


# A glimpse of gender differences in schizophrenia

Xin Li <sup>1,2</sup>, Wanyan Zhou,<sup>2</sup> Zhenghui Yi<sup>1,2</sup>

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Ample evidence suggests that gender affects the incidence, susceptibility, presentation, diagnosis and severity of many psychiatric disorders. Schizophrenia is one of the most prevalent severe mental disorders, with an incidence of 0.7%–1% among the total population, which causes suffering and pecuniary losses.<sup>1 2</sup> It has long been known that the age of schizophrenia onset differs in women compared with men. Some life events, such as pregnancy, fertility and menopause, are unique to women and can affect the onset and course of mental disorders. However, the role of gender in this association has received little attention. The female sex and reproductive transitions impact various aspects of brain biology and pathobiology. These biologic differences can impact differential gene expression or organ development. Evaluating gender-related differences is the first step in moving towards precision psychiatry. This article provides a brief overview of gender differences in the epidemiology, disease presentation, risk factors and management of schizophrenia.

## EPIDEMIOLOGY

The incidence of schizophrenia is higher among men than women, with a ratio of nearly 1.4:1, although several reviews did not find sex differences in the lifetime prevalence of the illness.<sup>3</sup> The onset of schizophrenia in males is 3.2–4.1 years earlier than in females.<sup>4</sup> Males and females have shown different susceptibilities to schizophrenia in different life stages. The prevalence of schizophrenia was higher among men aged <40 years, with the peak incidence between 20 and 29 years.<sup>5 6</sup> The sex gradient was the opposite for females with schizophrenia; a higher prevalence was found for those >40 years of age, with two incidence peaks—the first at the age of 20–39 years and the second at the perimenopause period.<sup>7</sup> The prevalence of the illness increases significantly after 40 years of age in women, which may be related to decreased

oestrogen levels after menopause. In addition, numerous psychosocial factors may contribute to the development of psychosis, including loneliness, adverse life events and the lack of family/social support, all of which may frequently be found in menopausal and postmenopausal women.<sup>8 9</sup>

## DISEASE PRESENTATION

Among patients with schizophrenia, males have a greater risk of experiencing prominent negative symptoms, while females display more affective symptoms, including depression, impulsivity, emotional instability, sexual misconduct and sexual delusions.<sup>10</sup> Regarding cognitive dysfunction, female patients performed better on measures of executive function, verbal memory and information processing speed than male patients (figure 1).<sup>11</sup> Previous studies have also found that male patients outperformed females regarding visual memory and attention.<sup>12</sup> However, male patients also reported worse premorbid functioning. The underlying biological mechanisms might be due to the sex differences in brain morphology, genetic risk factors and neuroprotective functions of oestrogen effects facilitated by gonadal and adrenal hormones and therefore depend on the gender of the individual.<sup>13</sup> It should be noted that similar symptoms can be interpreted differently for male and female patients. For example, isolation, withdrawal and avoidance of the outside world may indicate a depressive syndrome in female patients with schizophrenia but may indicate negative symptoms in male patients.

## RISK FACTORS

Important psychosocial factors, including education, occupation, pregnancy and marriage, are closely related to schizophrenia's occurrence, treatment response and recurrence. However, similar life events may have different effects on men and women.



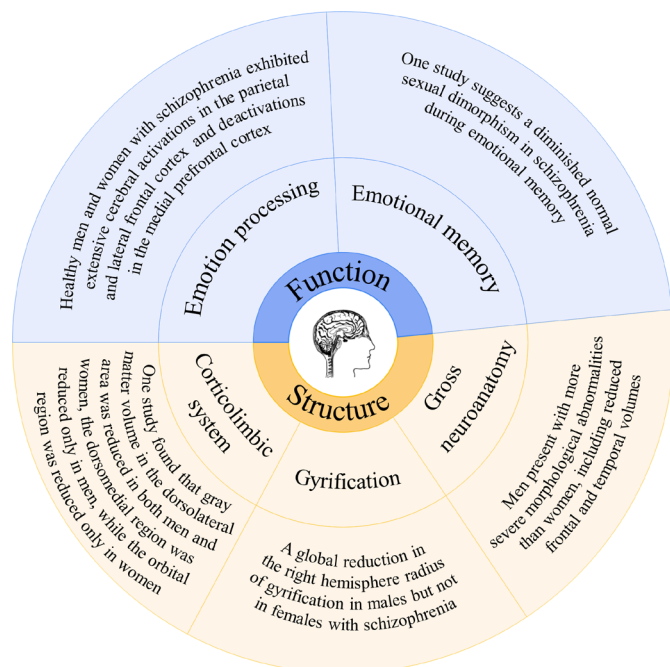
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<sup>1</sup>Department of Psychiatry, Huashan Hospital, Fudan University, Shanghai, China

