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Sex and Gender Differences in Symptoms of Early Psychosis: A Systematic Review and Meta-Analysis

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Abstract

Background: First-episode psychosis (FEP) can be quite variable in clinical presentation, and both sex and gender may account for some of this variability. Prior literature on sex or gender differences in symptoms of psychosis have been inconclusive, and a comprehensive summary of evidence on the early course of illness is lacking. The objective of this study was to conduct a systematic review and meta-analysis of the literature to summarize prior evidence on the sex and gender differences in the symptoms of early psychosis. ***Methods:*** We conducted an electronic database search (MEDLINE, Scopus, PsycINFO and CINAHL) from 1990 to present to identify quantitative studies focused on sex or gender differences in the symptoms of early psychosis. We used random effects models to compute pooled standardized mean differences (SMD) and risk ratios (RR), with 95% confidence intervals (CI), for a range of symptoms. ***Results:*** Thirty-five studies met the inclusion criteria for the systematic review, and 30 studies were included in the meta-analysis. All studies examined sex differences. Men experienced more severe negative symptoms (SMD=-0.15, 95%CI=-0.21,-0.09), whereas women experienced more severe depressive symptoms (SMD=0.21, 95%CI=0.14,0.27) and had higher functioning (SMD=0.16, 95%CI=0.10,0.23). Women also had a lower prevalence of substance use issues (RR=0.65, 95%CI=0.61,0.69). ***Conclusions:*** Symptoms of early psychosis varied between men and women; however, we were limited in our ability to differentiate between biological sex and gender factors. These findings may help to inform early detection and intervention efforts to better account for sex and gender differences in early psychosis presentation.

Keywords Sex differences**;** Psychosis; Symptoms; First-episode psychosis

Background

Psychotic disorders are characterized by dysfunction in cognition or perception (Lieberman & First, 2018), which may include the presence of positive symptoms (i.e. hallucinations, delusions), negative symptoms (i.e. anhedonia, social withdrawal), disorganized thoughts and behaviour, and impairments in functioning (Iyer et al., 2015). The symptoms of psychosis exist on a continuum with normal mental states, with each person's clinical presentation varying in severity along this continuum, defined by the level, number, and duration of symptoms (Heckers et al., 2013).

The first occurrence of psychotic symptoms, known as first-episode psychosis (FEP), usually presents in adolescence or early adulthood (Reed, 2008), and the clinical presentation at onset may be quite variable (Ochoa et al., 2012). Early intervention for psychotic disorders can optimize the course of illness and clinical prognosis of those affected, as a shorter duration of untreated psychosis is associated with a lower number of hospitalizations and a reduced risk of relapse (Iyer et al., 2015). In order for the duration of untreated psychosis to be minimized, clinicians must be able to identify psychotic symptoms in their varying presentations.

The sex and gender of a person experiencing FEP or early psychosis may account for some of the heterogeneity in clinical presentation, with respect to age of onset, symptom profile, level of functioning, and course of illness (Ochoa et al., 2012). Sex is comprised of the biological aspects of a person, such as chromosomes, anatomy, genes, and hormones; whereas gender is used to describe the nonphysiological components of a person, such as social labels/roles and cultural norms that are shaped by a person's environment and experience (Unger, 1979). Differences in age of onset of FEP have been well-documented in the literature, with the average age of onset of psychotic symptoms being higher in women than in men (Ochoa et al., 2012). This imbalance has been attributed to the difference in timing of puberty between boys and girls, and estradiol being a protective hormone for psychotic disorders in both men and women (Huber et al., 2005). This may also explain the second peak in psychosis incidence for women around menopause, when levels of these hormones decrease (Lodha & Karia, 2019). Similarly, some studies have found that

estrogen may modulate the severity of psychotic symptoms, resulting in a lower disease severity in women (Hochman & Lewine, 2004). Other studies have indicated that men experiencing psychotic symptoms have lower estradiol and testosterone levels compared to healthy controls, further indicating the protective effect of estradiol in men (Brzezinski-Sinai & Brzezinski, 2020; Lodha & Karia, 2019). Gender norms and behaviours may also play a role in symptom variation between males and females with psychotic disorders. For example, women tend to be more socially integrated, whereas men's social behaviours may be more passive and disconnected (Køster et al., 2008). In general, women tend to be more introspective toward their mental health, and are more willing to seek help than men (Fridgen et al., 2013; Gibbons et al., 2015). These gender roles may contribute to differential help-seeking behaviours between men and women, and willingness to comply with treatment plans (Køster et al., 2008). Adolescent girls are more likely to seek help on their own, whereas the parents of boys are more likely to seek help for them (Haavik et al., 2019). This behaviour carries over into adulthood, where women seek help for mental health reasons almost twice as often as men (Fridgen et al., 2013). Men are also more likely to engage in substance use than women, and gender-related factors may have an impact on this difference (Carliner et al., 2017; Køster et al., 2008). For example, there is more societal acceptance surrounding men that use cannabis than women (Carliner et al., 2017), and peer pressure to use cannabis is higher in men compared to women (El-Sawy, 2010; McCoy et al., 2019). These factors may influence the risk of psychotic disorders and impact clinical presentation (van Os et al., 2002). Sex and gender are often entangled in research, and it is difficult to differentiate the pathways between biological and social aspects that lead to differences in clinical presentation.

Sex and gender differences in symptoms of psychotic disorders generally have been studied extensively, although findings are often inconsistent across studies. It has been reported that men tend to experience more negative symptoms – including apathy, poverty of speech and thought, and social withdrawal – whereas affective symptoms, such as depression and mania, tend to occur more frequently in women (Riecher-Rössler et al., 2018). Additionally, men often experience more social isolation, have poorer social functioning, and have more substance use than women with psychotic disorders (Riecher-

Rössler et al., 2018). Conversely, many other studies have concluded that there were no significant differences in symptoms by sex or gender (Ochoa et al., 2012).

Prior literature on sex or gender differences in the symptoms of psychotic disorders are inconclusive, and have been limited by small sample sizes and methodological differences between studies (Riecher-Rössler et al., 2018). A comprehensive summary of the evidence base on symptoms in the early course of illness specifically is lacking. The aim of this study was to systematically review the literature on sex or gender differences in symptoms of early psychosis, and to quantify any observed differences. Specifically, we aimed to address the following questions: 1) How do men and women differ in symptoms of early psychosis? and 2) How should interventions be tailored differently for young men and women experiencing early psychosis? The findings from this systematic review and meta-analysis may be used to profile the clinical presentation of FEP or early psychosis more accurately by sex and gender to support early identification and intervention for psychotic disorders.

Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) reporting guidelines (Supplemental Table 1) (*PRISMA*, 2020).

Search Strategy and Study Selection

We searched four electronic databases – including Medline (ProQuest), Scopus, PsycINFO and Cumulative Index to Nursing and Allied Health Literature (CINAHL) – for studies related to sex or gender differences in symptoms of early psychosis or FEP. No limits were placed on language, and we restricted the search to studies published after 1990 to represent the current standard of care for treating psychosis (Coughlan et al., 2013). The specific search terms used for each database can be found in Supplemental Table 2. Results from the search were imported into the Covidence systematic review management platform (www.covidence.org) for article screening. Grey literature searching was using Google Scholar and Open

Grey, and unpublished work was searched in a pre-print database (medRxiv). Additional studies were identified using forward and backward citation tracing of included articles.

We included studies if the sample was described as first-episode or early psychosis, as defined by the authors of the original studies (Breitborde et al., 2009). Both affective and non-affective psychotic disorders were included, and no restrictions were placed on the age of the sample. To be included in the review, studies must have compared symptoms of psychosis or other features of clinical presentation by sex or gender. We included any type of observational study that provided quantitative results, or interventional studies that provided baseline symptom differences by sex or gender. We excluded studies that included people with chronic psychotic disorders, non-psychotic mental disorders, and ultra-high risk (UHR), clinical high-risk patients (CHR), or prodromal patients. Other experimental or interventional studies, case-reports, case-series, and qualitative studies were also excluded from the review. See Supplemental Table 3 for full inclusion and exclusion criteria.

