World Journal of Psychiatry

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World J Psychiatr 2018 November 9; 8(5): 125-136

DOI: 10.5498/wjp.v8.i5.125

ISSN 2220-3206 (online)

REVIEW

Women who suffer from schizophrenia: Critical issues

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Author contributions: Seeman MV is the sole author and responsible for every aspect of this paper; she received no assistance and no funding.

Conflict-of-interest statement: None.

Manuscript source: Unsolicited manuscript

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Received: July 18, 2018
Peer-review started: July 18, 2018
First decision: August 2, 2018
Revised: August 24, 2018
Accepted: October 11, 2018
Article in press: October 11, 2018
Published online: November 9, 2018

Abstract

Many brain diseases, including schizophrenia, affect men and women unequally - either more or less frequently, or at different times in the life cycle, or to varied degrees of severity. With updates from recent findings, this paper reviews the work of my research group over the last 40 years and underscores issues that remain critical to the optimal care of women with schizophrenia, issues that overlap with, but are not identical to, the cares and concerns of men with the same diagnosis. Clinicians need to be alert not only to the overarching needs of diagnostic groups, but also to the often unique needs of women and men.

Key words: Schizophrenia; Women; Gender differences; Unmet needs

Core tip: Schizophrenia and related disorders are expressed differently in men and women. Causative factors may differ, as can the expression, timing and severity of symptoms. Prevention, course of illness, and treatment response are all intimately linked to gender.

Seeman MV. Women who suffer from schizophrenia: Critical issues. *World J Psychiatr* 2018; 8(5): 125-136 Available from: URL: http://www.wjgnet.com/2220-3206/full/v8/i5/125.htm DOI: http://dx.doi.org/10.5498/wjp.v8.i5.125

INTRODUCTION

This review focuses on my experience dealing with clinical issues critical to women with schizophrenia. My work in this field began many years ago, and results are being continually updated as new information emerges. The paper is divided into the following main sections: Potential prevention strategies for women, the need for early and accurate diagnosis, the troubling complexities of the mental health system, effective treatment of schizophrenia and avoidance of adverse effects, the provision of access to vocational and avocational opportunities, attention to stigma, self-harm and suicide, the need for maintenance of physical, reproductive, and

emotional health. Many of these issues are not specific to schizophrenia, nor are they all specific to women. But, directly or indirectly, they all bear on the health and well being of women with schizophrenia.

In each of the sections listed above, I reference my own work plus recent key papers from the PubMed database. Most of these topic areas continue to be the focus of intense research, and many questions await resolution. The paper ends by broadly outlining future directions for the field.

POTENTIAL PREVENTION STRATEGIES

Schizophrenia is defined by its symptoms, which are thought to arise from the interaction of inherited or *de novo* genetic polymorphisms with exposure to environmental stressors at critical periods of a person's life. The details of specific gene mutations, the severity and identity of stressors, and critical chronology remain largely unknown. The strongest contributor to identifiable disease risk is a history of schizophrenia in close family members[1]. Knowledge of family history can now be combined with genetic risk scores from whole genome scans, which together, provide valuable information about a person's vulnerability to schizophrenia[2]. Nevertheless, when it comes to prevention, even in the era of Clustered Regularly Interspaced Short Palindromic Repeats (commonly known as CRISPR)[3], it is not possible to edit out the hundreds of genes that potentially contribute to schizophrenia in any one individual. Even if in the future all suspicious genes could be eliminated, profound ethical concerns make this form of prevention doubtful[4,5].

Some investigators believe that prevention strategies for men and women need to differ. The genetic predisposition to schizophrenia may, for instance, be sexually dimorphic[6-8], although evidence for this is sparse. On the other hand, because male and female DNA is so often exposed to somewhat dissimilar environmental inputs, it may well transpire that the turning off and on of genes in particular sets of cells - the domain of epigenetics - is relatively sex-specific. Therefore, developments in epigenetics may one day enable the prevention of sex-specific expression of schizophrenia-inducing genes[9,10]. However, for the time being, genetic counseling for women and men[11] and individual contraception counseling[12] are the best ways to try to prevent the transmission of schizophrenia at the gene level.

