Schizophrenia Research 243 (2022) 120–137

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Gender differences in the association between environment and psychosis

Aysegul Yay Pence [a,1], Lotta-Katrin Pries [b,1], Maria Ferrara [c,d,e], Bart P.F. Rutten [b], Jim van Os [b,f,g], Sinan Guloksuz [b,d,*]

[a] Department of Psychiatry, Gazi University Hospital, Ankara, Turkey
[b] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, the Netherlands
[c] Institute of Psychiatry, Department of Neuroscience and Rehabilitation, University of Ferrara, Ferrara, Italy
[d] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, United States of America
[e] Women Brain Project WBP, Pfisterwisstrasse 14, 8357 Guntershausen, TG, Switzerland
[f] Brain Centre Rudolf Magnus, University Medical Center Utrecht, the Netherlands
[g] King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, UK

ARTICLE INFO

Keywords:
Environment
Gender
Sex
Psychosis
Schizophrenia
Childhood adversity
Obstetric complication
Socioeconomic status
Substance use
Cannabis
Urbanicity
Migration
Season of birth

ABSTRACT

Various environmental exposures have been associated with psychosis spectrum disorder. However, the role of gender in this association has received little attention. Therefore, we conducted a systematic review to evaluate gender-related differences and identified 47 research articles investigating the associations of psychosis with childhood adversity, substance use, urbanicity, migration, season of birth, and obstetric complication in the PubMed database. The findings suggest that childhood abuse may be more strongly associated with a risk to develop psychosis and an earlier age at onset of illness in women than in men. Furthermore, childhood adversity has been associated with the severity of different symptom dimensions in men and women. Growing up in an urban environment and immigration are more strongly associated with psychosis risk in men than in women. Despite a higher prevalence of substance abuse comorbidity in men diagnosed with psychotic disorders, it appears that the association between substance use and psychosis risk may be stronger in women. These findings should be evaluated with caution considering several methodological limitations, limited number of studies, and lack of consistency across results. Overall, although further investigation is needed, our review shows that gender-related differences in the associations of environmental exposures with psychosis expression may exist.

1. Introduction

Environmental factors such as childhood adversity, substance abuse, urbanicity, minority status, birth season, and obstetric complications have been associated with clinical as well as subclinical outcomes of presentations in the psychosis spectrum. Childhood adversity is associated with an increased risk for psychosis (Varese et al., 2012), poor illness course (Gallagher and Jones, 2013), more frequent hospitalization (Rosenberg et al., 2007), and poor response to treatment (Misiak and Frydecka, 2016). Meta-analyses also show that substance use (Large et al., 2014), particularly continued use (Schoeler et al., 2016), is significantly associated with positive psychotic symptoms. Finally, cannabis use, especially higher potency cannabis (Di Forti et al., 2019), is associated with increased risk for schizophrenia (Arseneault et al., 2002; Di Forti et al., 2015; van Os et al., 2002).

Guided by the exposome paradigm (Erzin and Guloksuz, 2021; Guloksuz et al., 2018a; Guloksuz et al., 2018b; Pries et al., 2021), recent research has aimed to comprehend the totality of environmental vulnerability underlying the pathoetiology of psychosis spectrum disorder (PSD) (Erzin et al., 2021; Pries et al., 2020a; Pries et al., 2019; Pries et al., 2020b). Evidence suggests that environmental factors do not work in isolation but that they interact with each other and with genetic background. Interestingly, studies have provided evidence for dose-response relationships between environmental load scores and severity of mental health status as well as outcomes (Barzilay et al., 2019; Guloksuz et al., 2015; Pries et al., 2018; Suliman et al., 2009). Therefore, it is important to have a comprehensive understanding of the effects of the various environmental exposures linked to PSD.

* Corresponding author at: Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Center, P. O. Box 616, 6200 MD Maastricht, the Netherlands.
E-mail address: sinan.guloksuz@maastrichtuniversity.nl (S. Guloksuz).
[1] Shared first authors.

https://doi.org/10.1016/j.schres.2022.02.039
Received 12 August 2021; Received in revised form 27 February 2022; Accepted 27 February 2022
Available online 11 March 2022

Although exposomic liability for schizophrenia explained around 28% of the variance of case (schizophrenia)-control status (Pries et al., 2020a), not all individuals exposed to these environmental exposures develop psychosis. In this regard, it is plausible to argue that gender might play an important role given that the severity of psychosis outcomes is different between men and women (Abel et al., 2010; Ferrara and Srihari, 2021; Ochoa et al., 2012). Studies show that there are gender-related effects of environmental exposures such as childhood adversity (Comacchio et al., 2019b), migration (Cantor-Graae and Pedersen, 2013; Gayer-Anderson et al., 2015), urbanicity (Kelly et al., 2010), and birth season (Martínez-Ortega et al., 2011). Furthermore, environmental factors might have different effects on psychosis outcomes or dimensions of psychopathology in men and women, considering different hormonal (Seeman, 1997; Wise et al., 2001) as well as neurofunctional mechanisms (Kaufman, 2007; Lejbak et al., 2011) at the biological level. For instance, researchers have hypothesized that the neuroprotective effects of estrogens may account for differences in psychosis risk as well as a favorable outcome in women (Häfner et al., 1998; Seeman, 1997). Neurocognitive gender-related differences were also previously shown: Women commonly outperform in verbal tasks (Weiss et al., 2006), whereas men perform better in spatial tasks (Lejbak et al., 2011; Voyer et al., 1995). Finally, the specific society-assigned gender roles may lead to exposure to different stressors at the psychosocial level (Ferrara and Srihari, 2021).

To the best of our knowledge, no systematic review has examined the role of gender in the associations of various environmental factors with psychosis expression. The present review aims to evaluate gender differences in the association of childhood adversity, obstetric

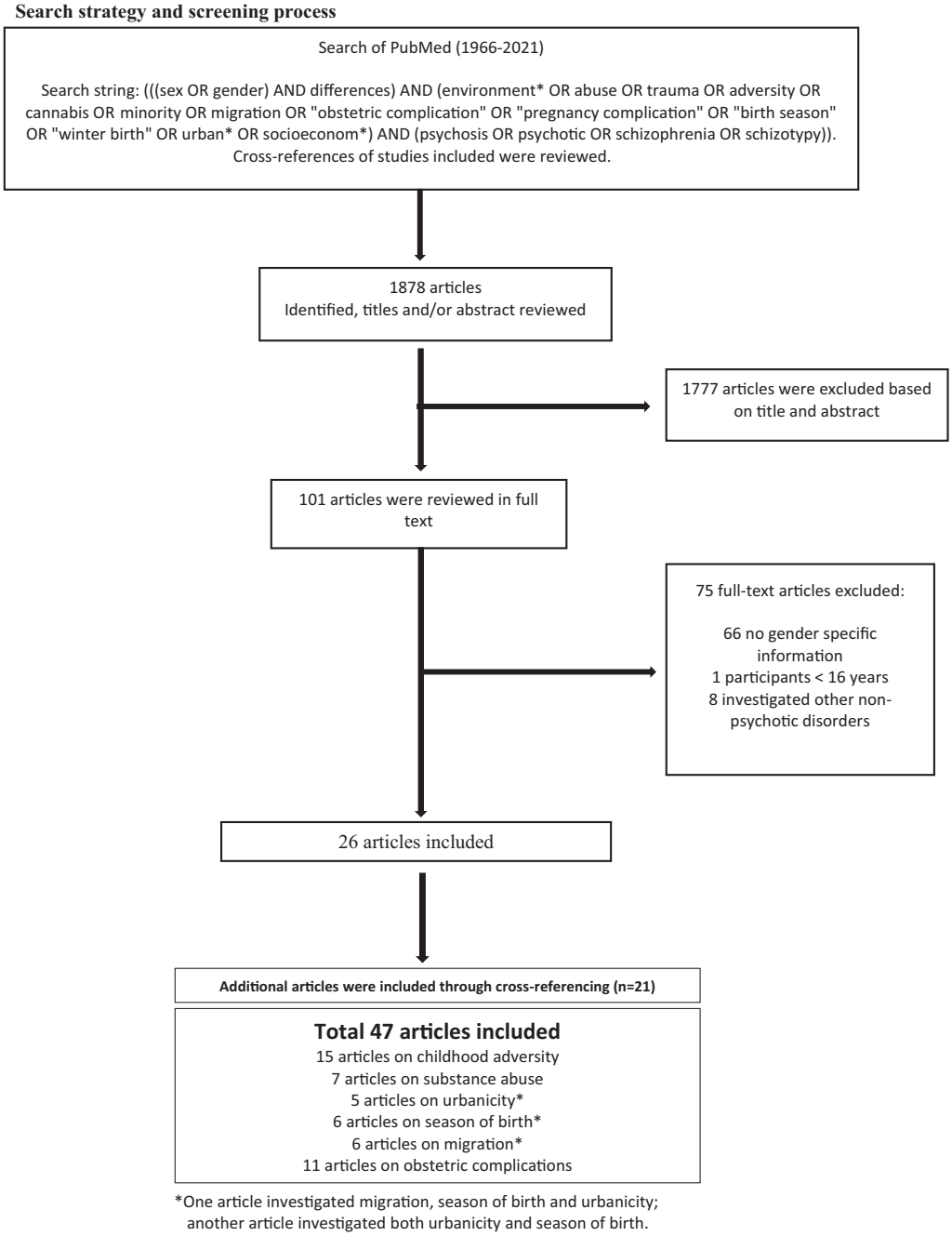

Fig. 1. Search strategy and screening process.
*One article investigated migration, season of birth and urbanicity; another article investigated both urbanicity and season of birth.

complication, socioeconomic status, substance use, urbanicity, migration, and season of birth with psychosis expression, both in clinical as well in general population samples. As studies were very heterogeneous in measures, outcomes and specific comparisons, meta-analysis of effect sizes was not attempted.

2. Methods

2.1. Search strategies

To examine gender differences of the influence of environmental exposure in patients with PSD and individuals with subclinical psychosis expression in the general population, we conducted a systematic search in the PubMed database (1966 up to December 15, 2021) by using the following search string: "(((sex OR gender) AND differences) AND (environment* OR abuse OR trauma OR adversity OR cannabis OR minority OR migration OR "obstetric complication" OR "pregnancy complication" OR "birth season" OR "winter birth" OR urban* OR socioeconom*) AND (psychosis OR psychotic OR schizophrenia OR schizotypy))". We additionally used cross-referencing to identify studies on gender-specific effects fulfilling our inclusion criteria.

2.2. Selection criteria

Our inclusion criteria were: (i) peer-reviewed publications in English; (ii) that examined gender differences in the role of environmental exposure in patients with PSD and individuals with subclinical psychosis expression; (iii) in participants ≥16 years old; (iv) reporting either interaction analyses or stratified analyses for female and male participants. We excluded systematic reviews, meta-analyses, and editorials.

3. Results

The search yielded 1878 articles, of which 47 met the inclusion criteria (see Fig. 1 for the details of the search strategy and the screening process). No original research paper examining the gender-related effects of socioeconomic status was found. We then categorized the findings per environmental factor: childhood adversity, substance abuse, urbanicity, birth season, immigration, and obstetric/pregnancy complications. Table 1 summarizes the main findings.

3.1. Childhood adversity

3.1.1. Risk for psychotic spectrum disorders (PSD) and psychosis expression

The terminology to describe childhood adversity varies across studies. To clarify, in this systematic review, childhood adversity was used to describe the overall childhood adversity that includes domains such as neglect, abuse, and non-intentional events (e.g. loss of parents); whereas the terms such as childhood abuse or childhood neglect were reserved to describe specific childhood adversity domains. Table 2 reports the studies that investigated childhood adversity.

In the ÆSOP study, women with PSD were more likely to report physical and sexual abuse than women without PSD (Fisher et al., 2009; Gayer-Anderson et al., 2015). In men, there were no statistically significant associations between a diagnosis of PSD and either physical or sexual abuse. Furthermore, a recent cohort study of sexually abused youth and matched controls from the general population revealed a significantly higher prevalence of psychotic disorders in individuals with a history of sexual abuse than in matched controls with no history of sexual abuse (Bourgeois et al., 2018). However, contrary to previous case-control studies, no sex differences in the prevalence of psychotic disorders in either the sexually abused or non-abused groups were found. Likewise, one cross-sectional study with a large sample size showed that sexual abuse (especially with penetration) was associated with an increased risk for psychotic disorders for both men (OR = 2.3,

Table 1
Summary of the main findings.