Level one title and abstract screening was performed by one reviewer (BC) in Covidence, and level two full-text screening was performed by two independent reviewers (BC, JW), applying the inclusion and exclusion criteria. Reasons for exclusion were recorded in Covidence, and discrepancies between reviewers were handled by group discussion and consensus.

Data Extraction and Risk of Bias Assessment

Data extraction was completed by one reviewer, then verified by a second independent reviewer, using a form created and pilot-tested in Microsoft Excel using the Cochrane guidelines (*Chapter 5*, n.d.). Three main categories for extraction were: study characteristics (e.g., study design, source of sample) sample characteristics (e.g., sample size, mean age of sample), and study findings (e.g., symptom scores by sex).

Risk of bias of each study was assessed by two independent reviewers using the “Tools to Assess Risk of Bias in Cohort Studies” by the CLARITY group at McMaster University (Lansche, n.d.), which fit the needs of this review topic. To ensure comprehensive assessment of other non-cohort studies, two items

from the "Risk of Bias for Cross-Sectional Surveys" created by the CLARITY group were also used. The domains assessed in the risk of bias tools included: representativeness of the sample, selection of cohorts, assessment of exposure/outcome, measurement and analysis of confounding factors, and missing data. For each study, each item was rated as low, intermediate, or high risk of bias.

Data Synthesis

We synthesized the data qualitatively data by summarizing sex/gender differences in the most common symptoms of psychosis across the included studies.

Stata version 17.0 (StataCorp, 2021) was used to conduct all meta-analyses. The *metan* command was used with random effect models to account for study heterogeneity (Harris et al., 2008). Meta-analyses were conducted for each symptom (with subgroup analyses by symptom measurement tool), which included each study that reported means and standard deviations on the symptom of interest. Studies that reported medians and interquartile ranges were not included in the meta-analysis. We computed the standardized mean difference (SMD) in symptoms between men and women, with 95% confidence intervals (CI). Statistical heterogeneity was assessed using the I^2 statistic, where a value of less than 25% is considered to be low heterogeneity, 50% is considered to be moderate heterogeneity, and greater than 75% is considered to be high heterogeneity.(Harris et al., 2008) For symptoms where SMD was not applicable (i.e. binary variable), prevalence ratios (PR) for cross-sectional studies and risk ratios (RR) for cohort studies were pooled (Alho, 1992).

Results

Study Selection and Characteristics

Our electronic database search yielded 4,955 studies published after 1990. Through a further search of pre-print databases, grey literature databases, and forward and backward citation tracing, 13 additional studies were obtained. After removing duplicates, 4,436 records were screened based on title and abstract,

in which we excluded 4,120 studies. The remaining 316 studies underwent full-text screening by two reviewers. Of those, 35 studies were retained for qualitative synthesis, and 30 studies included data suitable for a meta-analysis. Of the studies chosen for inclusion in the systematic review and meta-analysis, all looked at the sex of participants as a main exposure, with no studies measuring gender roles. The PRISMA diagram outlining numbers and reasons for exclusion is presented in Figure 1.

Table 1 shows the study and sample characteristics of the 35 included studies. Seven studies were published in North America, 18 studies were published in Europe, one study was published in Africa, five studies were published in Asia, and the remaining four studies were published in Australia. Most included studies used either a cohort (n=25) or cross-sectional (n=7) design, and most (n=18) recruited the sample from early psychosis intervention services. Other studies recruited their samples from other outpatient mental health services (n=3), inpatient services (n=9), a combination of inpatient and outpatient sources (n=3), or health administrative data (n=2). The sample size of included studies ranged from 39 to 3,350 patients, with males comprising a median of 64.2% (range = 33%-80%) of the sample across studies. Most studies used standardized interviews to establish a diagnosis of psychotic disorder, with the majority using DSM-IV or ICD-10 diagnostic criteria. Listed diagnoses included schizophrenia, schizoaffective disorder, schizophreniform disorder, drug-induced psychosis, bipolar disorder, major depressive disorder with psychotic features, affective psychosis with mood-incongruent delusions, brief psychotic episode, non-affective psychosis, and psychotic disorder not otherwise specified. A summary of the tools used to measure symptoms in each study can be found in Supplemental Table 4.

Risk of Bias

Figure 2 presents the findings from the risk of bias assessment. Representativeness of the source population was a concern in the majority of included studies, as only 37% of studies had a low risk of bias on this domain. Studies with a low risk of bias recruited samples though early psychosis intervention clinics or other mental health services. Small sample sizes – often consisting of many more males than females – account for a large portion of this intermediate and high risk across studies.

Measurement and adjustment for confounding factors in the analysis was another common risk of bias, with only half of studies having a low risk of bias in these domains (measurement = 49%; adjustment = 49%). There is potential for other factors, such as ethnicity or age of participants, to bias the relationship between sex and clinical presentation, although these factors were not mentioned or accounted for in many analyses.

Most studies had a low risk of bias in the domains of selection of exposed and non-exposed cohorts (77%), assessment of exposures (91%), and assessment of outcomes (86%), with the latter largely due to the use of standardized interviews and measures to obtain diagnoses and symptoms. There was also a low risk of bias due to missing data, with 83% of studies having a low risk of bias.

Summary of Findings

The results from individual studies can be found in Supplemental Tables 5-10 and are summarized in Table 2. Mean scores and standard deviations on each symptom scale were recorded from each study for both males and females. A wide range of psychotic symptoms were reported across the included studies, and the most common symptoms were compiled. Positive symptoms – such as hallucinations, delusions, and paranoia – and negative symptoms, such as apathy, poverty of speech/thought, and emotional/social withdrawal, were two of the main categories of symptoms recorded. Other common categories of symptoms assessed in the included studies were depression, general psychopathology symptoms, functioning, and substance use (alcohol and drug use). The results from the meta-analysis can be found in Figure 3.

Among the included studies that looked at positive symptoms of psychosis (n=31), 16 found more severe positive symptoms among men, 8 studies found more severe positive symptoms among women, and the remaining 7 studies found no differences between men and women (Supplemental Table 4). Twenty-one studies included data on positive symptom severity that were suitable for a meta-analysis (Figure 3, Supplemental Figure 1). The overall SMD for positive symptoms was -0.03 (95%CI: -0.09, 0.03; I^2=46.8%), which suggests no difference in positive symptoms between men and women, and the findings are largely consistent across measurement tools.

Thirty studies looked at negative symptoms of psychosis, and 25 studies found more severe negative symptoms among men, while only one study reported more severe negative symptoms among women, and four reported no difference between men and women (Supplemental Table 4). Twenty-one studies included data on negative symptoms suitable for a meta-analysis (Figure 3, Supplemental Figure 2), in which the overall SMD was found to be -0.15 (95%CI: -0.21, -0.09, I^2=50.9%), indicating that women experience significantly lower negative symptom severity than men. Consistent with the findings from the meta-analysis on positive symptoms, the findings are consistent across measurement tools.

Depressive symptoms were assessed in 20 of the included studies and of those, 14 found more severe depressive symptoms in women, three studies found more severe depressive symptoms in men, and three studies found no difference between men and women (Supplemental Table 5). Twelve studies included data on depressive symptoms suitable for meta-analysis, (Figure 3, Supplemental Figure 3) in which the overall SMD was 0.21 (95%CI: 0.14, 0.27, I^2=76.1%), indicating that women experience significantly more severe depressive symptoms than men.

Symptoms of general psychopathology were assessed in 14 of the included studies (Supplemental Table 6), in which six studies found more severe symptoms among men, four studies found more severe symptoms among women, and four studies found no difference between men and women. Twelve studies were included in the general psychopathology meta-analysis (Figure 3, Supplemental Figure 4), where the overall effect was found to be -0.06 (95%CI: -0.16, 0.04, I^2=50.0%), suggesting no significant difference between men and women.

Sixteen included studies assessed overall level of functioning (Supplemental Table 7), and of these, 13 studies reported that women had higher levels of functioning, two studies reported that men had higher levels of functioning, and one study reported that men and women had similar levels of functioning. Fifteen studies provided data suitable for a meta-analysis (Figure 3, Supplemental Figure 5), in which the pooled effect was 0.16 (95%CI: 0.10, 0.23, I^2=68.5%), suggesting that women have significantly higher levels of functioning than men.