Women with schizophrenia planning to be mothers and wanting to prevent schizophrenia in their offspring can be counseled (although this is, of course, impractical) to choose relatively young - but not too young - mates with no family history of psychosis[13] and to strategically plan the conception in order to avoid giving birth during late winter or early spring[14]. There is no direct evidence that this will work to prevent schizophrenia in the next generation, but there is an association (which does not imply causation) between season of birth and schizophrenia in offspring. The potential connection has been attributed either to fetal and/or neonatal exposure to infectious/immune factors or to the lack of sunlight and low levels of vitamin D. Associated preventive measures include adequate nutrition during pregnancy, and Vitamin D and folic acid supplements[15]. Other suggestions for mothers with schizophrenia to boost the health of their infants are: limits on maternal weight gain during pregnancy, appropriate immunization, low doses of antipsychotic (AP) drugs during pregnancy and lactation, abstention from tobacco, alcohol and other substances[16-18], and rapid treatment of infection and inflammation[19-21]. Nutritional deficiency, stress, and toxic substances in pregnant women have long been recognized to increase the risk for schizophrenia in offspring[22-24]. Infection, inflammation and immune reactivity have more recently been considered serious contributors to schizophrenia susceptibility[21,25].

Obstetric complications pose a potential risk to the infant brain. They are more common in the birth history of those who go on to develop schizophrenia than in their psychiatrically well peers, but it is not known whether obstetric complications arise from prior fetal problems or whether they result from substandard obstetric care[26,27]. Regardless, women with schizophrenia require exemplary care during pregnancy, labor, and delivery. The quality of maternal care of young children is also critical, as early physical and psychological trauma have been associated (again, this is an association that may not be contributory) with the later development of schizophrenia[26,28,29]. Such trauma is theoretically preventable through parent support and parent training groups, family health education, and child welfare monitoring, but interventions such as these require intensive collaborative work at the level of whole communities.

Further theoretical possibilities for prevention (based entirely on studies of association) are keeping children in their country of birth, since migration is a risk factor for schizophrenia[30,31], residing in rural rather than urban parts of the country[32,33], keeping children and adolescents away from alcohol and drugs[34] and teaching them emotion-regulating strategies (reappraising, accepting, and refocusing[35]) to prevent adversities such as discrimination and social defeat from culminating in paranoid delusions[36].

Given that fewer women than men are reported to develop schizophrenia (2/1 male/female ratio in the under-20 age bracket, although the discrepancy tends to even out with increasing age)[37], that the "female" hormone estrogen is known to be neuroprotective[38,39], and that women are especially vulnerable to psychosis during the postpartum period when estrogen levels precipitously drop[40], my research group predicted in the 1990s that, among women with schizophrenia, girls with early menarche (early pubertal rise in estrogen levels) would show a later onset of schizophrenia than girls who enter puberty at older ages[41]. This is precisely what we found in our clinic population, and this finding has been replicated by some groups, but not by all[42-44].

If accurate, this observation could lead to weight gain strategies[45] that bring menarche forward. This would, of course, not prevent schizophrenia, but might delay its onset in vulnerable women.

Knowing that low estrogen periods are times of special risk for psychotic episodes is especially useful for secondary prevention (prevention of recurrent episodes of psychosis) in women diagnosed with schizophrenia. Relapse can be prevented by increasing the dose of AP medication at low estrogen times in the menstrual month[46,47], during the postpartum period[48], after menopause[49,50], whenever therapeutic estrogen is stopped[51,52], or during therapy with anti-estrogen drugs[53,54]. These theoretical examples suggest that effective prevention of schizophrenia may, in the future, be possible in a sex-specific manner[55,56], though this is not the case presently.

EARLY ACCURATE DIAGNOSIS

It is well-established that delay in seeking treatment once psychotic symptoms have emerged is associated with impaired treatment response and a relatively poor prognosis[57]. Our group found that, on retrospective interview, the first sign of behavioral disturbance eventually leading to a diagnosis of schizophrenia occurred at approximately the same age in women and men, but that the pre-psychotic prodrome was almost twice as long for women[58]. The duration of untreated psychosis did not differ between the two sexes, but the interval between first behavioral sign and first treatment did - the lag was six years for men and nine years for women[58]. The corollary to this finding is that factors other than early diagnosis must determine prognosis because women's outcome relative to men's, despite a longer untreated interval, is generally superior, at least over the reproductive years[59,60]. Potential factors that favor women, besides estrogen levels, are premorbid functioning generally superior to that of premorbid men, more friendships, closer family relations, greater academic success, and a relative absence of substance abuse[61-63].

