

Depression and stroke risk

Valeria Caso*, Paola Santalucia¹ & Francesca Romana Pezzella²

Evaluation of: Pan A, Okereke OI, Sun Q *et al.* Depression and incident stroke in women. *Stroke* 42(10), 2770–2775 (2011). In the Nurses' Health Study, 80,574 women aged between 54 and 79 years, without a history of stroke, were followed-up from 2000 to 2006. In this cohort, depressive symptoms were assessed at multiple time points utilizing the Mental Health Index score (1992, 1996 and 2000), and clinically significant depressive symptoms were defined as a score ≤ 52 . A survey was carried out regarding antidepressant medication use biennially beginning in 1996, and physician-diagnosed depression was reported biennially from 2000. During this 6-year follow-up, 1033 incident strokes were documented. Having a history of depression was associated with an increased risk for total stroke, as well as the use of antidepressant medications with or without history of depression.

Pan *et al.* reported on the results from the Nurses' Health Study concerning depression and stroke risk [1]. The same research group observed a significant association between depression and cardiac events [2]. This relationship was strongest for fatal coronary heart disease, where the association remained significant even after controlling for vascular risk factors (hazard ratio [HR]: 1.49; 95% CI: 1.11–2.00). Depression was strongly associated with sudden cardiac death in multivariable models (HR: 2.33; 95% CI: 1.47–3.70), and this risk was primarily due to a specific relationship between antidepressant use and sudden cardiac death (HR: 3.34; 95% CI: 2.03–5.50).

Data on a possible association between depression and stroke risk are more limited, and even more so for stroke subtypes. Pan *et al.* have recently performed a systematic review and meta-analysis of prospective studies, assessing for an association between depression and risk of developing stroke [3]. The pooled adjusted HRs were 1.45 (95% CI: 1.29–1.63; p-value for heterogeneity < 0.001 ; random-effects model) for total stroke, 1.55 (95% CI: 1.25–1.93; p-value for heterogeneity 0.31; fixed-effects model) for fatal stroke and 1.25 (95% CI: 1.11–1.40; p-value for heterogeneity 0.34; fixed-effects model) for ischemic stroke. The estimated absolute risk differences associated with depression were 106 cases for total stroke, 53 cases for ischemic stroke and 22 cases for fatal stroke per 100,000 individuals per year, while the results for nonfatal stroke and hemorrhagic stroke were not significant (HR: 1.21; 95% CI: 0.91–1.62 and HR: 1.16; 95% CI: 0.80–1.70, respectively). The number of studies ($n = 3$ and $n = 2$, respectively) that separately addressed these stroke types was small. These results were also consistent with a

large case-control study, INTERSTROKE, for which the investigators found that self-reported depression (for ≥ 2 weeks in the last year) was associated with a significantly increased risk of stroke (odds ratio: 1.35; 99% CI: 1.10–1.66) in 3000 cases and 3000 matched controls from 22 countries [4].

Finally, antidepressant medication (ADM) use was associated with an increased incidence of stroke in the Nurses' Health Study, confirmed by Pan *et al.* in their meta-analysis [3]. The results from both of these studies need to be interpreted cautiously, as many of the analyzed studies lacked information on dose and duration of medication use. Moreover, Pan *et al.* suspect that ADM use is an expression of depression severity [3].

In summary, there is growing evidence that depression is a risk factor for vascular cardiac and cerebrovascular disease. Therefore, more studies are needed to explore these highly plausible underlying mechanisms and elucidate the causal pathways that are responsible for the association between depression and stroke. In the meantime, clinicians need to be alert for depression and ADM use as possible stroke risk factors.

Results

Pan *et al.* investigated whether depression is a risk factor in women included in the Nurses' Health Study [1]. This study examined 80,574 women aged 54 to 79 years, without a history of stroke, from 2000 to 2006. Depressive symptoms were assessed at multiple time points utilizing the Mental Health Index score (1992, 1996 and 2000), and clinically significant depressive symptoms were defined as a score ≤ 52 . A survey was carried out on ADM use biennially from the year 1996, and physician-diagnosed

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¹Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milano, Italy

²UO Medicina d'Urgenza Stroke Unit, AO S Camillo-Forlanini, Rome, Italy

*Author for correspondence: Stroke Unit and Division of Cardiovascular Medicine, University of Perugia, Santa Maria della Misericordia Hospital, Sant'Andrea delle Fratte, 06126 – Perugia, Italy
Tel.: +39 075 5782765
Fax: +39 075 5782765
vcaso@hotmail.com