The findings from studies looking at substance use can be found in Supplemental Table 8. Five studies assessed overall substance use among their sample, with all studies reporting a higher prevalence of substance use among men than women. Six studies assessed alcohol use among their sample, with four reporting a higher prevalence of alcohol use among men compared to women. Ten studies assessed drug use among their sample, and all reported a higher prevalence of drug use among men compared to women. Thirteen studies were used in the meta-analysis (Figure 3, Supplemental Figure 6), in which the pooled risk ratio was 0.65 (95%CI: 0.61, 0.69, I^2=0.0%), suggesting that women have a significantly lower risk of substance use compared to men.

Discussion

Summary of Evidence

The findings from our systematic review and meta-analysis suggest that men with FEP or early psychosis experience greater severity of negative symptoms and a higher likelihood of substance use, whereas women experience greater severity of depressive symptoms and a higher level of functioning. We did not find differences between men and women in positive symptoms or symptoms of general psychopathology. These findings on sex/gender differences in the symptoms of early psychosis are consistent with findings from previous reviews on sex differences in chronic schizophrenia (Leung M.D. & Chue M. R. C. Psych., 2000; Sami Räsänen, Antti Pakaslahti, Erk, 2000).

Prior literature suggests that men have a higher incidence of psychotic disorders than women (Ochoa et al., 2012), which accounts for the gender distributions observed in the study samples. Ochoa and colleagues discussed the differences in diagnoses of psychotic disorders between men and women, and alluded to the idea that although more cases of psychosis are recorded among men, this difference may be due to difficulties detecting the illness among women (Ochoa et al., 2012). The average age of onset for women with psychotic disorders tends to be later in life than men, which can be explained by the second peak in onset that women experience post-menopause, raising the group mean for women (Häfner et al.,

1993; Ochoa et al., 2012; Riecher-Rössler et al., 2018). It is still largely unknown why men may present with psychotic symptoms earlier in life than women, but some hypothesize that higher cannabis consumption in men (Riecher-Rössler et al., 2018), or protective hormones in women (Galdos et al., 1993) may account for this difference.

Previous research on sex differences in the symptoms of psychosis have been well documented, however; it is less clear whether sex differences are present at the initial presentation for psychotic disorders or emerge later in the course of illness due to differences in service engagement and treatment adherence. It is generally acknowledged that men present with more severe negative symptoms than women, whereas women display more severe affective symptoms, such as depression and lack of energy (Riecher-Rössler et al., 2018). This systematic review and meta-analysis clarifies these differences and provides evidence for sex differences in the early course of illness. It was found that men experienced more severe negative symptoms, such as apathy or social/emotional withdrawal, than women, whereas we did not find evidence of sex differences in positive symptoms, such as hallucinations and delusions. Additionally, we found that women experienced more severe depressive or affective symptoms than men. These findings align with a prior literature review on gender differences in schizophrenia symptoms, which found more severe negative symptoms in men, more severe affective symptoms in women, but inconclusive findings on positive symptoms (Ochoa et al., 2012). Lower symptom severity in women supports our finding that women have higher levels of functioning than men, however; further research is needed to confirm this relationship.

The studies included in this review focused on differences in clinical presentation of psychosis in men and women through the lens of biological sex; however, it is important to highlight the role that gender could play in this relationship. While examining these differences in terms of sex may provide information regarding the biological influences on psychosis presentation, examining these differences in terms of social implications of sex, referred to as gender may provide information regarding how factors related to socialization influence the presentation of psychosis. We did not identify any studies focused on how gender may impact psychosis presentation, but these influences could stem from differences in patterns of behaviour, thinking, and feeling between the genders (Køster et al., 2008). For example, men are more

likely to smoke cannabis, and women may exhibit more social behaviours and willingness to accept help (Køster et al., 2008). Some of the findings from the current review could also be explained through a gender lens, for example where men have higher rates of substance use and women have higher levels of functioning. Future research on the relative contributions of sex and gender to differences in clinical presentation in FEP or early psychosis is warranted.

It is generally accepted that men and women present with psychosis in different ways; however, there is still a considerable knowledge gap about the how the illness presents in the early stages with regards to sex/gender differences. Based on findings from this study and from prior literature, it is presumed that women with psychotic disorders present with more subtle symptoms than men, due to less severe negative symptoms and higher functioning. This may cause the illness to be harder to detect, especially in the early course. Clinicians may be able to tailor interventions specifically toward young men or women experiencing early psychosis by better recognizing how symptoms differ between the sexes. Early detection and intervention is of utmost importance in psychotic disorders (Iyer et al., 2015), and understanding sex and gender differences in clinical presentation can help advance the aim of early detection (Iyer et al., 2015).

Limitations

The evidence from this review should be interpreted with consideration of several limitations of the included studies, and of the review itself. Many of the studies included in the review had small sample sizes, with more men than women. Although this is representative of the distribution of FEP in clinical populations (Anderson et al., 2018), this may limit the ability to generalize the study results to all people experiencing FEP or early psychosis, especially to women who may be receiving care outside the context of specialized early intervention services (Anderson et al., 2018). Definitions of FEP or early psychosis varied among the included studies, which may have impacted the clinical presentation noted in each study. Many of the studies limited their sample to those of a certain age, duration from symptom onset, or to those that spoke a certain language. These restrictions may also limit the external validity of the study findings, as the results may not be applicable to all people with early psychosis. Furthermore, given that women tend

to have a later age at onset (Ochoa et al., 2012), any age restrictions would function to underrepresent women with FEP. Another limitation of most of the included studies is the omission of cognitive symptoms. Evidence suggests that men and women with early psychosis may differ in cognitive functioning (Ochoa et al., 2012), which may be due to the positive role that estrogen plays in cognition (Sherwin, 1998). However, these symptoms were not commonly reported throughout the literature. Lastly, sex and gender differences within the included studies were often conflated, with the role of gender in the incidence and presentation of psychosis being ignored. A major gap in the literature remains on the grey areas of gender, and how these impact the clinical presentation of early psychosis. Future research should explore exposures that differ between genders, such as childhood trauma or abuse, head injury, spring birth, in-utero or birth complications, or pregnancy (Dean & Murray, 2005; Forde et al., 2020), and areas of gender fluidity, including LGBTQ+ people, intersex individuals, or those with hormone dysfunction. Further research on the topic should include data from these individuals to create a more cohesive understanding of the role of gender on symptoms of psychosis.

There are also several limitations of the overall review to be considered. Inclusion and exclusion criteria differed significantly across the included studies. Criteria such as age of the patient, amount of time from symptom onset, inclusion of drug-induced psychosis, and criteria used to define FEP or early psychosis varied between studies, which limits our ability to draw conclusions about subgroups of early psychosis patients and increases the heterogeneity in our data. The exclusion of UHR, CHR, or prodromal patients may decrease generalizability of the findings, however; sex differences in symptoms for these populations are out of the scope of this review. Additionally, although validated scales were used in all included studies to obtain measures of symptomology, these scales differed between studies and may have introduced heterogeneity in our pooled estimates, although the findings were largely consistent across measurement tools in our subgroup analyses. Finally, the differentiation between sex and gender is unable to be determined in the present review. It is still unknown whether differences in psychotic symptoms are due to biologic sex differences or if gender may also play a role.

Conclusions

Our findings suggest that men with FEP or early psychosis experience more negative symptoms and substance use than women, whereas women experience more depressive symptoms and have higher functioning than men. Gender differences were not found for positive symptoms or general psychopathology. The evidence from this study may help to inform clinicians and researchers on better identifying FEP and early psychosis to facilitate early intervention. Further population-based studies are needed to provide more substantial evidence on sex/gender differences in clinical presentation of early psychosis, and additionally, how these symptoms present outside the context of specialized early intervention services. Further research on the role of biological sex and gender factors in the clinical presentation of psychotic disorders is warranted.

References

Alho, J. M. (1992). On prevalence, incidence, and duration in general stable populations. *Biometrics*, *48*(2), 587–592.