As important as the speed of diagnosis is its accuracy. Diagnosis leads, at least in theory, to disease-specific treatment, although this is not always true in psychiatry where illness categories often overlap and the same treatments are used for different diagnostic entities. Nevertheless, it is my clinical experience that women's diagnoses frequently changes from depression to posttraumatic stress syndrome to eating disorder to schizophrenia to bipolar disorder (not necessarily in that order). This may be because it is more difficult to apply textbook schizophrenia criteria to women than to men. Women do not always exhibit the characteristic symptoms; they show few "negative" symptoms, few cognitive symptoms, and they rarely show flattened affect[64-66]. Prior to being diagnosed with a schizophrenia-related disorder, women with psychosis are often considered to be suffering from a mood disorder whereas, in men, a first tentative diagnosis is frequently alcohol or drug-induced psychosis[67]. Differential diagnoses sometimes missed in women include thyroid disease, autoimmune disorder, corticosteroid treatment, and anorexia-related starvation. All these conditions are much more prevalent in women than in men[68,69] and need to be ruled out before a diagnosis of schizophrenia is made.

COMPLEXITY OF THE MENTAL HEALTH SYSTEM

The mental health system in most countries is very complex and leaves individuals who experience mental distress not knowing whether to turn to physicians or social workers or psychologists or spiritual counselors. Family doctors may or may not recognize symptoms of early psychosis and, even when they do, may not know where to refer their patients. Waiting lists for the various mental health professionals are often long. Visits may or may not be covered by available insurance. Navigation services that help patients identify financial, linguistic, cultural, logistical and educational barriers to mental health care and provide guidance to access are badly needed by both women and men[70]. The routes to care differ in the two sexes, obstetricians and midwives sometimes serving as intermediaries for women, and guidance counselors and police more often paving care routes for men.

EFFECTIVE TREATMENT

Treatment is known to be most effective when it is individualized to meet the specific needs of the person being treated. Gender, age, family situation, place of residence, state of health, and personal preferences all play a part in determining optimal intervention. One example is the decision-making process around drug dosing. In women of reproductive age, effective drug doses can usually be lower than doses recommended for men[71-75]. Women's ability to respond at lower doses has been attributed to the effects of female hormones on the absorption and metabolism of AP drugs and also to women's relatively increased blood flow to the brain, carrying with it more drug to cell receptor targets[76]. The presence of estrogen at the dopamine receptor site helps to slow the transmission of dopamine[77], an excess of which is thought responsible for psychotic symptoms.

In addition, because AP drugs are lipophilic and women's reserves of adipose tissue are on average larger than men's, women store these drugs in their bodies for comparatively longer periods. This means that psychotic relapse after drug discontinuation is not as rapid in women[78-80]. It also means that, in theory, the intervals between women's intramuscular depot AP injections can be longer than those in men, but the sex-specific spacing of AP depot drugs has not yet been researched.

Another reason why AP drug doses can generally be

Table 1 Side effects of antipsychotics that negatively affect appearance[124]

Weight gain
Bad teeth
Hirsutism
Acne
Hair loss
Salivation
Slurred speech
Blepharospasm
Parkinsonian gait
Dyskinesias
Urinary incontinence

lower in women than in men is because many women take more concomitant drugs than men do, notably antidepressants, mood stabilizers, analgesics, and contraceptives or hormone replacements, all of which can interact with and influence the blood level of AP medication[78,81].

An important aspect of pharmacotherapy for women is that levels of female hormones change over the course of a monthly cycle and also over reproductive phases such as pregnancy, lactation, and menopause. This affects the dosage requirement of AP medication, *i.e.*, there will be a need for higher doses during low estrogen phases[47-50,82,83]. Adjunctive estrogen or selective estrogen receptor modulators can make treatment more effective and can reduce AP doses and, thus, help to prevent side effects. This applies to both sexes, but is especially applicable to women[84-90].

Besides pharmacotherapy, other aspects of schizophrenia treatment need to be differentiated according to the patient's gender, *e.g.*, substance abuse treatment, cancer screening (breast, prostate, cervix)[91-96], interventions for sexual dysfunction[97-99], contraceptive prescribing[12], treatment of comorbidities (osteoporosis and cardiovascular care for instance[100,101]), safeguards against domestic abuse and victimization[102-108], screening for proclivity to violence[109], provision of parenting support and child custody issues[110-112].

