assessment. Depression may thus be a prodromal symptom of stroke, perhaps of vascular origin, generated by sub-clinical changes to the brain before the event.<sup>2</sup> Epidemiologists call this 'reverse causation' because stroke is the cause of the association of depression with stroke but the depression is not primary.

### **Methods of the study**

A new mega-study based on 0.5 million Chinese men and women concludes that depression is a risk factor for stroke.<sup>3</sup> At baseline, participants were aged 30-79 years and without a history of stroke, heart disease and cancer. The cohort was followed-up for median 7 years. Stroke events were ascertained through death certificates, medical records, and health insurance data. Depression was defined by the Chinese version of the Composite International Diagnostic Inventory (CIDI-Short Form), which yielded a small 'depressed' group at baseline, just 2988 (0.6%) of 487,377 participants. Sun et al checked their findings with a more inclusive definition based on fewer depression symptoms, which classified more than four times as many participants as depressed (13,601).

### **What does this paper add?**

- Both narrow and wide definitions of depression identified a 15% increase in stroke risk.
- The relative risk of stroke increased with increasing number of depression symptoms at baseline
- Until now the relation between depression and stroke has been little studied in the Chinese population. This study involves almost 3.5 million person-years of follow-up.

### **Limitations**

- Few depression cases were identified at baseline (0.6%), compared to a survey in Beijing and Shanghai (2.0%). The low prevalence of depression limits the statistical power of the study.

- If depression is a risk factor for stroke in the Chinese population, it seems to be a minor one. The proportion of stroke cases in the population attributable to depression identified by the CIDI-Short Form questionnaire is less than 0.1%.
- Transposed to the UK, where a recent survey<sup>4</sup> generated a prevalence estimate of common mental disorder of 15%, the attributable risk is 2.2%; still a small proportion but not ignorable if causation was to be established.
- The alternative explanation for the study's findings, that depression is a prodromal symptom of stroke (reverse causation) potentially explains why depression and stroke are linked in this prospective study. Three features of the study are relevant to this concern:
  - 1) The large size of the cohort does not reduce the probability that the alternative explanation is correct.
  - 2) As compared with the Whitehall II study where the depression-stroke association was seen only in the first five years after psychological assessment, the median follow-up here was 7.2 years. A sensitivity analysis, conducted to exclude the potentially prodromal cases in the early years of follow-up, would have provided valuable evidence about the nature of the association. Such an analysis was evidently not conducted.
  - 3) The observed dose-response relationship, such that report of more depression symptoms was linked with an increased stroke hazard, is equally compatible with reverse causation as it is with the hypothesised effect of depression on stroke risk. Reverse causation would operate if the number of depression symptoms tended to be higher among those with highest risk of impending stroke, as a consequence of the stroke pathology.

### **What next in research**

- Follow-up studies of older adults over 10 years or longer, ideally with one or more repeat determinations of mental health status, would provide more dependable evidence for the nature of the links, if any, between depression and risk of stroke.

### **Do these results change your practices and why?**

Yes. Depression is a burdensome condition. Although the results of this study are not definitive, they indicate that active support and treatment for patients with clinical depression or recurrent depressive symptoms may have longer as well as shorter term health benefits.

### **References**

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**Section heading: Causes and risk factors**

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