Gender differences in the association between environment and psychosis

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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.
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...
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 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 1 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 | * Several studies suggest that childhood abuse is more strongly associated with the risk of developing psychosis in women than men. |
|  | Comacchioro et al., 2019b, 2019b | |
|  | Fisher et al., 2009 | |
|  | Garcia, et al., 2016 | |
|  | Gayer-Anderson et al., 2015 | |
|  | Kokio-Bioger et al., 2018 | |
|  | Mansuetu et al., 2019 | |
|  | Pruenter et al., 2019 | |
|  | Ruby et al., 2017 | |
|  | Salokangas et al., 2019 | |
|  | Shah et al., 2014 | |
|  | Toutounidis et al., 2018 | |
|  | Kelly et al., 2016 | |
|  | Aas et al., 2011 | |
|  | Cutajar et al., 2010 | |
| Substance use | Arranz et al., 2015 | * 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 men. |
|  | Donoghue et al., 2014 | |
|  | Gerson and Bellack, 2000 | |
|  | Hodgins et al., 2016 | |
|  | Setien-Suero et al., 2017 | |
|  | Dekker et al., 2012 | |
|  | Rabinoivitz et al., 1998 | |
| Urbanicity | Kelly et al., 2010 | * Urban-birth appears to be more strongly associated with the risk of developing schizophrenia in men than in women. |
|  | Marcelis et al., 1998 | |
|  | Mimarakis et al., 2018 | |
|  | Wang and Zhang, 2017 | |
|  | Allardice et al., 2001 | |
| Migration | Canter-Graae and Pederson, 2013 | * Migration appears to be more strongly associated with the risk of developing psychosis in men. |
|  | Dykkhoorn et al., 2019 | |
|  | Kirkbridge et al., 2017 | |
|  | Mimarakis et al., 2018 | |
|  | Hollander et al., 2016 | |
| Season of birth | Veling et al., 2006 | * Winter-birth might be associated with PSD in both women and men. |
|  | Dassa et al., 1996 | |
|  | Marcelis et al., 1998 | |
|  | Martinez-Ortega et al., 2011 | |
|  | Mimarakis et al., 2018 | |
|  | Egles et al., 1995 | |
|  | Balestrieri et al., 1997 | |
| Obstetric/pregnancy complications | Byrne et al., 2000 | * Findings on the gender-specific effects of OCs are inconclusive. Individual OCs may have different effects on men and women. |
|  | Dalman et al., 1999 | |
|  | Hultman et al., 1997 | |
|  | Kirzo et al., 1996 | |
|  | Kendell et al., 1996 | |
|  | Canter-Graae et al., 1994 | |
|  | Verdoux and |

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neglect was associated with negative symptoms. In female patients, as well as global functioning at the 24-month follow-up, while emotional childhood adversity, a longitudinal study by Pruessner and colleagues in male patients, the only significant association was between physical abuse and general symptoms. Furthermore, one study that investigated 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).