DRUG SIDE EFFECTS

Effective treatment means the removal of symptoms and improvement of function; ideally, it also means freedom from adverse side effects. Side effects cause distress, stop patients from regularly taking the medicines they need, and often cause serious harm to health, perhaps even contributing to the high mortality rate among individuals with schizophrenia[113]. Unfortunately, AP medications have many side effects[114] and on average, women suffer more negative effects than men[115,116]. Women may be more vulnerable than men to adverse drug reactions because the doses recommended when a drug goes on the market are calculated on the basis of a 70 kg man.

There are well-known gender differences in drug reactions. In a recent study of over a thousand patients with psychosis, twice as many women as men described their side effect burden as severe. In this study[117], the effects that women complained of (more than men) included: Concentration difficulties, sedation, blurred vision, nausea, constipation, dizziness on rising, heart palpitations, pruritus, photosensitivity, increased pigmentation, weight change, galactorrhoea and headache.

Women have unique risk factors for some adverse effects of APs, such as Torsade de Pointes[118], which is a form of ventricular tachycardia that occurs in patients whose QT interval is relatively long. The QT interval is a measure of the time between the start of the Q wave and the end of the T wave on the electrocardiogram; it is the time it takes for the heart to come back to normal after depolarization, which, on average, is longer in postpubertal women than it is in men. For this reason, two-thirds of Torsade de Pointes occur in women[118]. That being said, more men with schizophrenia than women die of heart disease. Much remains unknown about gender differences in cardiovascular function and cardiac response to therapeutic drugs.

The hypercoagulability state induced by APs raises the risk for venous thromboembolism, pulmonary embolism, and cerebrovascular accident. The use of oral contraceptives, as well as hormone replacement therapies, pregnancy, the immediate postpartum state, and obstetrical complications are all risk factors for these complications[119]. There are many such factors, however, including ethnicity[120]. Despite the many contributing factors, pregnant women on APs have been shown to be at significantly higher risk for venous thromboembolism than pregnant women in the general population[121,122].

With respect to the potential for AP to heighten the risk of breast cancer *via* weight gain and prolactinemia, the jury is still out[94] on this important concern. What is known, however, is that the cancer death rate of women with schizophrenia is high relative to women in the general population[95], although this cannot be attributed to AP drugs. Many side effects of APs, *e.g.*, weight gain, skin blemishes, and hair loss[123], negatively affect appearance (Table 1)[124]. Women are more sensitive to such effects than men are.

APs also have negative reproductive effects. They can disrupt menstrual cycles[125], interfere with a woman's ability to conceive[126], increase the risk for gestational diabetes[127], increase the risk of premature labor[127] and, by entering breast milk, can make breastfeeding a risk for infants of mothers with schizophrenia[128]. The secondary effect of hyperprolactinemia can lead to hirsutism, amenorrhea, galactorrhea, pseudocyesis[129], and osteoporosis[125].

In addition, older women may be more susceptible than older men to tardive dyskinesia (TD)[114]. It is known that TD prevalence is influenced not only by age and sex, but also by many confounding factors, such as individual genetics[130], the specific AP used, its dose, treatment duration, alcohol, tobacco, and marijuana usage, ethnicity, the precise definition of TD, the rating

scale used to assess TD, the predominant symptoms (positive or negative) and the presence or absence of prior brain damage. Because estrogen modulates dopamine-mediated behaviors and protects against oxidative stress-induced cell damage caused by long-term exposure to AP medication, one hypothesis is that when all the confounding factors are controlled, TD prevalence is equal in women and men prior to menopause and becomes subsequently higher in women[131].

Because of sex differences in immunity, women are also more susceptible to the agranulocytosis inducible by clozapine[132]. In general, older individuals, men as well as women, are at relatively increased risk of adverse effects of all drugs[133].

VOCATIONAL AND AVOCATIONAL OPPORTUNITIES

Women with schizophrenia want meaning in their lives, as do men. Meaning comes in several forms: hope in the future, the belief that one is needed, interest in what one is doing, earning money, engaging in artistic endeavors, pursuing a goal. In our study of clinic members with longstanding schizophrenia, more women than men were working outside the home[134], probably because "women's" jobs were more plentiful at the time in our region. Job availability always depends on time, place, and economic conditions. When homeless, or living in room and board homes or with parents, the housewife role is not readily available to women with schizophrenia. Many prefer self-employment opportunities[135] and appreciate assistance in the form of supported employment, individual placement, and job buddies. They welcome opportunities to learn, to volunteer and to be of help to others. Like men, women need creative channels to enable self-expression as they seek ways to be meaningfully occupied[136].