Environmental factor	Author	Conclusions
Childhood adversity	Bourgeois et al., 2018 Comacchio et al., 2019a, 2019b Fisher et al., 2009 Garcia et al., 2016 Gayer-Anderson et al., 2015 Kocsis-Bogár et al., 2018 Mansueto et al., 2019 Pruessner et al., 2019 Ruby et al., 2017 Salokangas et al., 2019 Shah et al., 2014 Toutountzidis et al., 2018 Kelly et al., 2016 Aas et al., 2011 Cutajar et al., 2010	* Several studies suggest that childhood abuse is more strongly associated with the risk of developing psychosis in women than men. * Studies indicate associations between childhood adversity and various symptom patterns differing in men and women. * Childhood abuse seems to be more strongly associated with an earlier age at onset of psychosis in women than in men.
Substance use	Arranz et al., 2015 Donoghue et al., 2014 Gearon and Bellack, 2000 Hodgins et al., 2016 Setién-Suero et al., 2017 Dekker et al., 2012 Rabinowitz et al., 1998	* Substance abuse seems to be associated with PSD and an earlier age at onset of psychosis in both men and women. However, the association may be stronger in women than in men.
Urbanicity	Kelly et al., 2010 Marcelis et al., 1998 Mimarakis et al., 2018 Wang and Zhang, 2017 Allardyce et al., 2001	* Urban-birth appears to be more strongly associated with the risk of developing schizophrenia in men than in women.
Migration	Cantor-Graae and Pedersen, 2013 Dykxhoorn et al., 2019 Kirkbride et al., 2017 Mimarakis et al., 2018 Hollander et al., 2016 Veling et al., 2006	* Migration appears to be more strongly associated with the risk of developing psychosis in men. * Immigrating alone is a risk factor for developing schizophrenia in women, whereas having a child during immigration and immigration to join a family are risk factors in men.
Season of birth	Dassa et al., 1996 Marcelis et al., 1998 Martínez-Ortega et al., 2011 Mimarakis et al., 2018 Eagles et al., 1995 Balestrieri et al., 1997	* Winter-birth might be associated with PSD in both women and men.
Obstetric/pregnancy complications	Byrne et al., 2000 Dalman et al., 1999 Hultman et al., 1997 Kirov et al., 1996 Kendell et al., 1996 Cantor-Graae et al., 1994 Verdoux and	* Findings on the gender-specify effects of OCs are inconclusive. Individual OCs may have different effects on men and women.

(continued on next page)

Table 1 (*continued*)

Environmental factor	Author	Conclusions
	Bourgeois, 1993 Foerster et al., 1991 O'Callaghan et al., 1992 Preti et al., 2000 Zornberg et al., 2000	

PSD: psychosis spectrum disorder, OC: obstetric complication.

95% CI = 1.1–4.9, $p < 0.05$) and women (OR = 2.0, 95% CI = 1.3–3.2, $p < 0.01$) (Cutajar et al., 2010).

Regarding subclinical psychosis expression in the general population, physical and sexual abuse were correlated with schizotypy traits in women, whereas emotional abuse was associated with schizotypy traits in both men and women (Toutountzidis et al., 2018). In a healthy control sample, physically abused women were three times more likely to report psychotic experiences compared to women with no such history, although this association was not nominally statistically significant (OR = 3.1, 95% CI = 0.9–10.5, $p = 0.072$) (Fisher et al., 2009). No statistically significant differences were found in regard to physical abuse in men or in regard to sexual abuse in men and women.

3.1.2. Clinical features, severity, and illness course

Several studies investigated gender-related effects of childhood adversity on symptom severity and illness course. In a very small study, positive symptoms and dysthymia were significantly associated with childhood adversity in male patients with PSD (n = 20), while there were no significant associations in female patients (n = 8) (Ruby et al., 2017). In contrast, another study found associations between childhood adversity and total scores of the Positive and Negative Syndrome Scale (PANSS), negative and depressive symptoms in female patients with PSD and female healthy controls but not in male participants (Garcia et al., 2016). Furthermore, several studies revealed no evidence for gender differences regarding the association of childhood adversity with the severity of psychosis (Shah et al., 2014) or positive symptoms (Kocsis-Bogár et al., 2018) in PSD. A longitudinal study evaluating the course of symptomatic outcomes at three assessment points (baseline, 12 months, and 24 months) showed that childhood adversity was associated with negative symptoms and decreased global functioning in male patients with PSD, depressive symptoms in female patients, and positive symptoms in both (Pruessner et al., 2019).

There is some evidence that subdomains of childhood adversity might be associated with symptom severity. In addition to broad childhood adversity, a longitudinal study by Pruessner and colleagues also investigated the relationship between baseline subdomains of childhood adversity and psychopathology. In male patients with PSD, emotional abuse was associated with positive and depressive symptoms, as well as global functioning at the 24-month follow-up, while emotional neglect was associated with negative symptoms. In female patients, emotional, sexual, and physical abuse predicted depressive symptoms at the 12-month follow-up (Pruessner et al., 2019). Furthermore, in a cross-sectional study, several childhood adversity subdomains were associated with psychopathology in female patients with PSD, but particularly emotional neglect with general psychopathology, positive, negative, and depressive symptoms, as well as global functioning (Garcia et al., 2016). In male patients, the only significant association was between physical abuse and general symptoms. Furthermore, one study that investigated the interaction between sex and physical abuse in a sample of patients with schizophrenia and schizoaffective disorder found that women with abuse history experienced more positive psychotic and depressive symptoms than men with a history of abuse, as well as women and men without a history of abuse (Kelly et al., 2016). Another study showed no sex-related associations of childhood abuse (sexual or physical) with positive or negative symptoms in patients with first episode psychosis (Comacchio et al., 2019a). In both men and women, childhood abuse was associated with negative symptoms but not with positive symptoms.

A cross-sectional study of patients with PSD found that childhood abuse was associated with positive symptoms, disorganization, excitement, and emotional distress in both women and men (Mansueto et al., 2019). Childhood neglect was associated with all psychotic symptom domains in men but only with disorganization and emotional distress in women. Furthermore, in male patients with PSD, the association between childhood neglect and psychotic symptoms (negative symptoms, disorganization, excitement) was mediated by lower attention and vigilance as well as mentalization (Mansueto et al., 2019), while the association between childhood abuse and psychotic symptoms (disorganization, excitement, emotional distress) was mediated by poor working memory, meaning that the negative impact of early traumatic experience on neurocognition might increase the risk of psychosis. No statistically significant interaction was found between childhood abuse or neglect with neurocognition or social cognition on psychotic symptoms in men or women. Another study showed that male patients with childhood adversity performed significantly worse in cognitive functioning tests than male patients without traumatic experiences. However, there were no significant differences in the female group (Aas et al., 2011).

Two studies investigated the association between childhood adversity and suicide in PSD. In one study, childhood adversity was associated with lifetime suicide attempts in female patients with PSD (OR = 1.9, 95% CI = 1.4–2.7, $p < 0.05$), whereas this relationship was not observed in male patients (Shah et al., 2014). Furthermore, a prospective cohort study of clinical high risk for psychosis (Salokangas et al., 2019) investigated the association of suicidal ideation with childhood adversity and its subdomains. In women, total childhood adversity (OR = 1.1, 95% CI = 1.0–1.1, $p = 0.011$), emotional abuse (OR = 1.2, 95% CI = 1.0–1.5, $p = 0.028$), and emotional neglect (OR = 1.2, 95% CI = 1.0–1.4, $p = 0.02$) were associated with suicidal ideation but mainly mediated by clinical depression. In men, total childhood adversity (OR = 1.2, 95% CI = 1.2–1.3, $p < 0.001$), emotional (OR = 1.6, 95% CI = 1.3–2.0, $p < 0.001$), sexual (OR = 1.4, 95% CI = 1.2–1.8, $p = 0.001$), and physical abuse (OR = 1.6, 95% CI = 1.2–2.0, $p < 0.001$) as well as emotional neglect (OR = 1.4, 95% CI = 1.2–1.7, $p < 0.001$) were associated with suicidal ideation but only partially mediated by baseline depressive symptoms.

Research investigating the gender-related environmental effects on clinical features found that childhood physical abuse (Comacchio et al., 2019a; Kocsis-Bogár et al., 2018) and sexual abuse (Comacchio et al., 2019a) were associated with an earlier age at onset in female patients but not in male patients with PSD. On the other hand, non-intentional childhood adversity (e.g. loss of a parent, serious injury) was associated with hospitalization in male (d [Cohen's d] = 0.74) but not in female patients with PSD (Kocsis-Bogár et al., 2018).

3.2. Substance use

Table 3 reports the studies that investigated substance use. In a longitudinal study, male adolescents treated for substance misuse had around a four-fold increased risk for developing psychosis compared to matched male individuals from the general population (OR = 4.24, 95% CI = 2.1–8.2), while the increased risk was above seven-fold in females patients, (OR = 7.04, 95% CI = 2.4–12.2) (Hodgins et al., 2016), thus underlining a possible sex-related vulnerability to psychosis in women with substance misuse. A cohort study of patients with PSD showed that male cannabis users had more severe disorganized symptoms and less severe negative symptoms than male non-users at baseline, whereas there were no significant differences between female subgroups (i.e. substance users and non-users) (Setién-Suero et al., 2017). The longitudinal analysis demonstrated improvement in psychotic and disorganized symptoms regardless of gender and cannabis use. Additionally,

Table 2
Childhood adversity.

Author	Study type	Sample	Environmental exposure	N men/women	Outcome
Gayer-Anderson et al., 2015	Cross-sectional	FEP/HC	* Parental physical abuse * Sexual abuse (by any person ≥5 years older)	FEP: 100/102 HC: 105/161	* Odds of developing psychosis Physical abuse: Women: FEP > HC; Men: FEP = HC Sex-by-abuse interaction (trend significant) Sexual abuse: Women: FEP > HC; Men: FEP=HC Sex-by-abuse interaction (trend significant)
Fisher et al., 2009	Cross-sectional	FEP/HC	* Parental physical abuse * Sexual abuse (by any person ≥5 years older)	FEP: 97/84 HC: 103/143	* Odds of developing psychosis Physical abuse: Women: FEP > HC; Men: FEP = HC Sex-by-abuse interaction (trend significant) Sexual abuse: Women: FEP > HC; Men: FEP = HC Sexual + physical abuse: Women: FEP > HC; Men: FEP = HC * Odds of psychotic experiences in HC Physical abuse: Women: PE > no PE (trend significant); Men: PE = no PE Sexual abuse: Women: PE = no PE; Men: PE = no PE
Bourgeois et al., 2018	Cross-sectional	Youth with sexual abuse history/GP	* Sexual abuse	Each group 221/661	* Prevalence of psychotic disorders Sex-stratified analyses: sexually abused girls and boys are more likely to be diagnosed with a psychotic disorder than girls and boys from the general population. No difference in prevalence between girls and boys with sexual abuse history or girls and boys from the GP
Pruessner et al., 2019	Longitudinal: Baseline (T0) 12-Month (T1) 24-Month (T2)	FEP	* Childhood adversity * Subdomains: physical, emotional neglect, along with physical, emotional, and sexual abuse	144/66	***Symptom severity and functioning** Childhood adversity Women: more depressive (T0, T1), manic (T1) Men: more positive (T2), negative (T0, T2), depressive (T1, T2), total (T2) and lower functioning (T2) Subdomains: Women: emotional, sexual, physical abuse → more depressive (T1) Men: emotional abuse → more positive (T2), depressive (T2), lower functioning (T2); emotional neglect → more negative (T2) * Course of symptomatic outcome using T0, T1, and T2 Childhood adversity: Women: more positive, depressive Men: more positive, negative, and lower functioning
Shah et al., 2014	Cross-sectional	Individuals screened for psychotic experiences, antipsychotic medication, psychotic disorders	* Childhood adversity: sexual, physical, and emotional abuse, along with neglect	1087/738	* Symptom severity Women and men: No significant associations with type of psychosis, course of illness, age at onset of illness, or psychosis symptoms. * Poor functioning Women and men: adversity > no adversity * Lifetime suicidal attempts Women: adversity > no adversity
Kocsis-Bogár et al., 2018	Cross-sectional	Patients with schizophrenia and schizoaffective disorders	* Non-intentional adversities (e.g. loss of a parent) * Physical abuse	49/53	* Number of psychiatric admissions Women: adversity = no adversity; men: adversity > no adversity * Age of onset Women: physical abuse < no physical abuse; men: physical abuse = no physical abuse * Severity of positive symptoms Women: adversity = no adversity; men: adversity > no adversity (trend significant)
Comacchio et al., 2019a	Cross-sectional	FEP	* Sexual abuse * Parental physical abuse	260/184	* Symptom severity Women and men: sexual and physical abuse associated with negative symptoms, but not

(*continued on next page*)

Table 2 (*continued*)