Anderson, K. K., Norman, R., MacDougall, A. G., Edwards, J., Palaniyappan, L., Lau, C., & Kurdyak, P. (2018). Disparities in Access to Early Psychosis Intervention Services: Comparison of Service Users and Nonusers in Health Administrative Data. *The Canadian Journal of Psychiatry*, *63*(6), 395–403. https://doi.org/10.1177/0706743718762101

Arnold, L. M., Keck, P. E., Collins, J., Wilson, R., Fleck, D. E., Corey, K. B., Amicone, J., Adebimpe, V. R., & Strakowski, S. M. (2004). Ethnicity and first-rank symptoms in patients with psychosis. *Schizophrenia Research*, *67*(2), 207–212. https://doi.org/10.1016/S0920-9964(02)00497-8

Arranz, S., Mané, A., Bergé, D., Monserrat, C., cabezas, A., Vilella, E., & Sanchez-Gistau, V. (2020). The impact of sex and cannabis on clinical features in first–admitted patients with psychosis. *European Neuropsychopharmacology*, *36*, 235–243. https://doi.org/10.1016/j.euroneuro.2020.03.003

Austad, G., Joa, I., Johannessen, J. O., & Larsen, T. K. (2015). Gender differences in suicidal behaviour in patients with first-episode psychosis. *Early Intervention in Psychiatry*, *9*(4), 300–307. https://doi.org/10.1111/eip.12113

Ayesa-Arriola, R., Rodriguez-Sanchez, J. M., Gomez-Ruiz, E., Roiz-Santiáñez, R., Reeves, L. L., & Crespo-Facorro, B. (2014). No sex differences in neuropsychological performance in first episode psychosis patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *48*, 149–154. https://doi.org/10.1016/j.pnpbp.2013.09.009

Barajas, A., Baños, I., Ochoa, S., Usall, J., Huerta, E., Dolz, M., Sánchez, B., Villalta, V., Foix, A., Obiols, J., & Haro, J. M. (2010). Gender differences in incipient psychosis. *The European Journal of Psychiatry*, *24*(3), 176–194.

Bertani, M., Lasalvia, A., Bonetto, C., Tosato, S., Cristofalo, D., Bissoli, S., De Santi, K., Mazzoncini, R., Lazzarotto, L., Santi, M., Sale, A., Scalabrin, D., Abate, M., Tansella, M., & Ruggeri, M. (2012). The influence of gender on clinical and social characteristics of patients at psychosis onset: A report from the Psychosis Incident Cohort Outcome Study (PICOS). *Psychological Medicine*, *42*(4), 769–780. https://doi.org/10.1017/S0033291711001991

Breitborde, N. J. K., Srihari, V. H., & Woods, S. W. (2009). Review of the operational definition for first-episode psychosis. *Early Intervention in Psychiatry*, *3*(4), 259–265. https://doi.org/10.1111/j.1751-7893.2009.00148.x

Brzezinski-Sinai, N. A., & Brzezinski, A. (2020). Schizophrenia and Sex Hormones: What Is the Link? *Frontiers in Psychiatry*, *11*. https://www.frontiersin.org/article/10.3389/fpsyt.2020.00693

Buck, G., Lavigne, K. M., Makowski, C., Joober, R., Malla, A., & Lepage, M. (2020). Sex Differences in Verbal Memory Predict Functioning Through Negative Symptoms in Early Psychosis. *Schizophrenia Bulletin*, *46*(6), 1587–1595. https://doi.org/10.1093/schbul/sbaa054

Carliner, H., Mauro, P. M., Brown, Q. L., Shmulewitz, D., Rahim-Juwel, R., Sarvet, A. L., Wall, M. M., Martins, S. S., Carliner, G., & Hasin, D. S. (2017). The widening gender gap in marijuana use prevalence in the U.S. during a period of economic change, 2002–2014. *Drug and Alcohol Dependence*, *170*, 51–58. https://doi.org/10.1016/j.drugalcdep.2016.10.042

Caton, C. L. M., Xie, H., Drake, R. E., & McHugo, G. (2014). Gender Differences in Psychotic Disorders With Concurrent Substance Use. *Journal of Dual Diagnosis*, *10*(4), 177–186. https://doi.org/10.1080/15504263.2014.961882

Chang, W. C., Tang, J. Y. M., Hui, C. L. M., Chiu, C. P. Y., Lam, M. M. L., Wong, G. H. Y., Chung, D. W. S., Law, C. W., Tso, S., Chan, K. P. M., Hung, S. F., & Chen, E. Y. H. (2011). Gender Differences in Patients Presenting with First-Episode Psychosis in Hong Kong: A Three-Year Follow Up Study. *Australian & New Zealand Journal of Psychiatry*, *45*(3), 199–205. https://doi.org/10.3109/00048674.2010.547841

Chapter 5: Collecting data. (n.d.). Retrieved August 30, 2021, from https://training.cochrane.org/handbook/current/chapter-05

Chen, X., Xu, J., Li, B., Guo, W., Zhang, J., & Hu, J. (2018). Olfactory impairment in first-episode schizophrenia: A case-control study, and sex dimorphism in the relationship between olfactory impairment and psychotic symptoms. *BMC Psychiatry*, *18*(1), 199. https://doi.org/10.1186/s12888-018-1786-8

Cocchi, A., Lora, A., Meneghelli, A., La Greca, E., Pisano, A., Cascio, M. T., & Preti, A. (2014). Sex differences in first-episode psychosis and in people at ultra-high risk. *Psychiatry Research*, *215*(2), 314–322. https://doi.org/10.1016/j.psychres.2013.11.023

Cotton, S. M., Lambert, M., Berk, M., Schimmelmann, B. G., Butselaar, F. J., McGorry, P. D., & Conus, P. (2013). Gender differences in first episode psychotic mania. *BMC Psychiatry*, *13*(1), 82. https://doi.org/10.1186/1471-244X-13-82

Cotton, S. M., Lambert, M., Schimmelmann, B. G., Foley, D. L., Morley, K. I., McGorry, P. D., & Conus, P. (2009). Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis. *Schizophrenia Research*, *114*(1–3), 17–24. https://doi.org/10.1016/j.schres.2009.07.002

Coughlan, H., Cannon, M., Shiers, D., Power, P., Barry, C., Bates, T., Birchwood, M., Buckley, S., Chambers, D., Davidson, S., Duffy, M., Gavin, B., Healy, C., Healy, C., Keeley, H., Maher, M., Tanti, C., & McGorry, P. (2013). Towards a new paradigm of care: The International Declaration on Youth Mental Health. *Early Intervention in Psychiatry*, *7*(2), 103–108. https://doi.org/10.1111/eip.12048

Dama, M., Veru, F., Schmitz, N., Shah, J., Iyer, S., Joober, R., & Malla, A. (2019). Sex Differences in Clinical and Functional Outcomes among Patients Treated in an Early Intervention Service for Psychotic Disorders: An Observational Study. *The Canadian Journal of Psychiatry*, 070674371985406. https://doi.org/10.1177/0706743719854069

Danaher, H., Allott, K., Killackey, E., Hester, R., & Cotton, S. (2018). An examination of sex differences in neurocognition and social cognition in first-episode psychosis. *Psychiatry Research*, *259*, 36–43. https://doi.org/10.1016/j.psychres.2017.09.053

Dean, K., & Murray, R. M. (2005). Environmental risk factors for psychosis. *Dialogues in Clinical Neuroscience*, *7*(1), 69–80.