FREEDOM FROM STIGMA

Stigma (being devalued and discriminated against, with consequent loss of self-respect) is a significant problem in schizophrenia[137]. The diagnostic label of schizophrenia is itself frightening to many people, conjuring up fears of dangerousness, unprovoked and uncontrollable violence, irrationality, and incurability. The population at large does not always appreciate the fact that those who suffer from schizophrenia, and this is especially true for women, are more often victims than perpetrators of violence[138]. Different studies have used different definitions of both violence and of victimization, making these terms difficult to quantify across studies. Within a one-year period, it has been estimated that between 11% and 52% of persons with serious mental illness (SMI) exhibit violence at a 2-8 higher rate than that found in the general population[139]. The same study found rates of victimization in persons with SMI to be between 20% and 42%, 23 times that of the general population. Perpetration of violence and victimization are risk factors for each other and often overlap in the same person. Interestingly, Desmarais *et al*[139] reported higher rates of perpetration of violence among women with SMI than among men. They speculate that this is due to the fact that violence in this population most often occurs in the context of close relatives, and women with SMI are more likely than men to be living with family; consequently, they have more opportunity to vent their rage at domestic targets such as husbands and parents.

Women with schizophrenia are too often victims of sexual exploitation, domestic abuse, and random violence[106-108]. Risk factors are age, place of residence, and degree of psychopathology, in addition to personality and behavioral factors[140]. The factors that contribute to the perpetration of violence have been described by the same research team as substance abuse, young age, homelessness, unemployment, low educational attainment, low socioeconomic status, membership in an ethnic minority, past hospitalization for psychosis, past conviction for violent crime, personality factors, and residence in disorganized neighborhoods[140]. These are risk factors for both women and men, but they occur more frequently in men.

In general, schizophrenia is a heavily stigmatized illness, men perhaps suffering more than women because of the perception that they are prone to act out violently and indiscriminately. Women, however, suffer from a specific form of stigma - the frequent conviction of health workers that individuals with schizophrenia should not bear children, and, in the event of pregnancy, should seek abortion. Women with this illness are widely considered incapable of being good mothers, making prenatal care more problematic, as women fear disclosing that they are pregnant, afraid that their infants will be apprehended at birth[141,142]. Healthcare professionals may not be aware of their own discriminatory attitudes, often communicated inadvertently by words and gestures[143]. Finding effective ways of combating biased attitudes both in oneself and in others is a critical issue for all care providers treating patients with stigmatized illnesses.

RELIEF FROM THOUGHTS OF SELF-HARM AND SUICIDE

In the context of schizophrenia, triggers for male suicidal activity (ideation, attempts, and completed suicide) have been described as being: (1) psychotic symptoms and (2) the prospect of chronic disability, while triggers for suicidal activity in women have been mainly attributed to depression. Male suicides in this population decline with age, whereas this is not the case for women. In a longitudinal study, a 10.5% rate of suicide in the first two years after hospital discharge in men dropped to 0% twenty years later, while women's rate of suicide (6%) was spread more evenly over the twenty years[144].

Table 2 Existential concerns[179,180]

Meaning
Fear
Justice
Mortality
Identity
Relatedness
Freedom of choice

Suicide in women with schizophrenia is not as rare (relative to men) as it is in the general population[145]. The clinical implications are that both depression and substance abuse need to be vigorously treated in patients with schizophrenia because both contribute to impulsive acts of self-harm. In treatment settings, suicidal ideas are often "contagious"[146], with one completed suicide sometimes sparking a series of further self-harm attempts[147]. The index of suspicion needs to be high and suicidal ideation needs to be taken seriously[148].

PHYSICAL HEALTH

The life expectancy of individuals with schizophrenia is significantly shorter than that of the general population, with 90% of deaths attributable to physical illness. The assumption is that early mortality in schizophrenia is secondary, if not to suicide, then to lifestyle factors such as heavy smoking, alcohol abuse, and lack of physical activity[149-151]. More recently, a new understanding of the brain-gut connection[152] has implicated nutritional factors. In addition, there is the probability of shared susceptibility genes between schizophrenia and physical diseases that can decrease health-related quality of life and hasten death, auto-immune disease (*e.g.*, Crohn's disease, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, and ulcerative colitis) being one such category of illness[153].

