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Review article

Unraveling the gender divide: A systematic review of gender-specific differences at the first episode of psychosis

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ABSTRACT

This systematic review aims to explore gender differences in the first episode of psychosis (FEP) among individuals aged 13 to 24 years, focusing on clinical, demographic, and outcomecharacteristics, with an emphasis on how gender-related differences in symptom presentation maycontribute to misdiagnosis, particularly among females. A comprehensive search was conducted across PubMed, Embase, and PsycInfo databases, targeting-studies published between 2014 and 2024. Inclusion criteria were observational and experimentalstudies reporting gender-disaggregated data on the FEP in adolescents and young adults aged 13 to24 years. The screening and selection process followed a systematic approach, and data wereextracted focusing on gender-based differences in onset, clinical presentation, and outcomes ofpsychosis. The final section comprised six studies involving 3798 individuals with a diagnosis of FEP. Thefindings highlighted a later onset of psychosis in females, along with a more affective and atypicalsymptom presentation compared to males, who exhibited more overt psychotic features. Femaleswere more frequently misdiagnosed with mood disorders before receiving a correct psychosisdiagnosis, contributing to delayed interventions. Despite better short-term treatment responses inwomen, they showed higher vulnerability to relapse, particularly in hormonally sensitive periods. The differences in clinical presentation between males and females in FEP may contribute to highermisdiagnosis rates in women. By examining these gender differences, this review highlights theneed for more accurate diagnostic criteria and tailored interventions for both genders, which couldimprove early intervention.

1. Introduction

Schizophrenia spectrum disorders have a typical onset between adolescence and early adulthood, with the first episode of psychosis (FEP) most commonly emerging during adolescence and early adulthood, with peak incidence occurring between ages 15 and 25 (Kessler et al., 2007). Although psychotic onset may seem like an abrupt event, it is preceded by prodromal phases that can span several months or even years. During this time, individuals often experience a range of psychological and behavioral changes, as well as abnormalities (Larson et al., 2010). Research suggests that this prodromal phase can typically last around 5 years, during which emotional, cognitive, perceptual, and psychophysiological disturbances may arise, alongside a decline in motivation and functional abilities across various aspects of life (Häfner et al., 2000). This emphasizes the need for close monitoring of individuals aged 13–24 to facilitate early detection of psychotic symptoms and timely intervention, ultimately enhancing prognosis and quality of life.

This initial episode marks a critical juncture in the progression of these disorders, often shaping the trajectory of the illness and significantly influencing long-term outcomes (Baldini et al., 2025; Griffiths et al., 2022). Early identification and intervention during this period are

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vital for preventing long-term disability and improving the quality of life for individuals affected by psychosis (McGorry et al., 2018). However, the diagnostic process for FEP can be complex and challenging, mainly due to variations in symptom presentation across demographic and cultural subgroups, the continuum of pwomensychotic symptoms, and the overlap with other non-psychotic disorders (Malla et al., 2005). There is, for example, a growing interest in the literature in exploring the different clinical presentations in specific subgroups. The first step is to refine the tools for standardizing the measures used in different cultural contexts so that the various available variables can be comparable and analyzable to highlight the subtle differences in the clinical onset of psychosis (Whitmyre et al., 2024).

One key factor contributing to diagnostic challenges is not gender itself, but rather how gender-related differences in symptom presentation interact with clinical interpretation within current diagnostic criteria and healthcare systems.

In this review, we adopt the term "gender" to reflect the terminology used in most of the included studies. However, it is important to acknowledge that "sex" refers to biological characteristics, such as hormonal and chromosomal differences, whereas "gender" involves socially constructed roles, behaviors, and identities. Since the majority of the studies did not clearly differentiate between sex and gender, we use the term "gender differences" in a broad sense, although we recognize this conceptual limitation. In all included studies, the classification was binary and based on the original authors' reporting, without explicit assessment of gender identity. As a result, the term "gender differences" in this review likely reflects biological sex rather than gender identity, a limitation that should be addressed by future studies using standardized and prospective measures.

Research has shown significant gender and sex differences in the clinical manifestation of psychosis, particularly in its early stages (Fusar-Poli et al., 2016). While males often present with more overt and typical psychotic symptoms, females may exhibit more subtle or atypical signs that do not align with conventional diagnostic criteria. Gender differences in prodromal symptoms have also been observed: males more frequently exhibit negative or behavioral symptoms, while females tend to present with internalizing symptoms such as anxiety or depression, which can obscure early psychosis recognition (Abel et al., 2010; Ochoa et al., 2012).

Unlike previous reviews and meta-analyses, which primarily focused on symptom severity at presentation, our review delves deeper into gender-specific diagnostic biases, long-term prognostic trajectories, and the influence of hormonal fluctuations on relapse risk in adolescents and young adults with FEP (Carter et al., 2022). These disparities may contribute to alternative initial diagnostic formulations, particularly in females, when early psychotic symptoms present with prominent affective or atypical features. This does not imply bias in diagnostic criteria themselves, but rather challenges in clinical interpretation and longitudinal assessment before psychotic disorder criteria are clearly met.