El-Sawy, H. E.-D. (2010). P03-207—Gender differences in risks and pattern of drug dependence in Egypt. *European Psychiatry*, *25*, 1273. https://doi.org/10.1016/S0924-9338(10)71261-X

Forde, R., Peters, S., & Wittkowski, A. (2020). Recovery from postpartum psychosis: A systematic review and metasynthesis of women's and families' experiences. *Archives of Women's Mental Health*, *23*(5), 597–612. https://doi.org/10.1007/s00737-020-01025-z

Fridgen, G. J., Aston, J., Gschwandtner, U., Pflueger, M., Zimmermann, R., Studerus, E., Stieglitz, R.-D., & Riecher-Rössler, A. (2013). Help-seeking and pathways to care in the early stages of psychosis. *Social Psychiatry and Psychiatric Epidemiology*, *48*(7), 1033–1043. https://doi.org/10.1007/s00127-012-0628-0

Galdos, P. M., van Os, J. J., & Murray, R. M. (1993). Puberty and the onset of psychosis. *Schizophrenia Research*, *10*(1), 7–14. https://doi.org/10.1016/0920-9964(93)90071-P

Garcia, M., Montalvo, I., Creus, M., Cabezas, Á., Solé, M., Algora, M. J., Moreno, I., Gutiérrez-Zotes, A., & Labad, J. (2016). Sex differences in the effect of childhood trauma on the clinical expression of early psychosis. *Comprehensive Psychiatry*, *68*, 86–96. https://doi.org/10.1016/j.comppsych.2016.04.004

Gibbons, R. J., Thorsteinsson, E. B., & Loi, N. M. (2015). Beliefs and attitudes towards mental illness: An examination of the sex differences in mental health literacy in a community sample. *PeerJ*, *3*, e1004. https://doi.org/10.7717/peerj.1004

González-Rodríguez, A., Studerus, E., Spitz, A., Bugra, H., Aston, J., Borgwardt, S., Rapp, C., & Riecher-Rossler, A. (2014). Gender differences in the psychopathology of emerging psychosis. *The Israel Journal of Psychiatry and Related Sciences*, *51*(2), 85–92.

Haavik, L., Joa, I., Hatloy, K., Stain, H. J., & Langeveld, J. (2019). Help seeking for mental health problems in an adolescent population: The effect of gender. *Journal of Mental Health (Abingdon, England)*, *28*(5), 467–474. https://doi.org/10.1080/09638237.2017.1340630

Häfner, H., Maurer, K., Löffler, W., & Riecher-Rössler, A. (1993). The Influence of Age and Sex on the Onset and Early Course of Schizophrenia. *The British Journal of Psychiatry*, *162*(1), 80–86. https://doi.org/10.1192/bjp.162.1.80

Häfner, H., Riecher-Rössler, A., Maurer, K., Fätkenheuer, B., & Löffler, W. (1992). First onset and early symptomatology of schizophrenia. A chapter of epidemiological and neurobiological research into age and sex differences. *European Archives of Psychiatry and Clinical Neuroscience*, *242*(2–3), 109–118. https://doi.org/10.1007/BF02191557

Harris, R. J., Deeks, J. J., Altman, D. G., Bradburn, M. J., Harbord, R. M., & Sterne, J. A. C. (2008). Metan: Fixed- and Random-Effects Meta-Analysis. *The Stata Journal: Promoting Communications on Statistics and Stata*, *8*(1), 3–28. https://doi.org/10.1177/1536867X0800800102

Heckers, S., Barch, D. M., Bustillo, J., Gaebel, W., Gur, R., Malaspina, D., Owen, M. J., Schultz, S., Tandon, R., Tsuang, M., Van Os, J., & Carpenter, W. (2013). Structure of the psychotic disorders classification in DSM-5. *Schizophrenia Research*, *150*(1), 11–14. https://doi.org/10.1016/j.schres.2013.04.039

Heitz, U., Studerus, E., Menghini-Müller, S., Papmeyer, M., Egloff, L., Ittig, S., Navarra, A., Andreou, C., & Riecher-Rössler, A. (2019). Gender differences in first self-perceived signs and symptoms in patients with an at-risk mental state and first-episode psychosis. *Early Intervention in Psychiatry*, *13*(3), 582–588. https://doi.org/10.1111/eip.12528

Hochman, K. M., & Lewine, R. R. (2004). Age of menarche and schizophrenia onset in women. *Schizophrenia Research*, *69*(2), 183–188. https://doi.org/10.1016/S0920-9964(03)00176-2

Huber, T. J., Tettenborn, C., Leifke, E., & Emrich, H. M. (2005). Sex hormones in psychotic men. *Psychoneuroendocrinology*, *30*(1), 111–114. https://doi.org/10.1016/j.psyneuen.2004.05.010

Hui, C. L.-M., Leung, C.-M., Chang, W.-C., Chan, S. K.-W., Lee, E. H.-M., & Chen, E. Y.-H. (2016). Examining gender difference in adult-onset psychosis in Hong Kong: Gender difference in psychosis. *Early Intervention in Psychiatry*, *10*(4), 324–333. https://doi.org/10.1111/eip.12167

Irving, J., Colling, C., Shetty, H., Pritchard, M., Stewart, R., Fusar-Poli, P., McGuire, P., & Patel, R. (2021). Gender differences in clinical presentation and illicit substance use during first episode psychosis: A natural language processing, electronic case register study. *BMJ Open*, *11*(4), e042949. https://doi.org/10.1136/bmjopen-2020-042949

Iyer, S., Jordan, G., MacDonald, K., Joober, R., & Malla, A. (2015). Early intervention for psychosis: A Canadian perspective. *The Journal of Nervous and Mental Disease*, *203*(5), 356–364. https://doi.org/10.1097/NMD.0000000000000288

Køster, A., Lajer, M., Lindhardt, A., & Rosenbaum, B. (2008). Gender differences in first episode psychosis. *Social Psychiatry and Psychiatric Epidemiology*, *43*(12), 940–946. https://doi.org/10.1007/s00127-008-0384-3

Lang, X.-E., Zhu, D., Zhang, G., Du, X., Jia, Q., Yin, G., Chen, D., Xiu, M., Cao, B., Wang, L., Li, X., Soares, J. C., & Zhang, X. Y. (2018). Sex difference in association of symptoms and white matter deficits in first-episode and drug-naive schizophrenia. *Translational Psychiatry*, *8*(1), 281. https://doi.org/10.1038/s41398-018-0346-9

Lansche, J. (n.d.). *Tool to Assess Risk of Bias in Cohort Studies*. 7.

Leung M.D., Dr. A., & Chue M. R. C. Psych., Dr. P. (2000). Sex differences in schizophrenia, a review of the literature. *Acta Psychiatrica Scandinavica*, *101*(401), 3–38. https://doi.org/10.1111/j.0065-1591.2000.0ap25.x

Lieberman, J. A., & First, M. B. (2018). Psychotic Disorders. *New England Journal of Medicine*, *379*(3), 270–280. https://doi.org/10.1056/NEJMra1801490

Lodha, P., & Karia, S. (2019). Testosterone and schizophrenia: A clinical review. *Annals of Indian Psychiatry*, *3*(2), 92–92.

Malla, A. K., Norman, R. M. G., Manchanda, R., Ahmed, M. R., Scholten, D., Harricharan, R., Cortese, L., & Takhar, J. (2002). One year outcome in first episode psychosis: Influence of DUP and other predictors. *Schizophrenia Research*, *54*(3), 231–242. https://doi.org/10.1016/s0920-9964(01)00254-7

Mbewe, E., Haworth, A., Welham, J., Mubanga, D., Chazulwa, R., Zulu, M. M., Mayeya, J., & McGrath, J. (2006). Clinical and demographic features of treated first-episode psychotic disorders: A Zambian study. *Schizophrenia Research*, *86*(1), 202–207. https://doi.org/10.1016/j.schres.2006.03.046

McCoy, S. S., Dimler, L. M., Samuels, D. V., & Natsuaki, M. N. (2019). Adolescent Susceptibility to Deviant Peer Pressure: Does Gender Matter? *Adolescent Research Review*, *4*(1), 59–71. https://doi.org/10.1007/s40894-017-0071-2

Navarro, F., van Os, J., Jones, P., & Murray, R. (1996). Explaining sex differences in course and outcome in the functional psychoses. *Schizophrenia Research*, *21*(3), 161–170. https://doi.org/10.1016/0920-9964(96)00032-1

Ochoa, S., Usall, J., Cobo, J., Labad, X., & Kulkarni, J. (2012). Gender differences in schizophrenia and first-episode psychosis: A comprehensive literature review. *Schizophrenia Research and Treatment*, *2012*, 916198. https://doi.org/10.1155/2012/916198

Penney, D., Joober, R., Malla, A., & Lepage, M. (2020). Understanding sex differences in cognitive insight across first-and-multiple episode psychosis. *Schizophrenia Research*, *218*, 276–282. https://doi.org/10.1016/j.schres.2019.12.024

Preston, N. J., Orr, K. G., Date, R., Nolan, L., & Castle, D. J. (2002). Gender differences in premorbid adjustment of patients with first episode psychosis. *Schizophrenia Research*, *55*(3), 285–290. https://doi.org/10.1016/S0920-9964(01)00215-8