Social precipitants of early death are critical in this population: Poverty[154], homelessness[155], social isolation[156], poor hygiene[157], malnourishment[158], exposure to toxic substances[159] and adverse treatment effects[114]. High mortality from diabetes, cardiovascular disease and malignancies can, in part, be due to a relative lack of screening, delays in diagnosis, and suboptimal treatment[94,95,160-162]. Javatilleke *et al*[163] conclude their list of causes of lost life expectancy in severe mental illness by pointing out that the range of causes is very broad, with many putative causes varying according to gender.

REPRODUCTIVE HEALTH

Reproductive health includes sexual health (libido, sexual function, the ability to establish and maintain sexual relationships)[99,164,165], menstrual health[47,125,166], the preservation of fertility[167,168], contraception[12], prenatal care[122], pregnancy[18,169], postpartum care[170] and lactation support[171], parenting support and training groups, home visiting, peer support, respite care[111,112,172,173], and menopausal care[49,50,83,174].

Clinicians may not realize that during pregnancy, physiological changes such as delay in gastric emptying and increase in gastric pH prolong the time it takes for AP drugs to reach peak levels. Increased cardiac output steps up blood flow to the liver and may boost the speed of drug elimination. There is an overall increase in body water, which only affects hydrophilic drugs such as lithium, and there is also an increase in the lipid compartment, which provides extra storage space for lipophilic drugs (including APs). The blood flow to the kidneys is increased, as is the glomerular filtration rate, which means a greater degree of renal clearance. The plasma albumin concentration is reduced so that more free drug is available to the brain. Enzyme activity is affected by the increase in pregnancy hormones; some enzymes are affected more than others. For most APs, the net serum concentration in the third trimester is significantly decreased from what it was at the beginning of pregnancy. The exceptions are olanzapine and clozapine, both of which are inactivated by Cytochrome P450 enzyme 1A2, whose activity decreases during the 2nd and 3rd trimester of pregnancy because of rising estrogen levels. This enzyme is also highly inducible by smoking and, since women tend to reduce their cigarette smoking during pregnancy, the activity of this enzyme is further reduced. Therefore, the serum levels of olanzapine and clozapine rise during pregnancy[175-177].

FURTHER AREAS OF CONCERN

There are other areas of concern to women with schizophrenia. Some of these are the availability of crisis support[178], the achievement of nightmare-free restorative sleep[179-182], the safety of treatment settings[104,183], the safety and affordability of housing[184], access to skills training in new technologies[185] and assistance with existential concerns[186,187]. Whereas existential issues such as free will, personal identity, fears for the future, contemplation of mortality, justice concerns, finding meaning in life, and relating to others are all similar in men and women, as women age, they express more security fears, while aging men are more likely to report not being valued and fearing that they are a burden to others. Physical appearance may be more central to identity for women than for men[188] (Table 2).

FUTURE DIRECTIONS

Many of the issues that are critical to the care provision of women diagnosed with schizophrenia stem from a failure to recognize male/female differences in this illness. Sex differences are based in dimorphic brain structure and function, particularly evident in the dopaminergic system that is so crucial to the development of schizophrenia[189]. They are driven by sex hormones, but also depend, to an extent not yet fully understood, on non-gonadal functions of the X and

Y chromosomes because genes on sex chromosomes influence brain development disproportionally to their relatively small number. The number of sex chromosomes, X chromosome inactivation patterns, X-linked imprinting effects, and the indirect effects of sex chromosomes on the expression of autosomal genes all contribute to sex differences in neuropsychiatric disease[190].

Future research into sex differences in brain disorders such as schizophrenia will benefit from a fuller understanding of the causes of sex differences and their effects not only on brain and behavior but also on metabolic, cardiovascular, inflammatory and immune parameters. The field also needs to better understand the timing of the emergence of sex differences. Longitudinal studies that track developmental processes over time are needed. The effect of puberty with its influx of sex-specific hormones on brain maturation needs to be better understood. Biological sex differences need to be disentangled from environmental influences, an important issue for all psychiatric diseases. Sex differences in the brain, whether innate or secondary to exposure and learning, confer differential risk or resilience that fosters or inhibits the expression of specific symptoms, psychiatric diagnoses, and their outcomes.

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