Studies suggest that women may be more likely to receive alternative initial diagnostic formulations when early psychotic symptoms present with less typical or predominantly affective features, making early recognition more challenging (Abel et al., 2010). This does not imply a bias in diagnostic criteria themselves, but rather reflects difficulties in clinical interpretation and longitudinal assessment before psychotic disorder criteria are clearly met.

In addition to misdiagnosis, sex differences can also affect the course of the illness. For instance, the age of onset, severity of symptoms, and treatment response can vary significantly between males and females (Ochoa et al., 2012). Females may experience a later onset of psychosis or demonstrate a more insidious progression of symptoms, which could further complicate early detection. Moreover, there are indications that gender may influence the long-term prognosis of individuals with psychosis, including factors such as recovery, functional status, and the presence of psychiatric comorbidities (Seeman et al., 2019). Understanding gender differences does not imply the need for new diagnostic categories or instruments, but rather a more nuanced application of existing diagnostic frameworks. In clinical practice, this may translate into targeted clinician training to improve recognition of gender-related variations in early psychosis presentation, particularly the tendency for women to present with affective, internalizing, or atypical symptoms. A gender-informed perspective may also guide the interpretation of existing assessment tools, encouraging systematic evaluation of psychotic symptoms even when mood or anxiety symptoms predominate. Finally, structured and longitudinal early intervention pathways, with periodic diagnostic re-evaluation, may help reduce misdiagnosis in cases with initially ambiguous presentations. Together, these approaches may contribute to improved diagnostic accuracy without requiring formal changes to diagnostic criteria (Canuso et al., 2007).

Despite the significance of these differences, the literature on gender disparities in the onset and progression of psychosis remains somewhat limited, particularly among young individuals. Most studies have not sufficiently addressed how gender influences FEP nor explored how these disparities may lead to diagnostic challenges (Køster et al., 2008).

We targeted the age range of 13 to 24 years to specifically capture the developmental transition from early adolescence to young adulthood, a period marked by significant neurobiological, hormonal, and psychosocial changes that are highly relevant to the onset and clinical presentation of psychosis. Although some early intervention services extend into the late 20 s or early 30 s, this age range remains the primary focus for many youth mental health and early psychosis programs worldwide. Importantly, gender differences in symptom presentation, help-seeking behaviors, and diagnostic pathways seem to be especially prominent during this developmental stage, making it a clinically and conceptually meaningful focus for this review.

This systematic review aims to bridge this gap by comprehensively analyzing gender differences in FEP, focusing on clinical characteristics, demographic factors, and treatment outcomes. Special attention will be given to understanding how these differences might contribute to misdiagnosis, enhance diagnostic accuracy, and improve treatment strategies for both males and females. Through this review, we intend to offer valuable insights that can inform clinical practice, reduce gender-related diagnostic disparities, and ultimately enhance care and long-term outcomes for young individuals experiencing psychosis.

2. Method

This systematic literature review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The study protocol was registered in advance on PROSPERO (CDR42025647900).

2.1. Eligibility criteria

This systematic review examined gender differences in FEP among individuals aged 13 to 24 years.

This age range was chosen to ensure developmental consistency and to focus on the period of greatest risk for FEP onset, while reducing variability related to later-onset psychosis.

Studies were included if they specifically addressed this age group, if the study population predominantly fell within this range, or if age-specific analyses were provided. Studies with a broader age range were also considered eligible, as long as the sample characteristics or subgroup analyses permitted the extraction or inference of relevant data pertaining to adolescents and young adults. We excluded studies that did not allow for disaggregation of findings for this age group.

Only observational studies, including cohort, case-control, cross-sectional designs, and experimental studies, were considered to ensure methodological rigor and relevance to current clinical practices. Eligible studies were required to be published in English between 2014 and 2024