PRISMA. (n.d.). Retrieved August 30, 2021, from http://prisma-statement.org/prismastatement/Checklist.aspx

Pruessner, M., King, S., Vracotas, N., Abadi, S., Iyer, S., Malla, A. K., Shah, J., & Joober, R. (2019). Gender differences in childhood trauma in first episode psychosis: Association with symptom severity over two years. *Schizophrenia Research*, *205*, 30–37. https://doi.org/10.1016/j.schres.2018.06.043

Rapado-Castro, M., Bartholomeusz, C. F., Castro-Fornieles, J., González-Pinto, A., Otero, S., Baeza, I., Moreno, C., Graell, M., Janssen, J., Bargalló, N., Pantelis, C., Desco, M., & Arango, C. (2015). Gender effects on brain changes in early-onset psychosis. *European Child & Adolescent Psychiatry*, *24*(10), 1193–1205. https://doi.org/10.1007/s00787-014-0669-x

Reed, S. I. (2008). First-episode psychosis: A literature review. *International Journal of Mental Health Nursing*, *17*(2), 85–91. https://doi.org/10.1111/j.1447-0349.2008.00515.x

Riecher-Rössler, A., Butler, S., & Kulkarni, J. (2018). Sex and gender differences in schizophrenic psychoses-a critical review. *Archives of Women's Mental Health*, *21*(6), 627–648. https://doi.org/10.1007/s00737-018-0847-9

Sami Räsänen, Antti Pakaslahti, Erk. (2000). Sex differences in schizophrenia: A review. *Nordic Journal of Psychiatry*, *54*(1), 37–45. https://doi.org/10.1080/080394800427564

Segarra, R., Ojeda, N., Zabala, A., García, J., Catalán, A., Eguíluz, J. I., & Gutiérrez, M. (2012). Similarities in early course among men and women with a first episode of schizophrenia and schizophreniform disorder. *European Archives of Psychiatry and Clinical Neuroscience*, *262*(2), 95–105. https://doi.org/10.1007/s00406-011-0218-2

Sherwin, B. B. (1998). Estrogen and Cognitive Functioning in Women. *Proceedings of the Society for Experimental Biology and Medicine*, *217*(1), 17–22. https://doi.org/10.3181/00379727-217-44200

StataCorp. (2021). *Stata Statistical Software* (Version 17) [Computer software]. StataCorp.

Suhail, K., & Chaudhry, H. (2006). Evolution of Symptoms in the Early Course of Schizophrenia in Pakistan: Effect of Age and Gender. *Hong Kong Journal of Psychiatry*, *16*, 57–64.

Talonen, S., Väänänen, J., & Kaltiala-Heino, R. (2017). Gender differences in first onset Schizophrenia spectrum psychoses. *Nordic Journal of Psychiatry*, *71*(2), 131–138. https://doi.org/10.1080/08039488.2016.1245783

Thorup, A., Petersen, L., Jeppesen, P., Ohlenschlaeger, J., Christensen, T., Krarup, G., Jorgensen, P., & Nordentoft, M. (2007). Gender differences in young adults with first-episode schizophrenia spectrum disorders at baseline in the Danish OPUS study. *The Journal of Nervous and Mental Disease*, *195*(5), 396–405. https://doi.org/10.1097/01.nmd.0000253784.59708.dd

Unger, R. K. (1979). Toward a redefinition of sex and gender. *American Psychologist*, *34*(11), 1085–1094. http://dx.doi.org/10.1037/0003-066X.34.11.1085

van Os, J., Bak, M., Hanssen, M., Bijl, R. V., de Graaf, R., & Verdoux, H. (2002). Cannabis Use and Psychosis: A Longitudinal Population-based Study. *American Journal of Epidemiology*, *156*(4), 319–327. https://doi.org/10.1093/aje/kwf043

Vila-Badia, R., Del Cacho, N., Butjosa, A., Ochoa, S., Serra-Arumí, C., Esteban-Sanjusto, M., Pardo, M., Dolz, M., Casado-Ortega, A., Coromina, M., PROFEP Grup, & Usall, J. (2020). Cognitive functioning in first episode psychosis. Gender differences and relation with clinical variables. *Early Intervention in Psychiatry*, eip.13110. https://doi.org/10.1111/eip.13110

Table 1: Summary of study/sample characteristics of included studies (n=35)

Study ID, Author	Year	Country	Study Design	Sample Source	Sample Size	Age Range	Diagnoses Included	Definition of FEP/ Early Psychosis
1. (Arnold et al., 2004)	2002	United States	cohort	inpatient	180	18-45	SPR, SAD, NAP, BD, MDD	Presence of at least one psychotic symptom
2. (Arranz et al., 2020)	2020	Spain	cohort	inpatient	204	18-35	N/A	Admitted to inpatient unit for first time for FEP with psychotic symptoms of <1 year duration
3. (Austad et al., 2015)	2015	Norway	cohort	outpatient-EPI	246	15-65	SPR, SFD, SAD, BPD, DD, AP, PDN, DIP	<12 weeks of antipsychotic treatment,
4. (Ayesa-Arriola et al., 2014)	2014	Spain	cohort	outpatient-EPI	161	15-60	BPD, SFD, SPR, SAD, PDN	No prior antipsychotic treatment
5. (Barajas et al., 2010)	2010	Spain	cohort	outpatient-all	53	7-65	PDN	Two or more psychotic symptoms for <1 year, <6 months since first contact
6. (Bertani et al., 2012)	2012	Italy	cross-sectional	outpatient-all	397	15-54	NAP, AP	Presence of 1+ positive symptoms or 2+ negative symptoms
7. (Buck et al., 2020)	2020	Canada	cohort	outpatient-EPI	435	18-35	SPR, SAD, NAP, DD, BPD, PDN, BD, MDD	No past antipsychotic treatment for >1 month
8. (Caton et al., 2014)	2014	United States	cohort	inpatient	217	17-45	PDN	Presence of 1+ psychotic symptoms
9. (Chang et al., 2011)	2011	China	cohort	outpatient-EPI	700	18-55	SPR, AP, SAD, PDN	>3 years from first episode
10. (Chen et al., 2018)	2018	China	case-control	outpatient-all	110	18-35	SPR	No past antipsychotic treatment
11.(Cocchi et al., 2014)	2014	Italy	case-control	outpatient-EPI	152	17-30	SPR	DUP <24 months
12. (Cotton et al., 2009)	2009	Australia	cohort	outpatient-EPI	661	15-29	SAD, NAP	First treated psychotic episode
13. (Dama et al., 2019)	2019	Canada	cohort	outpatient-EPI	569	14-35	SAD, NAP	No past antipsychotic treatment for >1 month
14. (Danaher et al., 2018)	2018	Australia	cross-sectional	outpatient-EPI	134	15-25	SPR, SFD, SAD, BPD, DD, AP, PDN	>6 months remaining in EPI treatment
15. (Garcia et al., 2016)	2016	Spain	case-control	outpatient-EPI	79	18-35	SPR, SFD, BD, PDN	<3 years since onset of illness
16. (Heitz et al., 2019)	2016	Switzerland	cohort	outpatient-EPI	89	18+	PDN	Attenuated or brief limited intermittent psychotic symptoms
17. (Hui et al., 2016)	2016	China	cohort	population-based survey	360	26-55	SPR, DD, SFD, BPD, PDN, SAD	<1 year antipsychotic treatment
18. (Køster et al., 2008)	2008	Denmark	cohort	outpatient-EPI	269	16-35	PDN	First psychotic episode
19. (Lang et al., 2018)	2018	China	cohort	outpatient-EPI	39	16-45	SPR	Experiencing acute psychotic episode

Notes: SPR = Schizophrenia, SAD = Schizoaffective disorder, NAP = non-affective psychoses, BD = bipolar disorder, MDD = major depressive disorder, SFD= Schizophreniform disorder, BPD = brief psychotic disorder, DD = delusional disorder, AP = affective psychosis, PDN = psychotic disorder not otherwise specified, DIP = drug-induced psychosis, MD = mood disorders, AD = anxiety disorders, PD = personality disorders, FEPM= first episode psychotic mania. Symptoms were measured at index for all included studies.

