Why is depression more prevalent in women?

Paul R. Albert, PhD

Major depression is a chronic illness with a high prevalence and is a major component of disease burden. Depressive disorders were the second leading cause of years lived with disability in 2010 in Canada, the United States and globally.[1,2] When depression-related deaths due to suicide and stroke are considered, depression has the third highest global burden of disease.[3] Major depression is growing in overall disease burden in Canada and around the world; it is predicted to be the leading cause of disease burden by 2030, and it is already the leading cause in women worldwide.[4] Between 1990 and 2010 in Canada, major depressive disorder showed a 75% increase in disability-adjusted life years,[1] the second greatest increase in prevalence after Alzheimer disease; in comparison, the increase in the United States was 43%.[2] At the same time, the female:male ratio of global disability from major depression remained unchanged at 1.7:1. Although differences in socioeconomic factors, including abuse, education and income, may impact the higher rate of depression in women,[5] this editorial focuses on biological contributors that are experimentally tractable and may help to understand how and why depression is more prevalent in women and lead to better treatments.

The prevalence of major depression is higher in women than in men;[6,7] in 2010 its global annual prevalence was 5.5% and 3.2%, respectively, representing a 1.7-fold greater incidence in women.[1,8] In Canada, the prevalence was 5.0% in women and 2.9% in men in 2002 (1.7-fold greater incidence in women) and increased to 5.8% and 3.6%, respectively, in 2012 (1.6-fold greater incidence in women).[9,10] The finding of similar female:male prevalence ratios in developed countries and globally suggests that the differential risk may primarily stem from biological sex differences and depend less on race, culture, diet, education and numerous other potentially confounding social and economic factors. There is no clear evidence that the rate of depression is greater in countries where women have markedly lower socioeconomic status than men than in countries where there may be more equal footing.[5] Depression is more than twice as prevalent in young women than men (ages 14–25 yr), but this ratio decreases with age.[9,10] Indeed, starting at puberty, young women are at the greatest risk for major depression and mental disorders globally.[1] Importantly, before puberty, girls and boys have similar rates of depression; the rate is perhaps even higher for boys.[6] At ages older than 65 years, both men and women show a decline in depression rates, and the prevalence becomes similar between them.[9,11] A greater prevalence of depression in women is also reflected in prescriptions for antidepressant medications. In Canada between 2007 and 2011, antidepressants were prescribed more than twice as often to women than men (9.3% v. 4.2% in patients aged 25–44 yr, 2.2-fold; 17.2% v. 8.2% in patients aged 45–64 yr, 2.1-fold).[12] The age discrepancy between the peaks in the prevalence of depression (age 14–25 yr)[10] and the prevalence of antidepressant use (> 45 yr) suggests that young adults with depression may not always receive antidepressant treatment until many years after the onset of illness. This delay in medication could contribute to the higher rates of depression during adolescence and young adulthood and would be important to study more rigorously comparing treated and nontreated cohorts. Delay in antidepressant treatment might reflect stigma or underdiagnosis in adolescence. New antistigma and educational programs targeted to youth may help reduce depression in this age group.[13]

Why then is depression more prevalent among women? The triggers for depression appear to differ, with women more often presenting with internalizing symptoms and men presenting with externalizing symptoms.[14] For example, in a study of dizygotic twins, women displayed more sensitivity to interpersonal relationships, whereas men displayed more sensitivity to external career and goal-oriented factors.[15] Women also experience specific forms of depression-related illness, including premenstrual dysphoric disorder, postpartum depression and postmenopausal depression and anxiety, that are associated with changes in ovarian hormones and could contribute to the increased prevalence in women. However, the underlying mechanisms remain unclear; thus, treatments specific to women have not been developed.

The fact that increased prevalence of depression correlates with hormonal changes in women, particularly during puberty, prior to menstruation, following pregnancy and at perimenopause, suggests that female hormonal fluctuations may be a trigger for depression. However, most preclinical

Correspondence to: P. Albert, Department of Neuroscience, Ottawa Hospital Research Institute, University of Ottawa, 451 Smyth Rd, Ottawa ON K1H 8M5; palbert@uottawa.ca

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studies focus on males to avoid variability in behaviour that may be associated with the menstrual cycle. Nevertheless, primate and rodent studies consistently implicate a role for female hormones, such as estrogen, in depression. Perhaps the most naturalistic depression studies to date to address the role of female hormones involved small groups (n = 4–5) of female macaque primates that formed lifelong social hierarchies with dominant and subordinate females. The latter showed a depression-like phenotype[16] that has been associated with a brain-wide decrease in serotonin 1A (5-HT_{1A}) receptor levels and decreased hippocampal volume.[17,18] Interestingly, the reduced hippocampal volume was more extensive in postmenopausal monkeys than in ovarian-intact monkeys, suggesting that ovarian function may be protective. Consistent with this finding, the risk of depression appears to increase during the perimenopausal transition.[19] Emerging evidence indicates that hormone replacement therapy, particularly during the perimenopausal period, can be effective in the prevention of postmenopausal depression in women.[20] Another study involving female macaques examined relocation stress–sensitive alterations in their menstrual cycles and showed depression-related behaviours and reductions in the function of the brain serotonin system.[21] In this light, a recent study has indicated that women who reported using an oral contraceptive (especially monophasic contraceptives) showed reduced rates of major depression and anxiety compared with nonusers,[22] suggesting that moderating the cycling of estrogen may be protective. Taken together these studies suggest that estrogen may have a protective effect on the pathology that underlies depression and that decreases in estrogen may increase the risk for depression.

Why then do men, who lack systemic estrogen, have lower rates of depression than women? Accumulating research has shown that in the male brain testosterone is converted into estrogen by endogenous aromatase (CYP19). Estrogen could mediate protective actions through estrogen receptors expressed throughout the male brain (especially estrogen receptor β).[23] In addition, the presence of androgen receptors in men may confer protection, for example in hippocampal neurons.[24] Since testosterone does not cycle in men as estrogen does in women, there may be a more consistent protection in men. However, men also have sexually dimorphic brain nuclei, particularly in the hypothalamus, so the lower prevalence of depression in men is probably more complex owing not only to hormonal differences, but also to developmental differences in brain circuitry.[23]

In the most fundamental terms, the sex difference in depression rates reflects the fact the men and women are different: women have 2 copies of the X chromosome, while men have 1 copy each of X and Y chromosomes, the latter not being present in women. Understanding how this fundamental genetic difference confers sexual differences in predisposition to mental illness is a complex, multilevel puzzle that remains to be clarified. Society-driven risk factors for depression in women likely have a biological origin, such as differences in physical strength and personality traits, leading to a higher prevalence of depression in women. Perhaps what needs to change are social attitudes to promote equality; yet, this has been occurring in the West and has yielded no clear change in the female:male depression ratio.[5] However, despite this complexity, recent evidence suggests that biological factors, such as the variation in ovarian hormone levels and particularly decreases in estrogen, may contribute to the increased prevalence of depression and anxiety in women and that strategies to mitigate decreases in estrogen levels may be protective. Identifying ligands that more specifically target the brain (e.g., estrogen receptor-β-selective ligands) may protect from depression but avoid adverse effects of estrogen therapy.[25]

Affiliations: From the Department of Neuroscience, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada.

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