Author	Study type	Sample	Environmental exposure	N men/women	Outcome
					positive symptoms * Age at onset of illness Women: sexual and physical abuse reduced age of onset * Need of care Women and men: sexual and physical abuse associated with unmet functioning
Garcia et al., 2016	Cross-sectional	Early psychosis/HC	* Childhood adversity * Subdomains: sexual abuse, physical abuse, emotional abuse, physical neglect, emotional neglect	Early psychosis: 48/31 HC: 30/28	* Symptom severity in patients Childhood adversity Women: more positive, depressive and general symptoms, lower functioning; men: no association Subdomains: Women: emotional neglect → more positive, negative, general, depressive symptoms, and lower functioning; emotional abuse → more positive symptoms; physical abuse → more depressive symptoms, physical neglect → more negative symptoms Men: physical abuse → more general symptoms * Cognitive functioning Male and female patients: childhood adversity, physical and emotional neglect → poor social cognition Significant sex-by-patient status interaction → speed of processing; attention and vigilance
Mansueto et al., 2019	Cross-sectional	Patients with non-affective psychotic disorder	* Abuse: physical, sexual, emotional * Neglect: physical, emotional	568/189	* Symptom severity Neglect: Women: more disorganized, emotional distress Men: more positive, negative, disorganized, excitement, emotional distress Abuse: Women: more positive, disorganized, excitement, emotional distress Men: more positive, disorganized, excitement, emotional distress * Cognitive functioning Men: neglect and abuse → poor cognitive functioning (different domains) Women: no association between childhood adversities and cognitive functioning
Toutountzidis et al., 2018	Cross-sectional	GP	* Emotional abuse * Sexual abuse * Physical punishment	99/221	* Total schizotypy Significant sex-by-physical punishment interaction shows effect only in women * Schizotypy traits (interpersonal suspiciousness, social anhedonia, social isolation, physical anhedonia, social anxiousness, social discomfort, odd & eccentric, aberrant ideas, aberrant perception) Physical punishment: Women: all but social discomfort; men: no association Emotional abuse: Women: all; men: all but odd & eccentric and aberrant ideas Sexual abuse: Women: aberrant ideas and aberrant perception; men: no association
Salokangas et al., 2019	Longitudinal: Baseline (T0) 9-Month (T1) 18-Month (T2)	Help-seeking CHR	* Childhood adversity * Subdomains: emotional, physical, sexual abuse; emotional and physical neglect	107/131	* Suicidal ideation Women: total childhood adversity, emotional abuse and emotional neglect → suicidal ideation. All associations became nonsignificant when controlling for baseline depression. Men: total childhood adversity, emotional, sexual and physical abuse; emotional neglect → suicidal ideation. The association with sexual abuse and emotional neglect became nonsignificant when adjusting for depression at baseline and the follow ups.
Ruby et al., 2017			* Childhood adversity	20/8	

(*continued on next page*)

Table 2 (*continued*)

Author	Study type	Sample	Environmental exposure	N men/women	Outcome
	Cross-sectional	Patients with schizophrenia and schizoaffective disorders	* Subdomains: physical, emotional and sexual abuse; general trauma experiences		* Symptom severity, brain volume, diurnal salivary cortisol Women: no statistically significant associations with childhood adversity and symptom severity, brain volume, diurnal salivary cortisol Men: childhood adversity → increased positive symptoms and dysthymia; General trauma → reduced whole brain volume, increased amygdala (whole brain volume ratio), and decreased afternoon cortisol; emotional abuse → increased cortisol 30′ after awakening * Cognitive performance Women: general trauma → increased cognitive performance; men: no significant association
Kelly et al., 2016	Cross-sectional	Patients with schizophrenia and schizoaffective disorders	* Physical abuse	56/24	* Symptom severity Positive psychotic and depressive symptoms Significant sex-by-abuse interaction: women with abuse > men with/out abuse, women without abuse Negative psychotic symptom No significant sex-by-abuse interaction Total symptom severity No significant sex-by-abuse interaction * Cognitive functioning No significant sex-by-abuse interaction
Aas et al., 2011	Cross-sectional	FEP (Schizophrenia, bipolar and psychotic depressive disorder)/HC	* Childhood adversity * Subdomains: Physical, sexual abuse, parent loss or separation from a parent for at least 1 year	FEP: 73/65 HC: 64/74	* Neurocognitive performance Male patients: with CT < without CT (executive function and working memory; attention, concentration, and mental speed; language; verbal intelligence) Female patients: no significant association between childhood adversity and cognition
Cutajar et al., 2010	Cross-sectional	Individuals with sexual abuse history/controls from GP	* Sexual abuse	Patients with psychosis: 558/2201 HC: 622/2055	* Odds of psychotic disorders Any sexual abuse Women: associated with schizophrenia and any psychotic disorder Men: associated with any psychotic disorder No significant sex-by-abuse interaction No penetration No significant associations With penetration Women and men: associated with schizophrenia and any psychotic disorder

FEP: first episode psychosis patients, HC: healthy control group, CHR: clinical high risk; GP: general population, DUI: duration of untreated illness, DUP: duration of untreated psychosis.

both female subgroups showed improvement in negative symptoms, whereas male subgroups did not improve. No time-by-group interactions were found in neither men nor women. Similarly, another cross-sectional study with patients with psychosis found that male substance users had more psychiatric symptoms and more thought disturbances than male non-users (Rabinowitz et al., 1998). There was no significant difference in female patients. On the other hand, a smaller cross-sectional study of patients with schizophrenia showed that female and male substance users had more severe positive and general psychiatric symptoms than non-substance users, with larger effect sizes for women (d = 0.81) than men (d = 0.36), providing further evidence for a stronger negative effect of substance use in women compared to what was observed in men (Gearon and Bellack, 2000). A significant sex (male vs female) -by-group (substance vs no substance) interaction was found for global functioning, thereby suggesting that the commonly observed more benign clinical presentation of psychosis in women (Mendrek and Stip, 2011) may be replaced by a poorer clinical presentation (similar to that in men) in substance use comorbidity.

Both cannabis use and male sex were separately associated with an earlier age at onset of psychosis in patients with PSD (Arranz et al., 2015; Dekker et al., 2012; Donoghue et al., 2014; Gearon and Bellack, 2000). However, several studies investigating the age at onset of psychosis also revealed that there might be sex-related effects of cannabis use (Donoghue et al., 2014; Gearon and Bellack, 2000). One study found a reduced age at onset of psychosis in female substance users compared to female non-users, whereas no significant difference was found between the male groups (Rabinowitz et al., 1998). Another study showed that cannabis use reduced the previously found difference in age at onset between female and male patients with PSD (Donoghue et al., 2014). Furthermore, another study demonstrated that the association between substance abuse and a lower age of psychosis onset showed a higher effect size in women (d = 0.64) than in men (d = 0.30) (Gearon and Bellack, 2000). However, one study found that multiple substance use (alcohol, cannabis, cocaine) and male sex were both separately associated with an earlier age of onset, but the interaction between the number of substances and sex was only trend significant ($p = 0.089$) (Arranz et al., 2015).

3.3. Urbanicity

Urbanicity, defined as the impact of living in urban areas at a given time (Vlahov and Galea, 2002), was associated with increased risk for schizophrenia, with likely sex-related differences (Table 4) (Allardyce et al., 2001; Kelly et al., 2010; Marcelis et al., 1998; Wang and Zhang, 2017). Research indicated that the association between the risk to develop schizophrenia and urban settlement was significant in males

Table 3
Substance use.

Author	Study type	Sample	Environmental exposure	N men/ women	Outcome
Donoghue et al., 2014	Cross-sectional	FEP	Lifetime cannabis use before first contact with health service	87/56	* Age at onset of illness Men and cannabis use → earlier age at onset Cannabis use-by-sex interaction: decreased difference between men and women in cannabis users
Gearon and Bellack, 2000	Cross-sectional	Patients with schizophrenia and schizoaffective disorders	DSM-IV diagnosis of drug abuse/dependency 6 month before assessment	38/29	* Symptom severity Positive & general symptoms: users > non-users for men and women * Age at onset of psychosis Users < non-users for men and women * Number of hospitalizations No differences * Ratings of general functioning Cannabis use-by-sex interaction: non-user women > non-user men, user women, user men
Arranz et al., 2015	Cross-sectional	FEP	Using (alcohol, cannabis, cocaine) on a regular basis during the last 12 months, ≥3 times per week for a period of at least one month	85/29	* Age at onset of psychosis Both men and a higher number of substances used → earlier age of onset Trend significant number of substances used-by-sex interaction: higher number of substances → earlier age of onset in men
Hodgins et al., 2016	Longitudinal	Young people treated for substance misuse (CS1, CS2, CS3) & matched individuals from GP	CS1 & CS2: no or sporadic drug use (<1 times/ month); steady drug use (1–8 times/month or unspecified); frequent drug use (>3 times/ week) or drug abuse; dependence. CS3: no or sporadic drug use (<2 times/month); steady drug use (2–10 times/month); frequent drug use (>10 times/month) or drug abuse; dependence.	CS1: 1660/ 332 CS2: 1010/ 566 CS3: 81/ 99	* Risk of developing schizophrenia Women treated for substance misuse → >7-fold increased risk Men treated for substance misuse → ~4-fold increased risk
Setién-Suero et al., 2017	Longitudinal Baseline (T0) 1-Year (T1) 3-Month (T2)	FEP	Cannabis use prior to psychosis onset (verbal report by patients)	186/50	* Age at onset of illness Women and men: users < non-users, no significant difference between men and women among users. Men users had longer DUI and DUP than female users * Symptom severity Cross-sectional Women: no significant differences Men: users had lower negative symptoms, higher disorganized severity, better functioning (on one of two scales). Longitudinal Women and men: users and non-users improved in psychotic and disorganized symptoms, no difference for functioning. Women: users and non-users improved in negative symptoms * Cognitive functioning Cross-sectional Men: users > non-users (attention, motor dexterity, global cognitive functioning) Women: users = non-users Longitudinal Men: non-users improvement in motor dexterity Women: non-users improvement in executive function
Dekker et al., 2012	Cross-sectional	Patients with non-affective psychotic disorder	Cannabis and other drug use – No drug use – Only cannabis – Cannabis and other drugs	599/186	* Age at onset of illness Women: cannabis and other drugs < cannabis < non-users Men: cannabis and other drugs < cannabis < non-users No significant sex-by-use interaction
Rabinowitz et al., 1998	Cross-sectional	Patients with bipolar and major depressive disorder with	Different substances (alcohol, cannabis, stimulants cocaine, hallucinogens, sedatives,	299/242	* Age at onset of illness

(*continued on next page*)

Table 3 (*continued*)

Author	Study type	Sample	Environmental exposure	N men/women	Outcome
		psychotic features and non-organic psychosis	opioids) – No life time abuse or dependence – Remission/mild abuse/dependence – Moderate/severe abuse/dependence		Women: users < non-users; men: no difference * Previous substance abuse treatment, anti-social traits, suicide attempts, current smokers Men and women: users > non-users * Symptom severity (anxiety/depression, anergia, thought disturbance, activation/retardation, hostility/suspiciousness and total score) Men: users > non-users (total score, thought disturbance); women: no differences * Cognitive functioning Men: users > non-users Women: moderate/severe users > non-users

FEP: first episode psychosis patients, HC: healthy control group; GP: general population, DUI: duration of untreated illness, DUP: duration of untreated psychosis.

Table 4
Urbanicity.

Author	Study type	Sample	Environmental exposure	N men/women	Outcome
Marcelis et al., 1998	Longitudinal Birth cohorts followed up for psychiatric admission	GP	First definition: 3-Level population density/per km: lowest: <500; highest: >1500 Second definition: Birth in the highest population density area (the Netherlands)	42,115 cases of psychosis (the number of men and women were not reported)	* Incidence of schizophrenia, affective psychosis, and other psychosis Sex-by-urbanicity interaction: the effect of urbanicity on psychosis was 5% larger for men than women
Kelly et al., 2010	Cross-sectional	Patients with psychosis/GP	Urban: 15.11 persons/ha Rural: 0.29 and 0.41 persons/ha	Total number of patients with psychosis: 171 urban/153 rural (the number of men and women were not reported)	* Incidence of schizophrenia Women: urban > rural (trend significant) Men: urban > rural * Incidence of affective psychosis Women and men: urban < rural
Wang and Zhang, 2017	Cross-sectional	Chinese pre-famine, famine, and post-famine cohorts screened for schizophrenia	Urban-rural residency	Pre-famine: 60,637/59,650 Famine: 40,770/40,509 Post-famine: 74,959/75,470	* Risk for schizophrenia Women: urban < rural Men: urban > rural Women and men: famine > post-famine > pre-famine cohorts
Mimarakis et al., 2018	Cross-sectional	GP (Adolescents)	Urbanicity: <5000, 5000–10,000, 10,001–50,000, >50,000 inhabitants/km^2	192/253	* Schizotypy trait scores Women: total score/magical thinking/unusual experiences: urban > less urban Men: no differences
Allardyce et al., 2001	Cross-sectional	Patients with (OPCRIT-generated) schizophrenia & GP (census data)	Urban: Camberwell area/London Rural: Dumfries and Galloway area/Scotland	152/113	* Risk of schizophrenia Men and women: urban > rural Significant sex-by-urban interaction Men > women: increased risk due to urban living

HC: healthy control group; GP: general population, DUI: duration of untreated illness, DUP: duration of untreated psychosis.