<sup>2</sup>Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

## Correspondence to

Dr Zhenghui Yi;  
yizhenghui1971@163.com



**Figure 1** Main structural and functional differences of brain between males and females among schizophrenia patients.

Previous findings suggested that childhood abuse may be more strongly associated with a risk for the development of schizophrenia and an earlier onset of the illness in women than in men.<sup>14</sup> In addition, childhood adversity has been linked to the severity of different symptom dimensions in men and women.<sup>15</sup> However, due to a later onset of schizophrenia and relatively normal social function, females tend to receive more years of education than men; this contributes to the lower risk of the illness for females.<sup>16,17</sup> Stratified analyses found that urbanisation rates, divorce rates and socioeconomic conditions for female adults were positively associated with increased risk for schizophrenia.<sup>17</sup> However, for male adults, low socioeconomic conditions were related to decreased risk of schizophrenia, and there was no significant association between rates of divorce and risks for schizophrenia.<sup>14-17</sup>

A frequent topic discussed by young female patients with schizophrenia during routine psychiatric clinic visits is the presence or absence of a desire for pregnancy. Those who become pregnant are concerned about controlling their illness symptoms during the antenatal and postnatal periods and express fear of losing their marriage, congenital malformation of the fetus and stigma.

## DISEASE MANAGEMENT

In therapeutic strategies used to treat schizophrenia, classic symptomatic diagnoses often describe male presentations of the illness. Thus, an important area needing improvement is the early detection of gender-specific signs of first-episode schizophrenia to shorten the duration of untreated schizophrenia for females. Due to the different physical structures of males and females, the pharmacodynamics and pharmacokinetics

of antipsychotics may also be affected by gender. Previous studies have shown that the serum concentrations of most antipsychotics in premenopausal women are higher than in men, or if the serum concentrations are the same, the share of the dopamine receptors is higher in women than in men.<sup>18-21</sup> However, there are no gender-specific dosing recommendations in clinical practice, leading to unavoidable risks of over-medicating. A more comprehensive appreciation of the role of gender in the molecular basis of schizophrenia will encourage the development of novel and more effective pharmacotherapies. Considering the hormonal phases women commonly experience during their lives, ongoing management of the hormonal fluctuations of women being treated for schizophrenia is especially vital as they undergo events that trigger hormonal changes: pregnancy, childbirth, lactation and menopause. Moreover, societal prejudices against those with mental illness may more significantly impact female patients with schizophrenia. Thus, female patients require drugs with fewer adverse reactions, more comprehensive control of symptoms and greater restoration of social function. Closer cooperation with gynaecologists and obstetricians is also needed.

## CONCLUSION

Although gender differences are innate, the diverse outcomes of these differences in disease have been emphasised in recent years. Classical symptom recognition in medicine is often based on male presentations, an insufficiency in this present era of precision medicine. The most notable medical example is heart disease, in which men and women manifest different symptoms. For instance, when myocardial infarction occurs, men present with typical chest pain, while women present with pain between the shoulder blades, nausea or vomiting, resulting in an extension of 30–45 min for cardiac resuscitation.<sup>22</sup> At present, researchers studying gender differences in schizophrenia often focus on clinical symptoms but lack large-scale, high-quality clinical cohort studies, leading to various controversial conclusions. Meanwhile, more targeted treatment strategies are lacking. Sex differences in schizophrenia are well-recognised yet poorly understood clinical phenomena. Only by receiving gender-specific care will men and women with schizophrenia have optimal chances to fare well.

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#### ORCID iD

Xin Li <http://orcid.org/0000-0002-2214-7754>

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*Xin Li obtained a bachelor's degree in clinical medicine from Fudan University, Shanghai, China in 2021. Currently, he is a second-year doctoral student at the Department of Psychiatry, Huashan Hospital, Fudan University, in Shanghai, China. His main research interests include evidence-based medicine and the early identification and optimized treatment of affective disorders.*