Table 1 con't: Summary of study/sample characteristics of included studies (n=35)

Study ID, Author	Year	Country	Study Design	Sample Source	Sample Size	Age Range	Diagnoses Included	Definition of FEP/ Early Psychosis
20. (Malla et al., 2002)	2002	Canada	cohort	outpatient-EPI	88	N/A	SPR, SFD, BD, PDN	>1 week psychotic symptoms
21. (Mbewe et al., 2006)	2006	Zambia	cohort	inpatient	160	12-86	SPR, SFD, BD, PDN	Diagnosis of psychotic disorder by DSM-IV, positive on Psychosis Screening Questionnaire
22. (Navarro et al., 1996)	1996	UK	cohort	inpatient	166	16-60	SPR, SFD, SAD, AP, NAP	Presence of at least one positive symptom
23. (Penney et al., 2020)	2020	Canada	cross-sectional	outpatient-EPI	171	18-35	SPR, SAD, DD, SFD, DIP, PDN	<6 months from onset
24. (Preston et al., 2002)	2002	Australia	cross-sectional	outpatient-EPI	44	15-35	SPR, SFD, PDN	Diagnosis of FEP by Operational Checklist for Psychotic Illness and Affective Illness
25. (Pruessner et al., 2019)	2019	Canada	cohort	outpatient-EPI	210	14-35	AP, NAP	<1 month antipsychotic treatment
26. (Rapado-Castro et al., 2015)	2015	Spain	cohort	in/outpatient	61	7-17	SPR, BD, PDN	<6 months from onset
27. (Segarra et al., 2012)	2012	Spain	cohort	in/outpatient	231	15-65	SPR, SFD	Presence of positive symptoms, no prior antipsychotic treatment
28. (Suhail & Chaudhry, 2006)	2006	Pakistan	cross-sectional	inpatient	140	16-40	SPR	First admission, >4 weeks duration
29. (Talonen et al., 2017)	2017	Finland	cohort	inpatient	106	13-17	DIP, SPR, MD, AD, PD	First diagnosis of psychotic disorder
30. (Vila-Badia et al., 2020)	2020	Spain	cross-sectional	inpatient	70	13-55	PDN	Presenting with psychotic symptoms (positive, negative, disorganized) for at least one week and <5 years
31. (Irving et al., 2021)	2021	UK	cross-sectional	registry/admin data	3350	16-65	BD, DIP, SPR, SAD, PDN	<1 year from onset
32. (Cotton et al., 2013)	2013	Australia	cohort	outpatient-EPI	118	15-29	FEPM	First psychotic episode
33. (Häfner et al., 1992)	1992	Germany	cohort	inpatient	267	12-59	SPR	First admission for psychotic episode
34. (González-Rodríguez et al., 2014)	2014	Switzerland	cohort	outpatient-EPI	87	18+	FEP	FEP diagnosis by the Basel Screening Instrument for Psychosis, symptoms at least several times a week
35. (Thorup et al., 2007)	2007	Denmark	cohort	In/outpatient	578	18-45	SPR, DD, SAD, PDN	<12 weeks antipsychotic treatment

Notes: SPR = Schizophrenia, SAD = Schizoaffective disorder, NAP = non-affective psychoses, BD = bipolar disorder, MDD = major depressive disorder, SFD= Schizophreniform disorder, BPD = brief psychotic disorder, DD = delusional disorder, AP = affective psychosis, PDN = psychotic disorder not otherwise specified, DIP = drug-induced psychosis, MD = mood disorders, AD = anxiety disorders, PD = personality disorders, FEPM= first episode psychotic mania. Symptoms were measured at index for all included studies.

Table 2: Main findings by symptom category across studies

Symptom Category	Number of Studies	Overall Trend Direction
Positive	31	16/31 more severe symptoms in men
Negative	30	25/30 more severe symptoms in men
Depression	20	14/20 more severe symptoms in women
Psychopathology	14	6/14 more severe symptoms in men
Functioning	16	13/16 higher functioning in women
Substance Use (combined alcohol and drug use)	5	5/5 higher prevalence in men
Alcohol Use	6	4/6 higher prevalence in men
Drug Use	10	10/10 higher prevalence in men

Figure 1: PRISMA diagram of study identification and selection for systematic review and meta-analysis