(Incidence Risk Ratio [IRR] = 1.9, 95% CI = 1.5–2.4), while it was only trend significant in females (IRR = 1.3, 95% CI = 1.0–1.8) (Kelly et al., 2010). In another study, although urban living was associated with an increased risk for schizophrenia in both men and women, the significant interaction between sex and urbanicity (IRR = 0.7, 95% CI = 0.5–1.0) indicated that the increased risk was higher in men than in women (Allardyce et al., 2001). Similarly, another study revealed that the association between urban exposure and PSD was slightly but statistically significantly greater (likelihood ratio test = 10.6, $p < 0.001$) for men (IRR = 1.3, 95% CI = 1.3–1.3) than women (IRR = 1.3, 95% CI = 1.2–1.3) (Marcelis et al., 1998). Moreover, a large Chinese birth-cohort study (pre, post, and during a famine period) found that the risk for schizophrenia was higher in urban residents than in rural residents in the total sample (OR = 1.2, 95% CI = 1.2–1.2, $p < 0.001$) and in the male subsample (OR = 1.5, 95% CI = 1.5–1.6, $p < 0.001$), whereas the risk was lower in urban residents than in rural residents in the female subsample (OR = 0.9, 95% CI = 0.9–1.0, $p < 0.001$) (Wang and Zhang, 2017). Conversely, in another study, the risk for affective psychosis was lower in urban than in rural areas for both men (IRR = 0.5, 95% CI = 0.3–0.7) and women (IRR = 0.6, 95% CI = 0.4–0.8) (Kelly et al., 2010). An investigation of the association between urbanicity and schizotypy traits in non-clinical young population (age: 17 to 22 years) showed that urbanicity might be associated with magical thinking and unusual experiences in women, whereas no significant association between

schizotypy and urbanicity was detected in men (Mimarakis et al., 2018).

3.4. Migration

Six studies investigated the effect of migration by sex with PSD (Cantor-Graae and Pedersen, 2013; Dykxhoorn et al., 2019; Hollander et al., 2016; Kirkbride et al., 2017; Mimarakis et al., 2018; Veling et al., 2006) (See Table 5). In a large Danish birth-cohort study, both the first and the second-generation immigrant men were more likely to develop PSD than immigrant women. Among first generation immigrants, the probability of PSD before the age of 40 was 3.10% (95% CI = 2.6–3.8) in men and 1.96% (95% CI = 1.5–2.5) in women (Cantor-Graae and Pedersen, 2013). Furthermore, a study found an interaction between sex and the immigration status on non-affective psychotic disorders (Hollander et al., 2016). Although both men and women with immigration background were more likely to develop psychotic disorders than others, the association was more pronounced in men. Another study showed that both first and second-generation immigrant men and women had an increased incidence of schizophrenia (Veling et al., 2006).

Similarly, a recent study examining the sex-stratified effects of immigrant status on schizotypy traits in adolescents indicated that the immigration status was associated with unusual experiences and paranoid ideation in men but not in women (Mimarakis et al., 2018). However, another study investigating the incidence rates of first episode psychosis in different ethnic-minority groups in England found no sex-related effect of ethnicity on psychosis (Kirkbride et al., 2017).

A population-based cohort study of individuals who immigrated to Sweden showed sex-related differences in the impact of family networks during immigration (Dykxhoorn et al., 2019). Although the pattern and the strength of the associations varied by the region of origin, women immigrating alone (HR [Hazard ratio] = 1.3, 95% CI = 1.1–1.6) were at higher psychosis risk than women immigrating with their families (HR = 0.9, 95% CI = 0.8–1.1) in the whole sample. However, men immigrating to join a family (HR = 1.3, 95% CI = 1.2–1.5) and men immigrating with their dependent children (HR = 1.6, 95% CI = 1.1–2.4) had increased risk for psychosis.

3.5. Birth season

Six studies evaluated sex-related effects of the season of birth on the development of schizophrenia and schizotypy traits (Table 6) (Balestrieri et al., 1997; Dassa et al., 1996; Eagles et al., 1995; Marcelis et al., 1998; Martínez-Ortega et al., 2011; Mimarakis et al., 2018). A study including individuals with schizophrenia and other psychotic disorders demonstrated that compared with the expected estimates in the general population, winter-birth was more prevalent in male patients with schizophrenia, while autumn-birth was less prevalent (winter: 32.6% vs 25.9%; autumn: 19.6% vs 24.8%) (Martínez-Ortega et al., 2011). Furthermore, the proportion of men diagnosed with schizophrenia who were born in January was higher than expected. There were no significant differences in season of birth in female patients diagnosed with schizophrenia. Conversely, among patients diagnosed with psychotic disorders other than schizophrenia, winter-birth was more prevalent than expected in women (34.1% vs 24.3%), but there were no significant differences in men. In another study, the number of male patients with schizophrenia born in November–January was higher than expected, whereas no association was found in the total sample (Balestrieri et al., 1997). Another small sample sized study (Dassa et al., 1996) investigated the proportion of the season of birth in patients with schizophrenia in relation to a family history of psychiatric disorders. Female patients without a family history had more deliveries in the winter than what would be expected according to the estimated distribution of live birth from general population data; there were no differences in male patients. Another study examining the changes of the ratio of winter/

Table 5
Migration.

Author	Study type	Sample	Environmental exposure	N men/women	Outcome
Cantor-Graae and Pedersen, 2013	Longitudinal population registers	GP (living in Denmark)	Country of birth as well as mother's country of residence at person's birth	Total N: 1,859,419 (the number of men and women were not reported)	* Incidence of psychiatric disorders Increased incidence of schizophrenia and schizophrenia spectrum disorder for men compared to women among first and second generation (both parents) immigrants.
Kirkbride et al., 2017	Cross-sectional	FEP & Census data (to estimate population at risk) (living in the United Kingdom)	Self-rated ethnicity	FEP: 459/228	* Incidence rates of FEP No sex-specific effect of ethnicity on psychosis
Dykxhoorn et al., 2019	Longitudinal population registers	GP (individuals who immigrated to Sweden)	Family network during immigration	Total N: 423,788/414,929 Total psychosis: 3584/2432	*Incidence for non-affective psychotic disorder Women: immigrating not alone < immigrating alone Men: to join family > not to join family; with child > without child
Mimarakis et al., 2018	Cross-sectional	GP (young people living in Greece)	Immigrant status	192/253	* Schizotypy trait scores Women: no differences Men: total score/paranoid ideation/unusual experiences: immigration status > no immigration status
Hollander et al., 2016	Longitudinal population registers	GP (living in Sweden)	Immigrant status (Refugee, other migrant, person born to two Swedish-born parents)	Total N: 79,863/77,668 Patients: 2078/1626	* Incidence of non-affective psychotic disorder Refugee > Swedish-born (men and women) Migrant > Swedish-born (men and women) Refugee > migrant (only men) Significant sex-by-status interaction: men > women Immigrant/refugee > Swedish-born (especially from sub-Saharan Africa)
Veling et al., 2006	Cross-sectional	Patients with schizophrenic disorders (living in the Hague/the Netherlands)	Immigrant status (first and second generation)	217/91	* Incidence of schizophrenia First generation: Men and women: immigration > native-born Second generation: Men and women: immigrants > native-born

FEP: first episode psychosis patients, HC: healthy control group; GP: general population, DUI: duration of untreated illness, DUP: duration of untreated psychosis.

Table 6
Birth season.

Author	Study type	Sample	Environmental exposure	N men/women	Outcome
Martínez-Ortega et al., 2011	Cross-sectional	Patients with schizophrenia and other psychotic disorders & GP data	Winter: December–February Spring: March–May Summer: June–August Autumn: September–November	423/192	* Proportion of winter-birth Women: patients with schizophrenia > expected (trend significant); patients with other psychosis > expected Men: patients with schizophrenia > expected; patients with schizophrenia born in 1941–1959 > patients with schizophrenia born after 1959 * Proportion autumn-birth Men: patients with schizophrenia < expected * Proportion of January birth Male patients with schizophrenia < expected form population data, female patients with schizophrenia
Marcelis et al., 1998	Longitudinal Birth cohorts followed-up for psychiatric admission	GP	Winter: January–March and December–February	42,115 cases of psychosis (the number of men and women were not reported)	* Incidence of schizophrenia, affective psychosis, and other psychosis Winter birth → increased risk for psychosis with a stronger trend in women
Mimarakis et al., 2018	Cross-sectional	GP (young people)	Winter: December–April	192/253	* Schizotypy trait scores Women: no differences Men: total score/magical thinking/paranoid ideation: winter-birth > other Sex-by-winter birth interaction for total scores
Dassa et al., 1996	Cross-sectional	Patients with schizophrenia with/without a family history of psychotic disorders & GP data	Winter: December–February Spring: March–May Summer: June–August Autumn: September–November	296/172	* Proportion of winter birth vs other seasons Women: patients without family history > expected
Balestrieri et al., 1997	Cross-sectional	Patients with schizophrenia & GP data	– Individual month – Sets of 3 consecutive months	101/104	* Proportion of winter birth vs other seasons Individual month: No differences between patient's and expected birth month 3 consecutive months: Men were more likely to be born in November–January
Eagles et al., 1995	Cross-sectional	Patients with schizophrenia	Winter/spring: December–May Summer/autumn: June–November	1935/1620	* Changing of season-birth effect from 1900 to 1969 Men: increase in the proportion of winter/spring vs summer/autumn birth from 1900 to 1969 Women: no significant change

HC: healthy control group; GP: general population, DUI: duration of untreated illness, DUP: duration of untreated psychosis.

spring to summer/autumn births over seven decades found that male patients with schizophrenia had an increase in the proportion of winter/spring birth from 1900 to 1969 (Eagles et al., 1995). There was no significant change in female patients.

A cohort study investigating the effects of the season of birth of adolescents with schizophrenia traits found that men who were born in winter were more likely to report psychotic traits, such as magical thinking and paranoid ideation, compared to men who were born in other seasons, whereas such difference was not found in women (Mimarakis et al., 2018). However, a large Dutch longitudinal cohort study showed that winter-birth was associated with the risk of a later diagnosis of PSD, with a stronger association in women (both in urban and rural-born individuals) (women, IRR = 1.7, 95% CI = 1.5–1.9; men, IRR = 1.6, 95% CI = 1.4–1.7) (Marcelis et al., 1998).

3.6. Obstetric/pregnancy complications

The definition of obstetric complications (OCs) varies across studies that used a variety of OCs scales, including study-specific scales that were constructed by researchers for a particular study. Therefore, concurring with the terminology of these studies, the term OCs was used in the current review. Eleven studies analyzed sex-related effects of OCs on the risk for PSD, and two studies also examined the effect of OCs on age at onset of illness (Table 7).

The majority of the studies did not find a significant sex difference in the association of OCs with PSD (Foerster et al., 1991; Hultman et al., 1997; Kirov et al., 1996; Preti et al., 2000; Zornberg et al., 2000). Furthermore, studies that found significant sex differences had conflicting results. By applying sex-stratified analyses, one study found that female patients with schizophrenia had more perinatal and pregnancy complications than HCs, whereas male patients with schizophrenia showed no such significant differences (Verdoux and Bourgeois, 1993). In contrast, another study that used two different scales for measuring OCs (the Parnas Scale and the Lewis Scale) showed that male patients with schizophrenia (especially when diagnosed before the age of 30) had more OCs than HCs. For the female groups, either no differences between HCs and patients were found or patients were less frequently exposed to OCs than HCs (Byrne et al., 2000). Of note, the results were dependent on the OC scale that was used (Table 7). Another study found that both male and female patients experienced complications during pregnancy and delivery more often than their matched HCs (Kendell et al., 1996).

Table 7
Obstetric complications.