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). 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 female 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                                                                | FEP: 100/102 HC: 105/161                         | * Odds of developing psychosis                                  |
|                               |                                 |                                                                        | * Sexual abuse (by any person ≥5 years older)                                             |             | Physical abuse:                                                       |
|                               |                                 |                                                                        | Women: FEP > HC; Men: FEP = HC                                                           |             | Sex-by-abuse interaction (trend significant)                           |
|                               |                                 |                                                                        | Sexual abuse:                                                                           |             | Sex-by-abuse interaction (trend significant)                           |
|                               |                                 |                                                                        | Women: FEP > HC; Men: FEP = HC                                                           |             | Sexual abuse:                                                         |
|                               |                                 |                                                                        | Women: FEP > HC; Men: FEP = HC                                                           |             | Sex-by-abuse interaction (trend significant)                           |
|                               |                                 |                                                                        | * Odds of developing psychosis                                                            |             | Physical abuse:                                                       |
|                               |                                 |                                                                        | Women: FEP > HC; Men: FEP = HC                                                           |             | Sex-by-abuse interaction (trend significant)                           |
| Fisher et al., 2009           | Cross-sectional                 | FEP/HC                                                                  | * Parental physical abuse                                                                | FEP: 97/84 HC: 103/143                          | * Odds of developing psychosis                                  |
|                               |                                 |                                                                        | * Sexual abuse (by any person ≥5 years older)                                             |             | Physical abuse:                                                       |
|                               |                                 |                                                                        | Women: FEP > HC; Men: FEP = HC                                                           |             | Sex-by-abuse interaction (trend significant)                           |
|                               |                                 |                                                                        | Sexual abuse:                                                                           |             | Sex-by-abuse interaction (trend significant)                           |
|                               |                                 |                                                                        | Women: FEP > HC; Men: FEP = HC                                                           |             | Sexual abuse:                                                         |
| Bourgeois et al., 2018        | Cross-sectional                 | Youths with sexual abuse history/GP                                      | * Sexual abuse                                                                          | Each group 221/661 | * Odds of psychotic experiences in HC                                  |
|                               |                                 |                                                                        |                                                                                          |             | Physical abuse:                                                       |
|                               |                                 |                                                                        | Women: PE > no PE; Men: PE = no PE                                                       |             | Prevalence of psychotic disorders                                     |
|                               |                                 |                                                                        | Sex-stratified analyses: sexually abused girls and boys are more likely to be diagnosed |             | Sex-stratified analyses: sexually abused girls and boys from the     |
|                               |                                 |                                                                        | with a psychotic disorder than girls and boys from the general population.               |             | general population.                                                  |
|                               |                                 |                                                                        | No difference in prevalence between girls and boys with sexual abuse history or girls     |             |                                                                         |
|                               |                                 |                                                                        | and boys from the GP                                                                     |             |                                                                         |
|                               |                                 |                                                                        | * Prevalence of psychotic disorders                                                      |             |                                                                         |
|                               |                                 |                                                                        | Women: emotional, physical abuse → more depressive (T1)                                  |             |                                                                         |
|                               |                                 |                                                                        | Men: emotional abuse → more positive (T2), depressive (T2), 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)                                                   |             |                                                                         |
|                               |                                 |                                                                        | * Symptom severity                                                                       |             |                                                                         |
|                               |                                 |                                                                        | Women and men: No significant associations with type of psychosis, course of illness,    |             |                                                                         |
|                               |                                 |                                                                        | age at onset of illness, or psychosis symptoms.                                          |             |                                                                         |
|                               |                                 |                                                                        | * Course of symptomatic outcome using T0, T1,                                           |             |                                                                         |
|                               |                                 |                                                                        | and T2                                                                                  |             |                                                                         |
|                               |                                 |                                                                        | Childhood adversity                                                                      |             |                                                                         |
|                               |                                 |                                                                        | Women: more positive, depressive                                                         |             |                                                                         |
|                               |                                 |                                                                        | Men: more positive, negative, and lower functioning                                      |             |                                                                         |
|                               |                                 |                                                                        | * Severity of positive symptoms                                                          |             |                                                                         |
|                               |                                 |                                                                        | Women: adversity → no adversity                                                          |             |                                                                         |
|                               |                                 |                                                                        | * Life-time suicidal attempts                                                            |             |                                                                         |
|                               |                                 |                                                                        | Women: adversity → no adversity                                                          |             |                                                                         |
|                               |                                 |                                                                        | * 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)      |             |                                                                         |
|                               |                                 |                                                                        | * Symptom severity                                                                        |             |                                                                         |
|                               |                                 |                                                                        | Women and men: sexual and physical abuse associated with negative symptoms, but not     |             |                                                                         |
|                               |                                 |                                                                        | (continued on next page)                                                                  |             |                                                                         |

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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                                                             |
|                         |                     |                          |                        |             | * 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 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                                              |
|                         |                     |                          |                        |             | * 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                                                            |
|                         |                     |                          |                        |             | * 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                                                                       |
|                         |                     |                          |                        |             | * 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. |