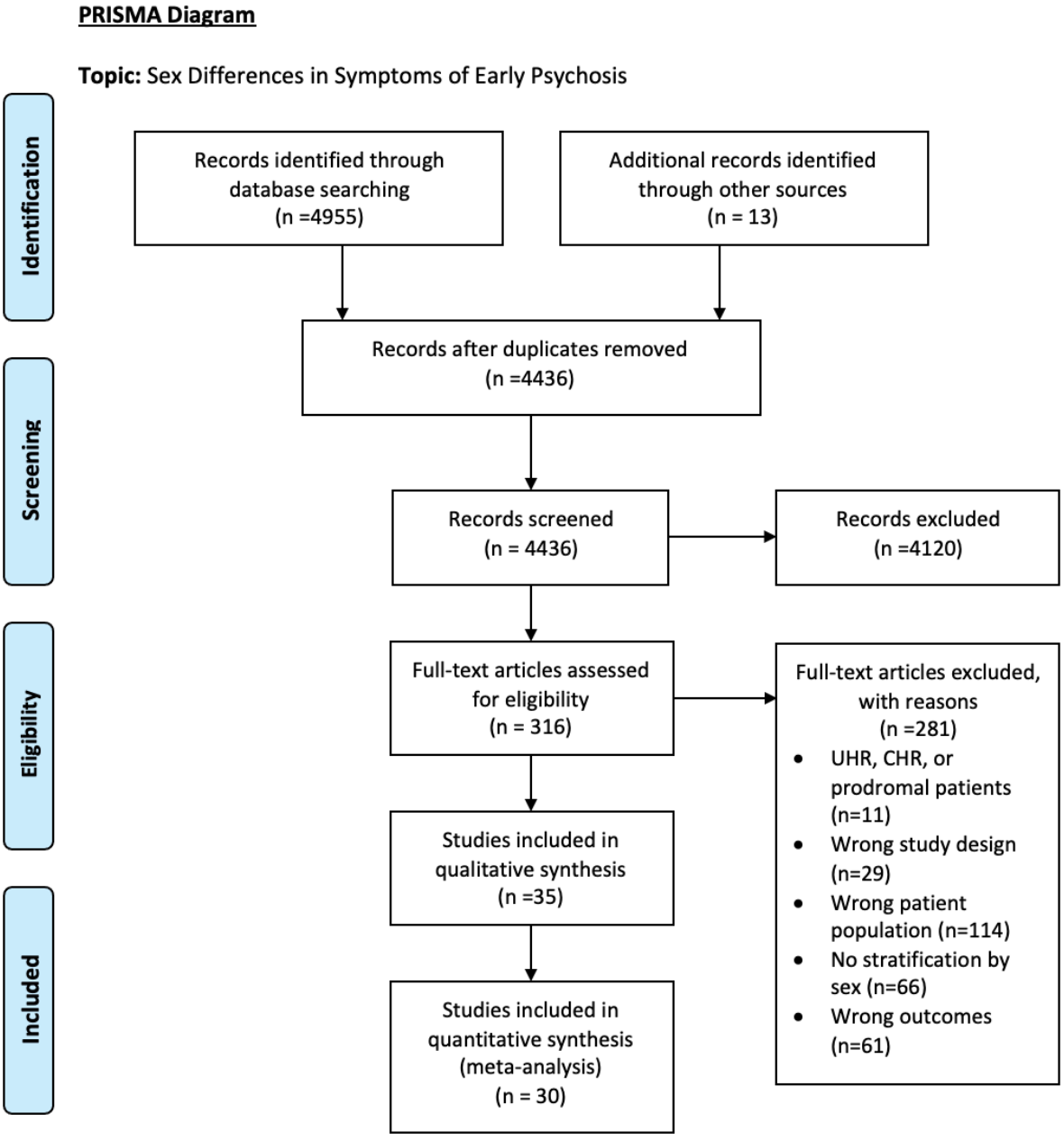

Figure 2: Summary of findings from the risk of bias assessment

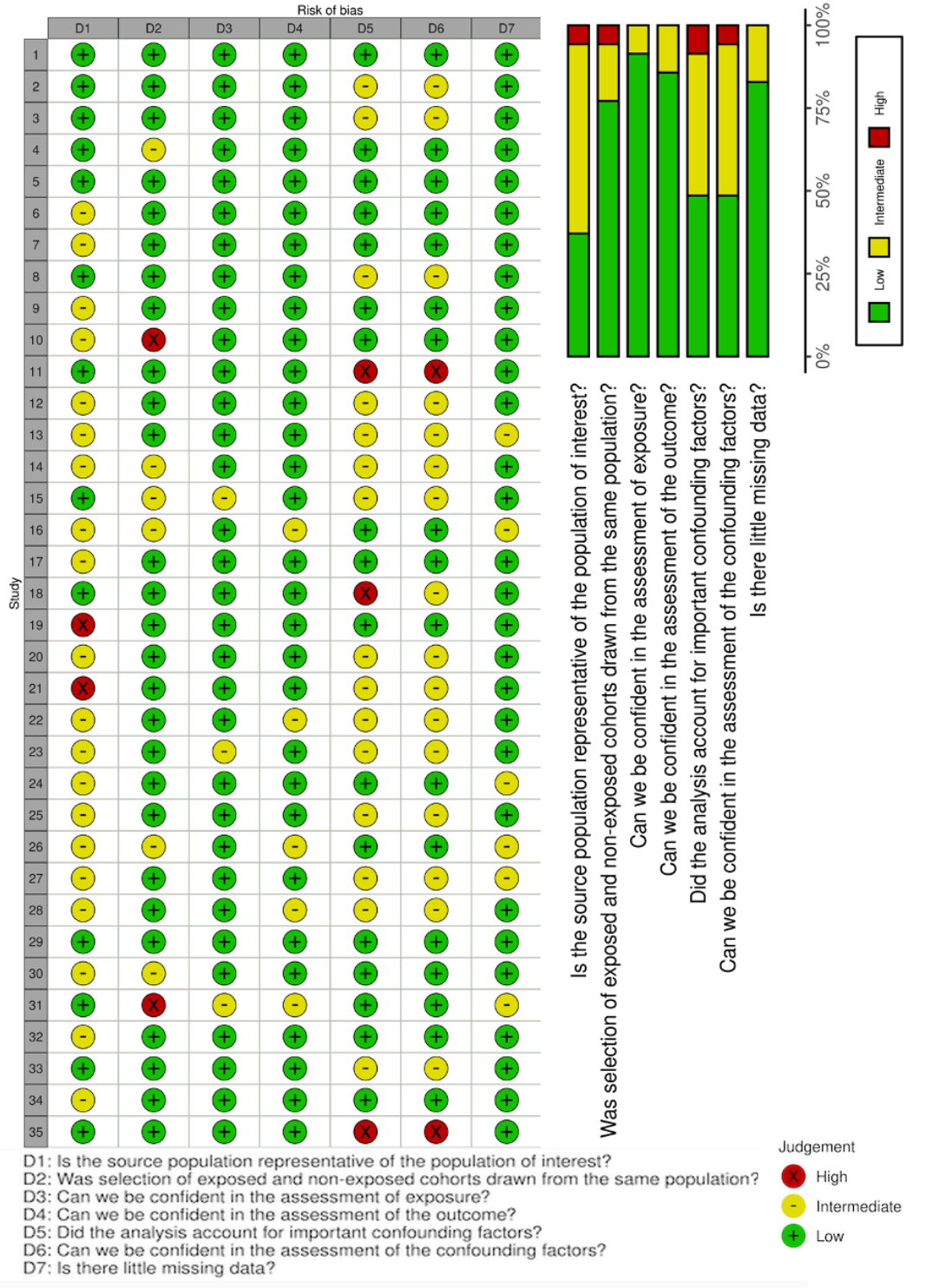

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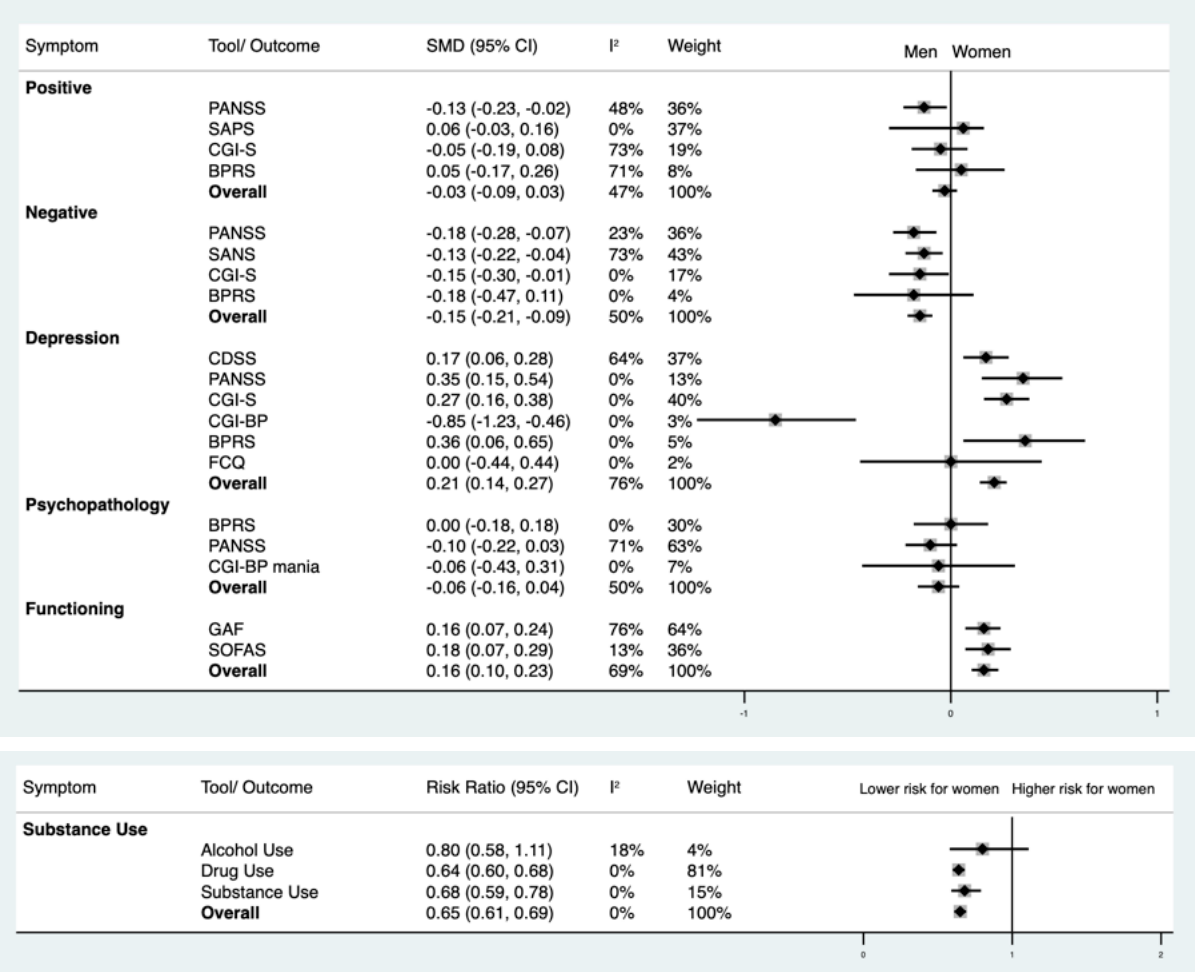
Figure 3: Results from meta-analysis by symptom measure, with subgroup analysis by measurement tool (n=30)



Notes: SMD = Standardized Mean Difference, PANSS = Positive and Negative Syndrome Scale, SAPS = Scale for the Assessment of Positive Symptoms, CGI-S/BP = The Clinical Global Impression-Severity Scale/ Bipolar, BPRS = Brief Psychiatric Rating Scale, SANS = Scale for the Assessment of Negative Symptoms, CDSS = The Calgary Depression Scale, FCQ = Frankfurt Complaint Questionnaire, GAF = Global Assessment of Functioning Scale, SOFAS = Social and Occupational Functioning Assessment Scale