Author	Study type	Sample	Environmental exposure	N men/women	Outcome
Byrne et al., 2000	Cross-sectional	Patients with schizophrenia/matched HC	* Lewis scale: definite, equivocal, any complications * Parnas scale: frequency, severity, total Source of information: – Birth records	Each group: 256/175	* Odds of schizophrenia Individual OCs Cesarean section: men: patients > HC Low birth weight: women: patients > HC Lewis scale Women any age: patients < HC (any OCs) Men any age: patients = HC; men diagnosed before the age of 30 years: patients > HC (definite OCs) Parnas scale Women any age: no association Men any age: patients > HC (frequency); men diagnosed before the age of 30 years: patients > HC (frequency, severity, total)
Dalman et al., 1999	Longitudinal Birth cohorts followed-up for diagnosis of schizophrenia	GP	* Etiological mechanisms: Fetal malnutrition (preeclampsia, small for gestational age, small ponderal index) Extreme prematurity (delivery < week 33) Hypoxia or ischemia around birth (cesarean section and vacuum extraction, breech delivery, placental abruption, low Apgar score) Source of information: – Birth records	Cohort population: 507,516 Patients with schizophrenia: 139/99	* Relative risk/odds for schizophrenia Individual adversities Women: maternal history of still-birth, lower birth weight (≤1499 g) → schizophrenia risk Men: parity ≥ 4, preeclampsia, uterine inertia, vacuum extraction, lower birth weight (1500 g–2499 g), ponder index < 20, small for gestational age, type 2 malformation → schizophrenia risk Etiological mechanism Men: malnutrition (especially preeclampsia) → schizophrenia risk Women: prematurity → schizophrenia risk
Hultman et al., 1997	Cross-sectional	Patients with schizophrenia and patients with transient psychotic symptoms/matched HC	* Non-optimality score: optimal = positive notion or discharged as healthy; Low risk: ≥ 0 points; Middle risk: 2–6 points; High risk: ≥ 7 points Source of information: – Birth records	Patients: 76/31 HC: 152/62	* Non-optimality score Patients > HC; no significant group-by-sex interaction * Birth size measures (Birth weight, head circumference, length) Group-by-sex interactions → birth weight/head circumference: female patients < female control < male control < male patients
Kirov et al., 1996	Cross-sectional	Patients with psychosis (schizophrenic, affective psychosis)/HC	Lewis scale * Only definite Source of information: – Relatives' reports (mother, father, and sibling) – Hospital record (just for one patient)	Patients: 116/68 HC: 66/34	* Frequency of obstetric complications No significant difference between male and female patients * Age at onset of psychosis (follow-up analyses in only white – British and Irish – individuals) Men: patients with OC < patients without OC No significant OC-by-sex interaction
Kendell et al., 1996	Cross-sectional	Patients with schizophrenia/matched HC	* Pre-existing maternal illness * Pregnancy * Delivery * Puerperal Source of information: – Birth records	Each group: 80/35	* Frequency of obstetric complications (follow-up analyses of significant associations) Preeclampsia, non-spontaneous delivery Men and women: no differences Any complications of pregnancy, any complications of delivery Men and women: patients > HC Detention in hospital for neonatal care: Men: no difference Women: patients > HC
Cantor-Graae et al., 1994	Cross-sectional	Patients with schizophrenia/matched HC	Revised McNeil-Sjöström Scale * Summary score with OCs of severity ≥ 4 Source of information: – Birth records	Each group: 42/28	* Odds for schizophrenia Frequency of OCs Stratified by sex Men and women: no differences Stratified by sex and season of birth Men born in winter: patients > HC (trend) Women: no differences Stratified by sex and family history Men with no family history:

(*continued on next page*)

Table 7 (*continued*)

Author	Study type	Sample	Environmental exposure	N men/women	Outcome
					patients > HC Women: no differences
Verdoux and Bourgeois, 1993	Cross-sectional	Patients with schizophrenia/patients with bipolar disorder/HC	* Pregnancy * Perinatal (adjusted Parnas scale: frequency, severity, total) Source of information: – Maternal report	Schizophrenia: 17/6 HC: 12/11 Bipolar: 12/11	* Risk for schizophrenia Pregnancy Women: schizophrenia > HC; schizophrenia > bipolar Men: no differences women with schizophrenia > men with schizophrenia (trend) Perinatal (frequency, severity, total) Women: schizophrenia > HCs; schizophrenia > bipolar Men: no difference Women with schizophrenia > men with schizophrenia (severity, total)
Foerster et al., 1991	Cross-sectional	Patients with schizophrenia/patients with affective psychosis	Lewis scale * Definite * Equivocal * Any Source of information: – Maternal report	Schizophrenia: 35/10 Affective psychosis: 12/16	* Frequency of obstetric complications No difference between male and female patients with schizophrenia * Birth weight Men: schizophrenia < affective Women: no differences No significant difference between male and female patients (problem: male patients with schizophrenia had lower birth weight than other patients, but higher birth weight than women)
O'Callaghan et al., 1992	Cross-sectional	Patients with schizophrenia/matched HC	Lewis scale * Definite + Equivocal Parnas scale * Frequency, severity, total Source of information: – Birth records	Each group: 35/30	* Frequency of obstetric complications Male patients > female patients Male HC = female HC * Age at onset of illness (explorative) Men: patients with OCs < patients without OCs Women: no difference
Preti et al., 2000	Cross-sectional	Patients with PSD/matched HC	* Any somatic complication occurring during pregnancy (with potential harm) * McNeil-Sjöström Scale: severity (OCs with the severity of 4–6) Source of information: – Birth records	Each group: 31/13	* Frequency of obstetric complications Male patients = female patients Male controls = female controls
Zornberg et al., 2000	Longitudinal	GP	Hypoxic-ischemia related fetal/neonatal complications *Severity Source of information: – Birth records	Sample population: 304/389 (19 with PSD)	* Odds for psychosis With OC > without OC No significant OC-by-sex interaction

HC: healthy control group; GP: general population; OC: obstetric complication; PSD: psychosis spectrum disorder.

The results were also inconclusive when comparing female and male patients with schizophrenia. Female patients with schizophrenia had more severe perinatal complications than male patients (Verdoux and Bourgeois, 1993). However, another study found that male patients with psychosis were significantly more likely to experience at least one OC than female patients (OR = 4.2, 95% CI = 1.4–12.9, $p = 0.02$) (O'Callaghan et al., 1992).

Several studies focused on the effects of individual obstetric complications and adversities, especially birth weight. One study found a group (case/control)-by-sex interaction and showed that female patients had lower birth weights compared to male patients (Hultman et al., 1997). Two studies found that more female patients had a low birth weight (<2500 g (WHO, 2022)) compared to female HCs (Byrne et al., 2000; Dalman et al., 1999), whereas only one study found a difference in male groups (Dalman et al., 1999). Eventually, Dalman et al. showed that a higher risk for schizophrenia was associated with malnutrition indicators such as preeclampsia, small for gestational age, as well as small ponderal index in males (OR = 2.3, 95% CI = 1.4–3.8), and with prematurity in female patients (OR = 5.0, 95% CI = 1.6–16.0) (Dalman et al., 1999). A case-control study found no sex difference in any OCs except that more female patients than their matched HCs were hospitalized for neonatal care (OR = 10.0, 95% CI = 1.4–434, $p = 0.01$) (Kendell et al., 1996). It must be noted that the methodological differences between studies make comparisons and drawing conclusions difficult.

Two studies investigated the sex effect of OCs on age at onset of PSD (Kirov et al., 1996; O'Callaghan et al., 1992). Both studies found an effect of OCs on age at onset in male patients but not in female patients. However, a follow-up analysis did not find a significant interaction between OCs and sex (Kirov et al., 1996).

4. Discussion

The present paper reviewed studies investigating gender-related effects of environmental factors such as childhood adversity, substance use, migration, urbanicity, season of birth, and obstetric complications in psychosis expression. Although inconsistent findings and methodological differences between studies make it difficult to draw clear

conclusions, our findings suggest that there may be gender-related differences in the impact of several environmental factors on psychosis expression, as well as clinical features, symptom severity, and illness course of PSD.

4.1. Childhood adversity

Findings from research investigating sex-related effects of childhood adversity on psychosis has been inconsistent. Some studies suggest that childhood abuse (specifically, sexual and physical) has a more prominent role in women than in men (Fisher et al., 2009; Gayer-Anderson et al., 2015; Toutountzidis et al., 2018), with two of these studies likely using overlapping samples from the ÆSOP study (Fisher et al., 2009; Gayer-Anderson et al., 2015). A recent study with a large sample size indicated no significant difference in the prevalence of PSD between women and men with sexual abuse history (Bourgeois et al., 2018).

In terms of symptomatology, female patients with PSD show a higher rate of depressive symptoms compared with male patients, especially during an acute episode, whereas male patients exhibit more negative symptoms (Ferrara and Srihari, 2021; Ochoa et al., 2012; Thorup et al., 2014). This pattern might be driven by sex-related influence of childhood adversity (Thorup et al., 2014); however, they may also represent generic sex-related effects. Although findings have been inconsistent, a few studies investigating symptom patterns provide support for these sex differences (Garcia et al., 2016; Kelly et al., 2016; Pruessner et al., 2019). Studies investigating the associations of childhood adversity domains (i.e., neglect and abuse) with symptom patterns varied methodologically and yielded inconclusive findings. These studies showed that neglect and abuse were associated with the severity of various symptom patterns in patients with PSD (Garcia et al., 2016; Kocsis-Bogár et al., 2018; Mansueto et al., 2019), in FEP (Comacchio et al., 2019a; Pruessner et al., 2019) as well as schizotypy in the general population (Toutountzidis et al., 2018).

Only two studies included in this review investigated the sex-stratified effect of childhood adversity on suicidal behaviors or thoughts. The early study indicated an association of childhood adversity with suicidal attempts in female patients with PSD (Shah et al., 2014), while the other study suggested an association with suicidal ideation in both male and female patients (Salokangas et al., 2019).

The onset of psychotic disorders is earlier in men, with an average of one to five years (Eranti et al., 2013). Childhood physical and sexual abuse are associated with an earlier age at onset in both men and women, but the association appears to be stronger in women (Comacchio et al., 2019a; Kocsis-Bogár et al., 2018). Given the decreased age gap at onset in those with childhood abuse history, it appears that childhood adversity in women may be associated with a reduced time to illness onset, which is associated with poor outcome over the course of PSD.

Of note, studies investigating childhood adversity have applied diverse methodological approaches. Some studies examined severe childhood adversity (Kocsis-Bogár et al., 2018; Shah et al., 2014), while others set the threshold lower, including moderate to severe childhood adversity (Fisher et al., 2009; Gayer-Anderson et al., 2015). The definition of childhood adversity varied across studies that focused on different domains and types, such as emotional abuse and physical neglect, and sexual abuse. In this regard, future studies that aim to investigate the sex-related differences in childhood adversity should apply consistent methodological approaches to allow for comparability and replication.

4.2. Substance use

Substance use (Large et al., 2011) has been associated with earlier age at onset of psychosis (Blanchard et al., 2000; Bühler et al., 2002; Sevy et al., 2010), with a stronger association in female patients (Donoghue et al., 2014; Hodgins et al., 2016; Rabinowitz et al., 1998). Although the age at onset of psychosis in men with a history of substance abuse was still earlier than women with substance abuse history, the gender gap in age at onset was substantially reduced in women with substance abuse history (Donoghue et al., 2014). Furthermore, women who were treated for substance misuse had 7-fold risk to develop psychosis. In comparison, the risk for psychosis in men with substance abuse history increased around 4-fold (Hodgins et al., 2016). In this regard, substance use, particularly cannabis use, may increase the risk for psychosis in women more than in men. This finding might be related to mechanisms such as the telescoping phenomenon, a fast progression from the initial onset of substance use to complaints and treatment, in women (Hernandez-Avila et al., 2004). However, findings from studies investigating the sex-related impact of substance abuse on symptom severity have been inconsistent, which might be explained by methodological differences across studies (Gearon and Bellack, 2000; Setién-Suero et al., 2017). Furthermore, female patients with comorbid substance abuse might have been underrepresented in studies thus far. Moreover, the majority of studies did not assess the timing, frequency, and amount/potency of substance use, which might impact outcomes differently in men compared to those in women.

4.3. Urbanization

Urbanicity may have a stronger association with schizophrenia risk in men than in women (Allardyce et al., 2001; Kelly et al., 2010; Marcelis et al., 1998; Wang and Zhang, 2017). However, only one study directly tested the interaction between sex and urbanicity in association with psychosis (Marcelis et al., 1998), and the difference in risk was very small. Furthermore, it is possible that the greater effect of urban-birth and urban-residency observed in men may be confounded by the greater risk for schizophrenia in men (Abel et al., 2010; Morgan et al., 2008).