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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 psychiatric symptoms and more thought disturbances than non-substance users, with larger effect sizes for women than men (Rabinowitz et al., 1998). There was no significant difference in age at onset of psychosis in patients with PSD (Arranz et al., 2015; Donoghue et al., 2010; Kelly et al., 2010; Marcelis et al., 1998; Wang and Zhang, 2001; Kelly et al., 2016; Dekker et al., 2012; 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) (Allardyc 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 2 (continued)

| Author | Study type | Sample | Environmental exposure | N men/women | Outcome |
|--------|------------|--------|-------------------------|-------------|---------|
| Aas et al., 2011 | Cross-sectional | Patients with schizophrenia and schizoaffective disorders | * Subdomains: physical, emotional and sexual abuse; general trauma experiences | 56/24 | * Symptom severity, brain volume, diurnal salivary cortisol |
| Kelly et al., 2016 | Cross-sectional | Patients with schizophrenia and schizoaffective disorders | * Physical abuse | | |
| | FEP (Schizophrenia, bipolar and psychotic depressive disorder)/HC | Childhood adversity | FEP: 73/65 |
| Cunajar et al., 2010 | Cross-sectional | Individuals with sexual abuse history/controls from GP | * Sexual abuse | | |
| | Patients with psychotic | | |
| | HC: 622/2055 | | |
| | Any sexual abuse | | |
| | Women: associated with schizophrenia and any psychotic disorder | |
| | Men: associated with any psychotic disorder | |
| | No significant sex-by-abuse interaction | |
| | With penetration | |

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.
| 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<br>Men and cannabis use → earlier age at onset<br>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<br>Positive & general symptoms: users > non-users for men and women      |
|                            |            |                                                                      |                                                                                                                        |             | * Age at onset of psychosis<br>Users < non-users for men and women                            |
|                            |            |                                                                      |                                                                                                                        |             | * Number of hospitalizations<br>No differences                                              |
| 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<br>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: 1660/322 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  | Baseline | 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 |
|                            | 1-Year     |                                                                      |                                                                                                                        |             | * Symptom severity
Women: no significant differences
Men: users had lower negative symptoms, higher disorganized severity, better functioning (on one of two scales). |
|                            | 3-Month    |                                                                      |                                                                                                                        |             | 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                                                                                           | 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, hallucinogens, sedatives) |                                                                                                                        | 299/242     | * Age at onset of illness |

(continued on next page)
significantly greater (likelihood ratio test – 1.2 (IRR (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 (Allardycse 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

Table 3 (continued)

| Author          | Study type   | Sample                              | Environmental exposure                                                                 | N men/women | Outcome                                                                 |
|-----------------|--------------|-------------------------------------|----------------------------------------------------------------------------------------|-------------|-------------------------------------------------------------------------|
| Marcelis et al., 1998 | Longitudinal | Birth cohorts followed up for psychiatric admission | 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, affective psychosis, and other psychosis Sex-by-urbanicity interaction: the effect of urbanicity on psychosis was 5% larger for men than women |
| 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 | 192/253 | * 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 |
| Mimarakis et al., 2018 | Cross-sectional | GP (Adolescents) | Urbanicity: <5000, 5000–10,000, 10,001–50,000, >50,000 inhabitants/km² | 152/113 | * Schizotypy trait scores Women: total score/magical thinking/unusual experiences: urban > less urban Men: no differences |
| Allardycse et al., 2001 | Cross-sectional | Patients with (OPCRIT-generated) schizophrenia & GP (census data) | Urban: Camberrwell 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 |

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 | 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, affective psychosis, and other psychosis Sex-by-urbanicity interaction: the effect of urbanicity on psychosis was 5% larger for men than women |
| 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 | 192/253 | * 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 |
| Mimarakis et al., 2018 | Cross-sectional | GP (Adolescents) | Urbanicity: <5000, 5000–10,000, 10,001–50,000, >50,000 inhabitants/km² | 152/113 | * Schizotypy trait scores Women: total score/magical thinking/unusual experiences: urban > less urban Men: no differences |
| Allardycse et al., 2001 | Cross-sectional | Patients with (OPCRIT-generated) schizophrenia & GP (census data) | Urban: Camberrwell 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.
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 origin of immigrant, 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; Martinez-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%) (Martinez-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 examined the changes of the ratio of winter/

| 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 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 |
| Dykxhoorn et al., 2019 | Longitudinal population registers | GP (individuals who immigrated to Sweden) | Family network during immigration | Total N: 423,788/414,929 | *Incidence for non-affective psychotic disorder |
| Mimarakis et al., 2018 | Cross-sectional | GP (young people living in Greece) | Immigrant status | 192/253 | * Schizotypy trait scores |
| 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 |
| 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 |

FEP: first episode psychosis patients, 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 = 1.6, 95% CI = 1.4–1.7) (Marcelis et al., 1998).

