Approximately 80% of women develop neuropsychiatric symptoms during perimenopause, most commonly sleep disturbances, cognitive dysfunction, and mood-related symptoms. In this study, the British authors tested the hypothesis that perimenopause (two years before and two years after the final menstrual period) is a period of increased risk of first-onset psychiatric disorders, such as major depressive disorder, mania, and schizophrenia spectrum disorders, and other categories, including anxiety/panic attacks, substance abuse/dependency, post-traumatic stress disorder, anorexia/bulimia, obsessive-compulsive disorder, or insomnia. The authors investigated the large sample size of more than 120,000 women from the UK Biobank biomedical database.

The relationship between perimenopause and changes in mood has been well established. Although perimenopause is considered a high-risk period for the onset or exacerbation of psychiatric disorders, knowledge of the risk of a broad spectrum of psychiatric disorders associated with reproductive aging is insufficient.



About the study

The UK Biobank is a large-scale biomedical database designed to enable research into genetic and environmental determinants of various diseases. This study dataset was restricted to women recruited between 2006 and 2010. Psychiatric disorders were assessed using interviews and a self-report web-based questionnaire (the UK Biobank mental health questionnaire).

The study investigated the first onset of major depressive disorder, mania, schizophrenia spectrum disorders, and an “other diagnoses” category that included anxiety/panic attacks, substance abuse/dependency, post-traumatic stress disorder, anorexia/bulimia/other eating disorders, stress, obsessive-compulsive disorder, and insomnia during premenopause (6-10 years before the final menstrual period), perimenopause (2 years before and 2 years after the final menstrual period), and postmenopause (6-10 years after the final menstrual

period). Based on previous studies, which show the link between childbirth and these disorders, these periods were chosen because they share hormone-driven etiological pathways.

Results

A total of 128,294 women from the UK Biobank met the inclusion criteria, with a mean age at recruitment of 59.6 years (40–69 years) and a mean age at menopause of 50.6 years. The average follow-up period was 2.98 years.

The first onset of a psychiatric disorder was diagnosed in perimenopause in 1,133 women (0.9% of the study group, incidence rate 2.33 *per* 1,000 person-years), in 753 women in premenopause (0.6% of the study group, incidence rate 1.53 *per* 1,000 person-years), and in 637 women in postmenopause (0.5% of the study group, incidence rate 1.66 *per* 1,000 person-years).

These results show that incidence rates of the first onset of psychiatric disorders in the perimenopause were higher than in the premenopause and postmenopause periods.

Disorder-specific analysis

The incidence rate of major depressive disorder during perimenopause was higher than in premenopause, but it became significantly lower in postmenopause compared with premenopause. Of note, while rates of first-onset major depressive disorder decreased in postmenopause, rates of first-onset depressive symptoms remained high in postmenopause. As depression is likely an umbrella term for several conditions with heterogeneous disease pathways, the mechanisms underpinning the link between first-onset depressive symptoms and reproductive aging may, therefore, be complex and include not only hormonal changes associated with perimenopause but also biopsychosocial challenges associated with aging.

The incidence rate of mania significantly increased in perimenopause compared with premenopause and returned to premenopause levels during postmenopause. Participants without a previous history of mania were over twice as likely to develop mania for the first time in perimenopause as in the late reproductive stage. According to the authors, the disease-specific and narrow time window (4 years) of increased risk for mania suggests that specific changes associated with perimenopause may trigger mania in women without a previous psychiatric history of mania. These results support the theory that there is a link between mania/bipolar disorder and reproductive events, such as the previously reported link between mania and childbirth.

Contrary to mania, perimenopause was not significantly associated with a change in the incidence rate of schizophrenia spectrum disorders compared with the premenopause stage. These results are consistent with a large study of over 130,000 incident cases of schizophrenia, which found a decline in new onsets in women after the age of 40. According to the authors, these findings do not support the widely debated hypothesis that hypoestrogenism may trigger the first onset of schizophrenia.

The incidence rates of other diagnoses, including anxiety/panic attacks, substance abuse/dependency, post-traumatic stress disorder, anorexia/bulimia/other eating disorders, stress, obsessive-compulsive disorder, or insomnia, were higher in both perimenopause and postmenopause than in the period of premenopause.

Conclusion

This study was focused on the first onset of psychiatric disorders during perimenopause, so the recurrence of preexisting psychiatric disorders was beyond its scope. The results showed that perimenopause (2 years before and 2 years after the final menstrual period) is a period of increased risk of first-onset major depressive disorder and mania. No association was found between perimenopause and the first onset of schizophrenia spectrum disorders.

The link with mania was particularly striking and significant, showing that perimenopause represents a period of increased risk of first-onset mania in those without a previous psychiatric history of mania.

A major strength of this work over many previous studies is that it estimates the pre-, peri-, and postmenopausal periods, whereas many previous studies have often used chronological age as a proxy for menopause, despite the wide variability in reproductive timing between individuals.

This article was published in Nature Mental Health.

Journal Reference

Shitomi-Jones L.M., Dolman C., Jones I, et al. Exploration of first onsets of mania, schizophrenia spectrum disorders and major depressive disorder in perimenopause. *Nat. Mental Health 2024;* 2, 1161–1168 (Open Access).
https://doi.org/10.1038/s44220-024-00292-4