4.4. Migration

There are only a few studies examining the sex-related effects of immigration on the incidence of PSD (Cantor-Graae and Pedersen, 2013; Dykxhoorn et al., 2019; Hollander et al., 2016; Veling et al., 2006), incidence of FEP (Kirkbride et al., 2017), and the manifestation of schizotypy (Mimarakis et al., 2018). Therefore, it is difficult to draw a conclusion on whether there might be sex-related differences. Nevertheless, some of the sex differences observed in these studies are noteworthy. It seems that immigrant men have a higher risk than women to develop PSD (Cantor-Graae and Pedersen, 2013) and schizotypy traits (Mimarakis et al., 2018). Gender roles, in other words, different societal expectations for men and women, may help understand these differences (Geist and McManus, 2012; Greenman and Xie, 2008; Shauman and Noonan, 2007). For instance, family structures during immigration may have different effects on women and men. It appears that being alone without a family connection or support while immigrating might be a risk factor for psychosis in women but not in men, whereas immigrating with a dependent child might be a risk factor in men but not in women (Dykxhoorn et al., 2019). These differences may be explained by the fact that women already take major responsibility for their children (Ferrara and Srihari, 2021), and immigrating with them does not add additional stress. For men, taking care of a dependent child may create a significant amount of stress. On the other hand, the importance of the family network for female migrants might be explained by the family's social support protecting them from the stressors of immigration, such as social isolation and discrimination (Anjara et al., 2017). Additionally, although immigration can be a burden for women, potential employment opportunities can be a protective factor by increasing their independence and empowerment in society (Foner, 1998; MenjÍVar, 1999).

4.5. Season of birth

We retrieved six studies that investigated the sex-related impact of the month of birth on the risk for psychotic disorders (Balestrieri et al., 1997; Dassa et al., 1996; Eagles et al., 1995; Marcelis et al., 1998; Martínez-Ortega et al., 2011) and schizotypy in the general population (Mimarakis et al., 2018). Interestingly, a study suggested that winter birth is associated with schizophrenia in men but with psychotic disorders other than schizophrenia in women (Martínez-Ortega et al., 2011). It is possible that similar prenatal stressors might have sex-related effects (Bale and Epperson, 2015; DiPietro and Voegtline, 2017; Martin et al., 2017). However, psychotic disorders other than schizophrenia in women might indeed be a representation of schizophrenia with better outcomes considering that women with psychosis generally display a less severe form of psychosis with better functioning and fewer hospitalizations, which—as some have suggested—may be attributed to the effect of estrogen (Grossman et al., 2006; Wise et al., 2001). The largest study investigating the link between season of birth and schizophrenia indicated that winter birth was associated with increased risk for psychosis in the general population, especially in women (Marcelis et al., 1998). However, the researchers only found weak associations and information on the sample size per sex was not provided. The scarcity of studies investigating the sex-related effects of winter-birth on psychosis and their limited sample size prevent further interpretation.

4.6. Obstetric/pregnancy complications

We retrieved eleven studies investigating the sex-related impact of OCs on PSD. Five studies did not find sex-related differences (Foerster et al., 1991; Hultman et al., 1997; Kirov et al., 1996; Preti et al., 2000; Zornberg et al., 2000). A study indicated male patients were more frequently exposed to OCs than female patients (O'Callaghan et al., 1992), whereas another study with a very small sample size found that female patients had more severe perinatal complications than male patients (Verdoux and Bourgeois, 1993). Furthermore, the findings of studies conducting sex-stratified analyses were inconclusive. One study found that both male and female patients had more OCs than their matched HCs (Kendell et al., 1996), whereas another study showed no differences in both male and female patients compared to their matched HCs (Cantor-Graae et al., 1994). Another study found that only male patients had more OCs than their matched HCs (Byrne et al., 2000). Furthermore, some studies found a sex difference when focusing on the severity of OCs (Byrne et al., 2000). A study showed that only male patients had significantly more severe OCs than HCs (Byrne et al., 2000), whereas another study found more severe OCs in female patients than HCs (Verdoux and Bourgeois, 1993).

Meta-analyses on the association between pre-and perinatal complications and schizophrenia showed that results differ across the types of OCs (Cannon et al., 2002; Davies et al., 2020). For instance, hypoxia, premature rupture of membranes, polyhydramnios, definite OCs small for gestational age, congenital malformations were found to be significant risk factors for schizophrenia. Therefore, we further evaluated whether particular complications showed sex-specific effects. It appears that an increased risk for schizophrenia might be associated with a low birth weight especially in women (Byrne et al., 2000; Dalman et al., 1999). However, due to different definitions and the focus on different types of OCs across studies, it is difficult to draw definite conclusions.

When evaluating the literature, it is crucial to consider that heterogeneous definitions have been used across the studies. There were even differences in studies using the same OC scales (i.e. using any or only definite OCs) (Foerster et al., 1991; Kirov et al., 1996). Furthermore, some of the studies used birth records to retrieve information on OCs, while others used reports by relatives. Using the latter approach is a limitation considering the recall bias (McIntosh et al., 2002). Altogether, these differences make comparison of findings challenging. Many studies focused on the presence and frequency of OCs, but it appears that specific OCs rather than the occurrence of any OCs may have sex-specific effects on PSD. Overall, these studies are not sufficient to draw conclusions on sex differences of OCs in PSD. Sex differences in OCs and their impact on PSD require further research in larger samples.

4.7. Limitations

To our knowledge, this is the first systematic review investigating gender-related differences of the effects of environmental factors in PSD. However, studies included in this review used different research methodologies, with different rating scales, cut-off points, and various criteria, thereby making an interpretation of the contrasting findings very challenging. Many studies included in this review were cross-sectional and mostly based on retrospective self-report questionnaires, which increase the risk for recall bias (Fergusson et al., 2000). Furthermore, another limitation was that some studies did not consistently provide the statistical reports in detail, such as effect sizes. Although gender-related effects of childhood adversity have been studied to a greater extent (n = 15), the literature search identified only a few studies that investigated the gender effect of substance abuse (n = 7), urbanicity (n = 5), migration (n = 6), season of birth (n = 6), and obstetric and pregnancy complications (n = 11), with no studies investigating socioeconomic status."

5. Conclusion

Overall, our findings demonstrate that there may be gender differences in the association of environmental exposures with PSD. However, these findings, particularly the contrasting ones, require further replication and longitudinal studies. There is a pressing need to elucidate the gender patterns underlying the link between exposome and psychosis. To gain insight into these gender-driven patterns, future analyses should therefore go beyond treating gender as a mere covariate and also investigate gender as a potential effect-moderating factor.

Role of funding source

The funding sources had no further role in the current study.

CRediT authorship contribution statement

Aysegul Yay Pence: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Validation. **Lotta-Katrin Pries:** Conceptualization, Methodology, Data curation, Writing – original draft, Validation. **Maria Ferrara:** Writing – review & editing, Validation. **Bart P.F. Rutten:** Writing – review & editing, Validation. **Jim van Os:** Writing – review & editing, Validation. **Sinan Guloksuz:** Conceptualization, Methodology, Writing – review & editing, Validation.

Declaration of competing interest

None.

Acknowledgment

Dr. Pries is supported by the Kootstra Talent Fellowship of Maastricht University. Dr. Rutten was funded by a VIDI award number 91718336 from the Netherlands Scientific Organisation. Drs Guloksuz and van Os are supported by the Ophelia Research Project, ZonMw grant number: 636340001.

References

Aas, M., Dazzan, P., Fisher, H.L., Morgan, C., Morgan, K., Reichenberg, A., Zanelli, J., Fearon, P., Jones, P.B., Murray, R.M., Pariante, C.M., 2011. Childhood trauma and