Table 6
Birth season.

| Author          | Study type | Sample                                      | Environmental exposure | N men/women | Outcome                                                                 |
|-----------------|------------|---------------------------------------------|------------------------|-------------|-------------------------------------------------------------------------|
| Martinez-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<br>Women: patients with schizophrenia > expected (trend significant); patients with other psychosis > expected<br>Men: patients with schizophrenia > expected; patients with schizophrenia born in 1941–1959 > patients with schizophrenia born after 1959 |
| 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<br>Winter birth > increased risk for psychosis with a stronger trend in women |
| 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 → Individual month – Sets of 3 consecutive months | 296/172     | * Proportion of winter birth vs other seasons<br>Women: patients without family history > expected |
| Balestrieri et al., 1997 | Cross-sectional | Patients with schizophrenia & GP data | Winter/spring: December–May Summer/autumn: June–November | 101/104     | * Proportion of winter birth vs other seasons<br>Individual month: No differences between patient's and expected birth month<br>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<br>Men: increase in the proportion of winter/spring vs summer/autumn birth from 1900 to 1969<br>Women: no significant change |

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

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).
## 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 | 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 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 |
| 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 | * Frequency of obstetric complications No significant difference between male and female patients |
| Kiörv 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 |
| Kendall et al., 1996    | Cross-sectional | Patients with schizophrenia/matched HC                      | Pre-existing maternal illness Pregnancy Delivery Source of information: Birth records | Each group: 80/35 | * 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 * 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 of schizophrenia Frequency of OCs Stratified by sex Men and women: no differences Strafified 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) |
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

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Table 7 (continued)

| Author                  | Study type | Sample population | Environmental exposure | N men/women | Outcome                                                                 |
|------------------------|------------|-------------------|------------------------|-------------|-------------------------------------------------------------------------|
| Verroust et al., 1991  | 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 | 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 > HC, schizophrenia > bipolar |
|                        |            |                   |                        |             | Men: no difference |
|                        |            |                   |                        |             | Women with schizophrenia > men with schizophrenia (severity, total) |
|                        |            |                   |                        |             | * 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) |
|                        |            |                   |                        |             | * Age at onset of illness (explorative) |
|                        |            |                   |                        |             | Men: patients with OCs < patients without OCs |
|                        |            |                   |                        |             | Women: no difference |
| Foerster et al., 1991  | Cross-sectional | Patients with schizophrenia/patients with affective psychosis | Lewis scale Source of information: Maternal report | Schizophrenia: 35/10 Affective psychosis: 12/16 | Frequency of obstetric complications |
|                        |            |                   |                        |             | Male patients > female patients |
|                        |            |                   |                        |             | Male HC – female HC |
|                        |            |                   |                        |             | * Frequency of obstetric complications |
|                        |            |                   |                        |             | Male patients – female patients |
|                        |            |                   |                        |             | Male controls – female controls |
| O’Callaghan et al., 1999 | Cross-sectional | Patients with schizophrenia/matched HC | Lewis scale Source of information: Maternal report | 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 | Lewis scale 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 | Birth records Source of information: 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.
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 (Fishier et al., 2009; Gayer-Anderson et al., 2015; Toutountzidis et al., 2018), with two of these studies likely using overlapping samples from the AESOP study (Fishier 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 influences 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 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 (Fishier 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; Setten-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 schizotypia 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; Menjivar, 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; Martinez-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 (Martinez-Ortega et al., 2011). It is possible that similar prenatal stressors might have sex-related effects (Bale and Epperson, 2015; DiPietro and Voeltline, 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 definitive 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.

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