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depression was reported biennially from the year 2000. Overall, during the 6 years of follow-up, 1033 incident strokes were documented (538 ischemic, 124 hemorrhagic and 371 unknown). The reported prevalence of depression was 22.3% in 2000. Compared with women without a history of depression, depressed women were younger, more likely to be single, had a higher BMI, smoked cigarettes and were less likely to be physically active. The prevalence of major vascular comorbidities was also higher in depressed women. In age-adjusted analyses, depression was associated with an increased risk of total stroke with a HR of 1.49 (95% CI: 1.30–1.70). The HR was attenuated but remained significant after adjusting for various covariates including major comorbidities (HR: 1.29; 95% CI: 1.13–1.48). Results were not significant for either hemorrhagic or ischemic strokes separately, and no significant interactions among depression, age and major comorbidities with total stroke risk were found. Women who used ADMs were at an increased risk for stroke, whether they also had a Mental Health Index score ≤ 52 or diagnosed depression (HR: 1.39; 95% CI: 1.15–1.69), or not (HR: 1.31; 95% CI: 1.03–1.67). This risk was significant for selective serotonin reuptake inhibitors (HR: 1.39; 95% CI: 1.13–1.72), the largest use category, but not for other ADMs (HR: 1.14; 95% CI: 0.82–1.58). Furthermore, for each cycle, women who reported current depression had an increased risk of stroke (HR: 1.41; 95% CI: 1.18–1.67), whereas women who only had a history of depression were not at a significantly elevated risk (HR: 1.23; 95% CI: 0.97–1.56) compared with women who never reported a diagnosis of depression or ADM use.

Significance

The findings from this well-described cohort of >80,000 US women with a 6-year follow-up add to the growing evidence that depression is associated with stroke risk. In this study, a biennially repeated assessment of risk factors and disease outcomes was performed, and time-dependent Cox models were utilized. Furthermore, three different sources of information (five-item Mental Health Inventory, ADM use and physician-diagnosed depression) were used to determine depression status. Depression is highly prevalent in the general population, and it is estimated that 5.8% of men and 9.5% of women will experience a depressive episode over the next 12-month period [5]. This percentage is even higher in the female age-group

between 55 and 75 years of age, as confirmed in this study (22.3%). This possible association between depression and stroke will hopefully open new insights into pathogenesis of stroke, which is believed to be different between men and women. In fact, the lifetime risk of stroke for women aged 55 to 75 years is approximately 20%, which is notably higher than that for men (14–17%) [6]. Given that women tend to have fewer vascular risk factors, depression may play a crucial role in stroke pathogenesis. Depression may contribute to stroke through a variety of mechanisms:

- Neuroendocrine and immunological/inflammation effects [7]
- Poor health behaviors (i.e., smoking [8], physical inactivity or lack of medication [9])
- Correlations with other major comorbidities, such as diabetes and hypertension

In fact, in this study, women with a history of depression tended to have major vascular comorbidities, but their HR remained significant even after adjusting for these. Therefore, the authors hypothesize that the most likely underlying pathway in stroke pathogenesis is: depression induces sympathetic nervous system activation together with dysregulation of the hypothalamic–pituitary–adrenocortical axis and, thereby, platelet aggregation dysfunction [10].

Future perspective

Further research is necessary to confirm the role of depression as a risk factor for stroke pathogenesis in women. More importantly, future studies need to examine ethnicity, age and social groups for their specific impact on the association between depression and stroke pathogenesis. In addition, the role of ADM must be clarified in the pathogenesis of stroke due to its widespread prescription for women. Finally, future studies will also need to track the duration, dosage and types of ADM in order to obtain a complete picture of its role.

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Executive summary

- The history of depression was associated with a hazard ratio (HR) of 1.29 (95% CI: 1.13–1.48) for total stroke in women aged between 54 and 79 years of age without history of stroke.
- Women who used antidepressant medications were at an increased risk for stroke, whether they had a diagnosed depression (HR: 1.39; 95% CI: 1.15–1.69) or not (HR: 1.31; 95% CI: 1.03–1.67).
- Women with current depression had an increased risk of stroke (HR: 1.41; 95% CI: 1.18–1.67), whereas those who only had a history of depression were not at a significantly elevated risk (HR: 1.23; 95% CI: 0.97–1.56).

References

1. Pan A, Okereke OI, Sun Q *et al.* Depression and incident stroke in women. *Stroke* 42, 2770–2775 (2011).
2. Whang W, Kubzansky LD, Kawachi I *et al.* Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses' Health Study. *J. Am. Coll. Cardiol.* 53, 950–958 (2009).
3. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA* 306, 1241–1249 (2011).
4. O'Donnell MJ, Xavier D, Liu L *et al.*; INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 376, 112–123 (2010).
5. WHO. *The World Health Report 2001 – Mental Health: New Understanding, New Hope*. WHO, Geneva, Switzerland (2001).
6. Seshadri S, Beiser A, Kelly-Hayes M *et al.* The lifetime risk of stroke: estimates from the Framingham Study. *Stroke* 37, 345–350 (2006).
7. Strine TW, Mokdad AH, Dube SR *et al.* The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *Gen. Hosp. Psychiatry* 30, 127–137 (2008).
8. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ* 298(6676), 789–794 (1989).
9. Luppino FS, de Wit LM, Bouvy PF *et al.* Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch. Gen. Psychiatry* 67(3), 220–229 (2010).
10. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch. Gen. Psychiatry* 55, 580–592 (1998).