cognitive function in first-episode affective and non-affective psychosis. Schizophr. Res. 129 (1), 12–19.
Abel, K.M., Drake, R., Goldstein, J.M., 2010. Sex differences in schizophrenia. Int. Rev. Psychiatry 22 (5), 417–428.
Allardyce, J., Boydell, J., Van Os, J., Morrison, G., Castle, D., Murray, R.M., McCreadie, R.G., 2001. Comparison of the incidence of schizophrenia in rural Dumfries and Galloway and urban Camberwell. Br. J. Psychiatry 179, 335–339.
Anjara, S.G., Nellums, L.B., Bonetto, C., Van Bortel, T., 2017. Stress, health and quality of life of female migrant domestic workers in Singapore: a cross-sectional study. BMC Womens Health 17 (1), 98.
Arranz, B., Safont, G., Corripio, I., Ramirez, N., Dueñas, R.M., Perez, V., Alvarez, E., San, L., 2015. Substance use in patients with first-episode psychosis: is gender relevant? J. Dual Diagn. 11 (3–4), 153–160.
Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., Moffitt, T.E., 2002. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 325 (7374), 1212–1213.
Bale, T.L., Epperson, C.N., 2015. Sex differences and stress across the lifespan. Nat. Neurosci. 18 (10), 1413–1420.
Balestrieri, M., Rucci, P., Nicolaou, S., 1997. Gender-specific decline and seasonality of births in operationally defined schizophrenics in Italy. Schizophr. Res. 27 (1), 73–81.
Barzilay, R., Calkins, M.E., Moore, T.M., Wolf, D.H., Satterthwaite, T.D., Scott, J.C., Jones, J.D., Benton, T.D., Gur, R.C., Gur, R.E., 2019. Association between traumatic stress load, psychopathology, and cognition in the Philadelphia Neurodevelopmental Cohort. Psychol. Med. 49 (2), 325–334.
Blanchard, J.J., Brown, S.A., Horan, W.P., Sherwood, A.R., 2000. Substance use disorders in schizophrenia: review, integration, and a proposed model. Clin. Psychol. Rev. 20 (2), 207–234.
Bourgeois, C., Lecomte, T., Daigneault, I., 2018. Psychotic disorders in sexually abused youth: a prospective matched-cohort study. Schizophr. Res. 199, 123–127.
Bühler, B., Hambrecht, M., Löffler, W., an der Heiden, W., Häfner, H., 2002. Precipitation and determination of the onset and course of schizophrenia by substance abuse–a retrospective and prospective study of 232 population-based first illness episodes. Schizophr. Res. 54 (3), 243–251.
Byrne, M., Browne, R., Mulryan, N., Scully, A., Morris, M., Kinsella, A., Takei, N., McNeil, T., Walsh, D., O'Callaghan, E., 2000. Labour and delivery complications and schizophrenia. Case-control study using contemporaneous labour ward records. Br. J. Psychiatry 176, 531–536.
Cannon, M., Jones, P.B., Murray, R.M., 2002. Obstetric complications and schizophrenia: historical and meta-analytic review. Am. J. Psychiatry 159 (7), 1080–1092.
Cantor-Graae, E., McNeil, T.F., Sjöström, K., Nordström, L.G., Rosenlund, T., 1994. Obstetric complications and their relationship to other etiological risk factors in schizophrenia. A case-control study. J. Nerv. Ment. Dis. 182 (11), 645–650.
Cantor-Graae, E., Pedersen, C.B., 2013. Full spectrum of psychiatric disorders related to foreign migration: a Danish population-based cohort study. JAMA Psychiatry 70 (4), 427–435.
Comacchio, C., Howard, L.M., Bonetto, C., Lo Parrino, R., Furlato, K., Semrov, E., Preti, A., Mesiano, L., Neri, G., De Girolamo, G., de Santi, K., Miglietta, E., Tosato, S., Cristofalo, D., Lasalvia, A., Ruggeri, M., 2019a. The impact of gender and childhood abuse on age of psychosis onset, psychopathology and needs for care in psychosis patients. Schizophr. Res. 210, 164–171.
Comacchio, C., Lasalvia, A., Ruggeri, M., 2019b. Current evidence of childhood traumatic experiences in psychosis - focus on gender differences. Psychiatry Res. 281, 112507.
Cutajar, M.C., Mullen, P.E., Ogloff, J.R., Thomas, S.D., Wells, D.L., Spataro, J., 2010. Schizophrenia and other psychotic disorders in a cohort of sexually abused children. Arch. Gen. Psychiatry 67 (11), 1114–1119.
Dalman, C., Allebeck, P., Cullberg, J., Grunewald, C., Köster, M., 1999. Obstetric complications and the risk of schizophrenia: a longitudinal study of a national birth cohort. Arch. Gen. Psychiatry 56 (3), 234–240.
Dassa, D., Azorin, J.M., Ledoray, V., Sambuc, R., Giudicelli, S., 1996. Season of birth and schizophrenia: sex difference. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 20 (2), 243–251.
Davies, C., Segre, G., Estradé, A., Radua, J., De Micheli, A., Provenzani, U., Oliver, D., Salazar de Pablo, G., Ramella-Cravaro, V., Besozzi, M., Dazzan, P., Miele, M., Caputo, G., Spallarossa, C., Crossland, G., Ilyas, A., Spada, G., Politi, P., Murray, R. M., McGuire, P., Fusar-Poli, P., 2020. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. Lancet Psychiatry 7 (5), 399–410.
Dekker, N., Meijer, J., Koeter, M., van den Brink, W., van Beveren, N., Kahn, R.S., Linszen, D.H., van Os, J., Wiersma, D., Bruggeman, R., Cahn, W., de Haan, L., Krabbendam, L., Myin-Germeys, I., 2012. Age at onset of non-affective psychosis in relation to cannabis use, other drug use and gender. Psychol. Med. 42 (9), 1903–1911.
Di Forti, M., Marconi, A., Carra, E., Fraietta, S., Trotta, A., Bonomo, M., Bianconi, F., Gardner-Sood, P., O'Connor, J., Russo, M., Stilo, S.A., Marques, T.R., Mondelli, V., Dazzan, P., Pariante, C., David, A.S., Gaughran, F., Atakan, Z., Iyegbe, C., Powell, J., Morgan, C., Lynskey, M., Murray, R.M., 2015. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry 2 (3), 233–238.
Di Forti, M., Quattrone, D., Freeman, T.P., Tripoli, G., Gayer-Anderson, C., Quigley, H., Rodriguez, V., Jongsma, H.E., Ferraro, L., La Cascia, C., La Barbera, D., Tarricone, I., Berardi, D., Szöke, A., Arango, C., Tortelli, A., Velthorst, E., Bernardo, M., Del-Ben, C.M., Menezes, P.R., Selten, J.-P., Jones, P.B., Kirkbride, J.B., Rutten, B.P.F., de Haan, L., Sham, P.C., van Os, J., Lewis, C.M., Lynskey, M., Morgan, C., Murray, R.M., Amoretti, S., Arrojo, M., Baudin, G., Beards, S., Bernardo, M., Bobes, J., Bonetto, C., Cabrera, B., Carracedo, A., Charpeaud, T., Costas, J., Cristofalo, D., Cuadrado, P., Díaz-Caneja, C.M., Ferchiou, A., Franke, N., Frijda, F., García Bernardo, E., Garcia-Portilla, P., González, E., Hubbard, K., Jamain, S., Jiménez-López, E., Leboyer, M., López Montoya, G., Lorente-Rovira, E., Marcelino Loureiro, C., Marrazzo, G., Martínez, C., Matteis, M., Messchaart, E., Moltó, M.D., Nacher, J., Olmeda, M.S., Parellada, M., González Peñas, J., Pignon, B., Rapado, M., Richard, J.-R., Rodríguez Solano, J.J., Roldán Díaz, L., Ruggeri, M., Sáiz, P.A., Sánchez, E., Sanjuán, J., Sartorio, C., Schürhoff, F., Seminerio, F., Shuhama, R., Sideli, L., Stilo, S.A., Termorshuizen, F., Tosato, S., Tronche, A.-M., van Dam, D., van der Ven, E., 2019. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry 6 (5), 427–436.
DiPietro, J.A., Voegtline, K.M., 2017. The gestational foundation of sex differences in development and vulnerability. Neuroscience 342, 4–20.
Donoghue, K., Doody, G.A., Murray, R.M., Jones, P.B., Morgan, C., Dazzan, P., Hart, J., Mazzoncini, R., Maccabe, J.H., 2014. Cannabis use, gender and age of onset of schizophrenia: data from the ÆSOP study. Psychiatry Res. 215 (3), 528–532.
Dykxhoorn, J., Hollander, A.C., Lewis, G., Dalman, C., Kirkbride, J.B., 2019. Family networks during migration and risk of non-affective psychosis: a population-based cohort study. Schizophr. Res. 208, 268–275.
Eagles, J.M., Hunter, D., Geddes, J.R., 1995. Gender-specific changes since 1900 in the season-of-birth effect in schizophrenia. Br. J. Psychiatry 167 (4), 469–472.
Eranti, S.V., MacCabe, J.H., Bundy, H., Murray, R.M., 2013. Gender difference in age at onset of schizophrenia: a meta-analysis. Psychol. Med. 43 (1), 155–167.
Erzin, G., Guloksuz, S., 2021. The exposome paradigm to understand the environmental origins of mental disorders. Alpha Psychiatry 22, 171–176.
Erzin, G., Pries, L.K., van Os, J., Fusar-Poli, L., Delespaul, P., Kenis, G., Luykx, J.J., Lin, B. D., Richards, A.L., Akdede, B., Binbay, T., Altınyazar, V., Yalınçetin, B., Gümüş-Akay, G., Cihan, B., Soygür, H., Ulaş, H., Cankurtaran, E., Kaymak, S.U., Mihaljevic, M.M., Andric-Petrovic, S., Mirjanic, T., Bernardo, M., Mezquida, G., Amoretti, S., Bobes, J., Saiz, P.A., García-Portilla, M.P., Sanjuan, J., Aguilar, E.J., Santos, J.L., Jiménez-López, E., Arrojo, M., Carracedo, A., López, G., González-Peñas, J., Parellada, M., Maric, N.P., Atbaşoğlu, C., Ucok, A., Alptekin, K., Saka, M. C., Arango, C., O'Donovan, M.C., Rutten, B.P.F., Guloksuz, S., 2021. Examining the association between exposome score for schizophrenia and functioning in schizophrenia, siblings, and healthy controls: results from the EUGEI study. Eur. Psychiatry 64 (1), e25.
Fergusson, D.M., Horwood, L.J., Woodward, L.J., 2000. The stability of child abuse reports: a longitudinal study of the reporting behaviour of young adults. Psychol. Med. 30 (3), 529–544.
Ferrara, M., Srihari, V.H., 2021. Early intervention for psychosis in the United States: tailoring services to improve care for women. Psychiatr. Serv. 72 (1), 5–6.
Fisher, H., Morgan, C., Dazzan, P., Craig, T.K., Morgan, K., Hutchinson, G., Jones, P.B., Doody, G.A., Pariante, C., McGuffin, P., Murray, R.M., Leff, J., Fearon, P., 2009. Gender differences in the association between childhood abuse and psychosis. Br. J. Psychiatry 194 (4), 319–325.
Foerster, A., Lewis, S.W., Owen, M.J., Murray, R.M., 1991. Low birth weight and a family history of schizophrenia predict poor premorbid functioning in psychosis. Schizophr. Res. 5 (1), 13–20.
Foner, N., 1998. Benefits and burdens: immigrant women and work in New York City. Gend. Issues 16 (4), 5–24.
Gallagher 3rd, B.J., Jones, B.J., 2013. Childhood stressors and symptoms of schizophrenia. Clin. Schizophr. Relat. Psychoses 7 (3), 124–130.
Garcia, M., Montalvo, I., Creus, M., Cabezas, Á., Solé, M., Algora, M.J., Moreno, I., Gutiérrez-Zotes, A., Labad, J., 2016. Sex differences in the effect of childhood trauma on the clinical expression of early psychosis. Compr. Psychiatry 68, 86–96.
Gayer-Anderson, C., Fisher, H.L., Fearon, P., Hutchinson, G., Morgan, K., Dazzan, P., Boydell, J., Doody, G.A., Jones, P.B., Murray, R.M., Craig, T.K., Morgan, C., 2015. Gender differences in the association between childhood physical and sexual abuse, social support and psychosis. Soc. Psychiatry Psychiatr. Epidemiol. 50 (10), 1489–1500.
Gearon, J.S., Bellack, A.S., 2000. Sex differences in illness presentation, course, and level of functioning in substance-abusing schizophrenia patients. Schizophr. Res. 43 (1), 65–70.
Geist, C., McManus, P.A., 2012. Different reasons, different results: implications of migration by gender and family status. Demography 49 (1), 197–217.
Greenman, E., Xie, Y., 2008. Double jeopardy? The interaction of gender and race on earnings in the U.S. Soc. Forces 86 (3), 1217–1244.
Grossman, L.S., Harrow, M., Rosen, C., Faull, R., 2006. Sex differences in outcome and recovery for schizophrenia and other psychotic and nonpsychotic disorders. Psychiatr. Serv. 57 (6), 844–850.
Guloksuz, S., Rutten, B.P.F., Pries, L.K., Ten Have, M., de Graaf, R., van Dorsselaer, S., Klingenberg, B., van Os, J., Ioannidis, J.P.A., <collab>European Network of National Schizophrenia Networks Studying Gene-Environment Interactions Work Package, G.</collab>, 2018. The complexities of evaluating the exposome in psychiatry: a data-driven illustration of challenges and some propositions for amendments. Schizophr. Bull. 44 (6), 1175–1179.
Guloksuz, S., van Nierop, M., Lieb, R., van Winkel, R., Wittchen, H.-U., van Os, J., 2015. Evidence that the presence of psychosis in non-psychotic disorder is environment-dependent and mediated by severity of non-psychotic psychopathology. Psychol. Med. 45 (11), 2389–2401.
Guloksuz, S., van Os, J., Rutten, B.P.F., 2018b. The exposome paradigm and the complexities of environmental research in psychiatry. JAMA Psychiatry 75 (10), 985–986.
Häfner, H., an der Heiden, W., Behrens, S., Gattaz, W.F., Hambrecht, M., Löffler, W., Maurer, K., Munk-Jørgensen, P., Nowotny, B., Riecher-Rössler, A., Stein, A., 1998.

Causes and consequences of the gender difference in age at onset of schizophrenia. Schizophr. Bull. 24 (1), 99–113.
Hernandez-Avila, C.A., Rounsaville, B.J., Kranzler, H.R., 2004. Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. Drug Alcohol Depend. 74 (3), 265–272.
Hodgins, S., Larm, P., Westerman, J., 2016. Individuals developing schizophrenia are hidden among adolescent substance misusers. Psychol. Med. 46 (14), 3041–3050.
Hollander, A.C., Dal, H., Lewis, G., Magnusson, C., Kirkbride, J.B., Dalman, C., 2016. Refugee migration and risk of schizophrenia and other non-affective psychoses: cohort study of 1.3 million people in Sweden. BMJ 352, i1030.
Hultman, C.M., Ohman, A., Cnattingius, S., Wieselgren, I.M., Lindström, L.H., 1997. Prenatal and neonatal risk factors for schizophrenia. Br. J. Psychiatry 170, 128–133.
Kaufman, S.B., 2007. Sex differences in mental rotation and spatial visualization ability: can they be accounted for by differences in working memory capacity? Intelligence 35 (3), 211–223.
Kelly, B.D., O'Callaghan, E., Waddington, J.L., Feeney, L., Browne, S., Scully, P.J., Clarke, M., Quinn, J.F., McTigue, O., Morgan, M.G., Kinsella, A., Larkin, C., 2010. Schizophrenia and the city: a review of literature and prospective study of psychosis and urbanicity in Ireland. Schizophr. Res. 116 (1), 75–89.
Kelly, D.L., Rowland, L.M., Patchan, K.M., Sullivan, K., Earl, A., Raley, H., Liu, F., Feldman, S., McMahon, R.P., 2016. Schizophrenia clinical symptom differences in women vs. men with and without a history of childhood physical abuse. Child Adolesc. Psychiatry Ment. Health 10, 5.
Kendell, R.E., Juszczak, E., Cole, S.K., 1996. Obstetric complications and schizophrenia: a case control study based on standardised obstetric records. Br. J. Psychiatry 168 (5), 556–561.
Kirkbride, J.B., Hameed, Y., Ioannidis, K., Ankireddypalli, G., Crane, C.M., Nasir, M., Kabacs, N., Metastasio, A., Jenkins, O., Espandian, A., Spyridi, S., Ralevic, D., Siddabattuni, S., Walden, B., Adeoye, A., Perez, J., Jones, P.B., 2017. Ethnic minority status, age-at-immigration and psychosis risk in rural environments: evidence from the SEPEA study. Schizophr. Bull. 43 (6), 1251–1261.
Kirov, G., Jones, P.B., Harvey, I., Lewis, S.W., Toone, B.K., Rifkin, L., Sham, P., Murray, R.M., 1996. Do obstetric complications cause the earlier age at onset in male than female schizophrenics? Schizophr. Res. 20 (1–2), 117–124.
Kocsis-Bogár, K., Mészáros, V., Perczel-Forintos, D., 2018. Gender differences in the relationship of childhood trauma and the course of illness in schizophrenia. Compr. Psychiatry 82, 84–88.
Large, M., Mullin, K., Gupta, P., Harris, A., Nielssen, O., 2014. Systematic meta-analysis of outcomes associated with psychosis and co-morbid substance use. Aust. N. Z. J. Psychiatry 48 (5), 418–432.
Large, M., Sharma, S., Compton, M.T., Slade, T., Nielssen, O., 2011. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch. Gen. Psychiatry 68 (6), 555–561.
Lejbak, L., Crossley, M., Vrbancic, M., 2011. A male advantage for spatial and object but not verbal working memory using the n-back task. Brain Cogn. 76 (1), 191–196.
Mansueto, G., Schruers, K., Cosci, F., van Os, J., 2019. Childhood adversities and psychotic symptoms: the potential mediating or moderating role of neurocognition and social cognition. Schizophr. Res. 206, 183–193.
Marcelis, M., Navarro-Mateu, F., Murray, R., Selten, J.P., Van Os, J., 1998. Urbanization and psychosis: a study of 1942–1978 birth cohorts in the Netherlands. Psychol. Med. 28 (4), 871–879.
Martin, E., Smeester, L., Bommarito, P.A., Grace, M.R., Boggess, K., Kuban, K., Karagas, M.R., Marsit, C.J., O'Shea, T.M., Fry, R.C., 2017. Sexual epigenetic dimorphism in the human placenta: implications for susceptibility during the prenatal period. Epigenomics 9 (3), 267–278.
Martínez-Ortega, J.M., Carretero, M.D., Gutiérrez-Rojas, L., Díaz-Atienza, F., Jurado, D., Gurpegui, M., 2011. Winter birth excess in schizophrenia and in non-schizophrenic psychosis: sex and birth-cohort differences. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35 (7), 1780–1784.
McIntosh, A.M., Holmes, S., Gleeson, S., Burns, J.K., Hodges, A.K., Byrne, M.M., Dobbie, R., Miller, P., Lawrie, S.M., Johnstone, E.C., 2002. Maternal recall bias, obstetric history and schizophrenia. Br. J. Psychiatry 181, 520–525.
Mendrek, A., Stip, E., 2011. Sexual dimorphism in schizophrenia: is there a need for gender-based protocols? Expert. Rev. Neurother. 11 (7), 951–959.
MenjÍVar, C., 1999. The intersection of work and gender: central American immigrant women and employment in California. Am. Behav. Sci. 42 (4), 601–627.
Mimarakis, D., Roumeliotaki, T., Roussos, P., Giakoumaki, S.G., Bitsios, P., 2018. Winter birth, urbanicity and immigrant status predict psychometric schizotypy dimensions in adolescents. Eur. Psychiatry 47, 9–18.
Misiak, B., Frydecka, D., 2016. A history of childhood trauma and response to treatment with antipsychotics in first-episode schizophrenia patients: preliminary results. J. Nerv. Ment. Dis. 204 (10), 787–792.
Morgan, V.A., Castle, D.J., Jablensky, A.V., 2008. Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders. Aust. N. Z. J. Psychiatry 42 (1), 74–82.
O'Callaghan, E., Gibson, T., Colohan, H.A., Buckley, P., Walshe, D.G., Larkin, C., Waddington, J.L., 1992. Risk of schizophrenia in adults born after obstetric complications and their association with early onset of illness: a controlled study. BMJ 305 (6864), 1256–1259.
Ochoa, S., Usall, J., Cobo, J., Labad, X., Kulkarni, J., 2012. Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. Schizophr. Res. Treat. 2012, 916198.
Preti, A., Cardascia, L., Zen, T., Marchetti, M., Favaretto, G., Miotto, P., 2000. Risk for obstetric complications and schizophrenia. Psychiatry Res. 96 (2), 127–139.
Pries, L.-K., Erzin, G., Rutten, B.P.F., van Os, J., Guloksuz, S., 2021. Estimating aggregate environmental risk score in psychiatry: the exposome score for schizophrenia. Front. Psychiatry 12 (834).
Pries, L.-K., Guloksuz, S., Ten Have, M., De Graaf, R., Van Dorsselaer, S., Gunther, N., Rauschenberg, C., Reininghaus, U., Radhakrishnan, R., Bak, M., 2018. Evidence that environmental and familial risks for psychosis additively impact a multidimensional subthreshold psychosis syndrome. Schizophr. Bull. 44 (4), 710–719.
Pries, L.K., Dal Ferro, G.A., van Os, J., Delespaul, P., Kenis, G., Lin, B.D., Luykx, J.J., Richards, A.L., Akdede, B., Binbay, T., Altinyazar, V., Yalincetin, B., Gumus-Akay, G., Cihan, B., Soygur, H., Ulas, H., Sahin Cankurtaran, E., Ulusoy Kaymak, S., Mihaljevic, M.M., Andric Petrovic, S., Mirjanic, T., Bernardo, M., Mezquida, G., Amoretti, S., Bobes, J., Saiz, P.A., Garcia-Portilla, M.P., Sanjuan, J., Aguilar, E.J., Santos, J.L., Jimenez-Lopez, E., Arrojo, M., Carracedo, A., Lopez, G., Gonzalez-Penas, J., Parellada, M., Maric, N.P., Atbasoglu, C., Ucok, A., Alptekin, K., Can Saka, M., Genetic, R., <collab>Outcome of Psychosis, i.</collab>, Arango, C., O'Donovan, M., Tosato, S., Rutten, B.P.F., Guloksuz, S., 2020. Examining the independent and joint effects of genomic and exposomic liabilities for schizophrenia across the psychosis spectrum. Epidemiol. Psychiatr. Sci. 29, e182.
Pries, L.K., Lage-Castellanos, A., Delespaul, P., Kenis, G., Luykx, J.J., Lin, B.D., Richards, A.L., Akdede, B., Binbay, T., Altinyazar, V., Yalincetin, B., Gumus-Akay, G., Cihan, B., Soygur, H., Ulas, H., Cankurtaran, E.S., Kaymak, S.U., Mihaljevic, M.M., Petrovic, S.A., Mirjanic, T., Bernardo, M., Cabrera, B., Bobes, J., Saiz, P.A., Garcia-Portilla, M.P., Sanjuan, J., Aguilar, E.J., Santos, J.L., Jimenez-Lopez, E., Arrojo, M., Carracedo, A., Lopez, G., Gonzalez-Penas, J., Parellada, M., Maric, N.P., Atbasoglu, C., Ucok, A., Alptekin, K., Saka, M.C., Genetic, R., <collab>Outcome of Psychosis, i.</collab>, Arango, C., O'Donovan, M., Rutten, B. P.F., van Os, J., Guloksuz, S., 2019. Estimating exposome score for schizophrenia using predictive modeling approach in two independent samples: the results from the EUGEI study. Schizophr. Bull. 45 (5), 960–965.
Pries, L.K., van Os, J., Ten Have, M., de Graaf, R., van Dorsselaer, S., Bak, M., Lin, B.D., van Eijk, K.R., Kenis, G., Richards, A., O'Donovan, M.C., Luykx, J.J., Rutten, B.P.F., Guloksuz, S., 2020b. Association of recent stressful life events with mental and physical health in the context of genomic and exposomic liability for schizophrenia. JAMA Psychiatry 77 (12), 1296–1304.
Pruessner, M., King, S., Vracotas, N., Abadi, S., Iyer, S., Malla, A.K., Shah, J., Joober, R., 2019. Gender differences in childhood trauma in first episode psychosis: association with symptom severity over two years. Schizophr. Res. 205, 30–37.
Rabinowitz, J., Bromet, E.J., Lavelle, J., Carlson, G., Kovasznay, B., Schwartz, J.E., 1998. Prevalence and severity of substance use disorders and onset of psychosis in first-admission psychotic patients. Psychol. Med. 28 (6), 1411–1419.
Rosenberg, S.D., Lu, W., Mueser, K.T., Jankowski, M.K., Cournos, F., 2007. Correlates of adverse childhood events among adults with schizophrenia spectrum disorders. Psychiatr. Serv. 58 (2), 245–253.
Ruby, E., Rothman, K., Corcoran, C., Goetz, R.R., Malaspina, D., 2017. Influence of early trauma on features of schizophrenia. Early Interv. Psychiatry 11 (4), 322–333.
Salokangas, R.K.R., Patterson, P., Hietala, J., Heinimaa, M., From, T., Ilonen, T., von Reventlow, H.G., Schultze-Lutter, F., Juckel, G., Linszen, D., Dingemans, P., Birchwood, M., Klosterkötter, J., Ruhrmann, S., 2019. Childhood adversity predicts persistence of suicidal thoughts differently in females and males at clinical high-risk patients of psychosis. Results of the EPOS project. Early Interv. Psychiatry 13 (4), 935–942.
Schoeler, T., Monk, A., Sami, M.B., Klamerus, E., Foglia, E., Brown, R., Camuri, G., Altamura, A.C., Murray, R., Bhattacharyya, S., 2016. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. Lancet Psychiatry 3 (3), 215–225.
Seeman, M.V., 1997. Psychopathology in women and men: focus on female hormones. Am. J. Psychiatry 154 (12), 1641–1647.
Setién-Suero, E., Neergaard, K., Ramírez-Bonilla, M., Correa-Ghisays, P., Fañanás, L., Crespo-Facorro, B., Ayesa-Arriola, R., 2017. Cannabis use in male and female first episode of non-affective psychosis patients: long-term clinical, neuropsychological and functional differences. PLoS One 12 (8), e0183613.
Sevy, S., Robinson, D.G., Napolitano, B., Patel, R.C., Gunduz-Bruce, H., Miller, R., McCormack, J., Lorell, B.S., Kane, J., 2010. Are cannabis use disorders associated with an earlier age at onset of psychosis? A study in first episode schizophrenia. Schizophr. Res. 120 (1–3), 101–107.
Shah, S., Mackinnon, A., Galletly, C., Carr, V., McGrath, J.J., Stain, H.J., Castle, D., Harvey, C., Sweeney, S., Morgan, V.A., 2014. Prevalence and impact of childhood abuse in people with a psychotic illness. Data from the second Australian National Survey of Psychosis. Schizophr. Res. 159 (1), 20–26.
Shauman, K., Noonan, M., 2007. Family migration and labor force outcomes: sex differences in occupational context. Social Forces 85, 1735–1764.
Suliman, S., Mkabile, S.G., Fincham, D.S., Ahmed, R., Stein, D.J., Seedat, S., 2009. Cumulative effect of multiple trauma on symptoms of posttraumatic stress disorder, anxiety, and depression in adolescents. Compr. Psychiatry 50 (2), 121–127.
Thorup, A., Albert, N., Bertelsen, M., Petersen, L., Jeppesen, P., Le Quack, P., Krarup, G., Jørgensen, P., Nordentoft, M., 2014. Gender differences in first-episode psychosis at 5-year follow-up–two different courses of disease? Results from the OPUS study at 5-year follow-up. Eur. Psychiatry 29 (1), 44–51.
Toutountzidis, D., Gale, T.M., Irvine, K., Sharma, S., Laws, K.R., 2018. Sex differences in the association between childhood adversities and schizotypal personality traits. Psychiatry Res. 269, 31–37.
van Os, J., Bak, M., Hanssen, M., Bijl, R.V., de Graaf, R., Verdoux, H., 2002. Cannabis use and psychosis: a longitudinal population-based study. Am. J. Epidemiol. 156 (4), 319–327.
Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., van Os, J., Bentall, R.P., 2012. Childhood adversities increase the risk of psychosis: a

meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr. Bull. 38 (4), 661–671.
Veling, W., Selten, J.P., Veen, N., Laan, W., Blom, J.D., Hoek, H.W., 2006. Incidence of schizophrenia among ethnic minorities in the Netherlands: a four-year first-contact study. Schizophr. Res. 86 (1–3), 189–193.
Verdoux, H., Bourgeois, M., 1993. A comparative study of obstetric history in schizophrenics, bipolar patients and normal subjects. Schizophr. Res. 9 (1), 67–69.
Vlahov, D., Galea, S., 2002. Urbanization, urbanicity, and health. J. Urban Health 79 (1), S1–S12.
Voyer, D., Voyer, S., Bryden, M.P., 1995. Magnitude of sex differences in spatial abilities: a meta-analysis and consideration of critical variables. Psychol. Bull. 117 (2), 250–270.
Wang, C., Zhang, Y., 2017. Schizophrenia in mid-adulthood after prenatal exposure to the Chinese Famine of 1959–1961. Schizophr. Res. 184, 21–25.
Weiss, E.M., Ragland, J.D., Brensinger, C.M., Bilker, W.B., Deisenhammer, E.A., Delazer, M., 2006. Sex differences in clustering and switching in verbal fluency tasks. J. Int. Neuropsychol. Soc. 12 (4), 502–509.
WHO, 2022.
Wise, P.M., Dubal, D.B., Wilson, M.E., Rau, S.W., Böttner, M., 2001. Minireview: neuroprotective effects of estrogen-new insights into mechanisms of action. Endocrinology 142 (3), 969–973.
Zornberg, G.L., Buka, S.L., Tsuang, M.T., 2000. Hypoxic-ischemia-related fetal/neonatal complications and risk of schizophrenia and other nonaffective psychoses: a 19-year longitudinal study. Am. J. Psychiatry 157 (2), 196–202.