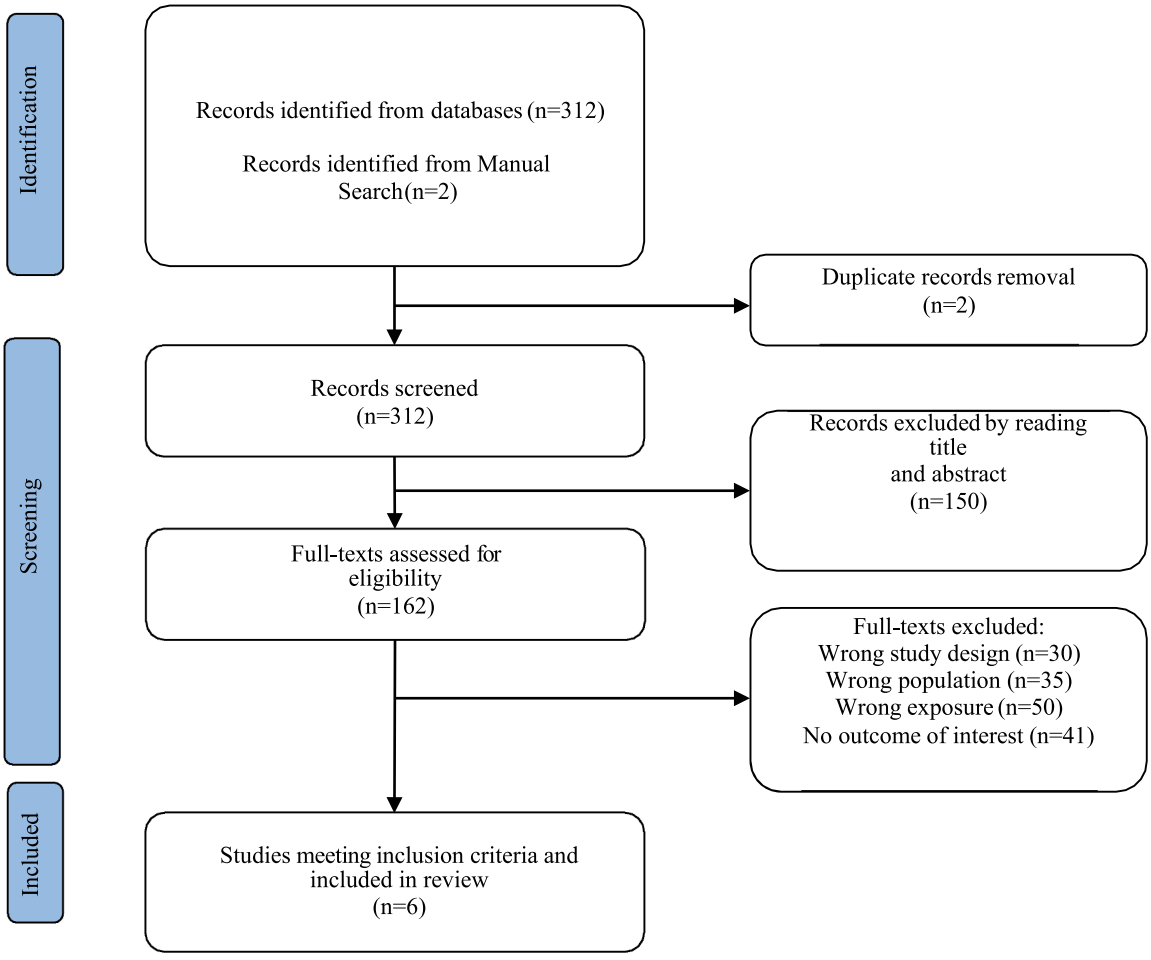

Fig. 1. PRISMA flow-chart summarizing the study selection process.

and provide gender-disaggregated data or direct comparisons between males and females to evaluate gender differences comprehensively.

Studies that did not align with these criteria were excluded, particularly those examining non-primary psychotic disorders such as substance-induced or organic psychoses, as well as those involving populations outside the specified age range. Research that failed to distinguish between FEP and subsequent episodes or lacked gender-specific data was not considered. Additionally, qualitative studies, narrative reviews, expert opinions, and works that did not present primary data were excluded, along with abstracts without full-text access and letters to the editor. Methodological limitations, including small sample sizes or significant biases that were not sufficiently addressed, also constituted grounds for exclusion. By applying these criteria, this review ensured the selection of high-quality studies that contributed to a refined understanding of gender disparities in FEP, supporting the advancement of more precise and equitable diagnostic and treatment approaches.

No restrictions based on country, ethnicity, or cultural background were applied, as the primary aim of the review was to explore gender-related patterns in first-episode psychosis across diverse clinical and sociocultural settings.

2.2. Search strategy

The search for relevant literature involved multiple databases to ensure comprehensive topic coverage. The primary databases searched for studies addressing gender differences in FEP were PubMed, Embase, and PsycInfo. A systematic search was conducted using the following search criteria ("first episode psychosis" OR "first-episode-psychosis" OR psychosis OR "ultra-high-risk" OR "at-risk mental state" OR "clinical high risk" OR "early psychosis" OR "prodromal " OR "psychotic " OR "schizophrenia " OR "schizotypy " OR "early intervention") AND ("gender" OR "gender bias" OR "gender differences" OR "gender predictors"). The search was restricted to studies published between 2014 and 2024.

2.3. Selection of the studies

All retrieved articles underwent an initial screening to eliminate duplicate records and identify studies relevant to the research question. This process involved reviewing the titles and abstracts of the studies to determine whether they fulfilled the basic inclusion criteria. Following this initial screening, we evaluated the full-text articles of potentially eligible studies to confirm compliance with the inclusion and exclusion criteria. This step required a thorough review of each study's methodology, participant characteristics, and data concerning gender differences in FEP. Reasons for study exclusion were systematically documented using a predefined eligibility assessment form, which included criteria such as study population, diagnostic criteria, outcome measures, and data availability. Studies were excluded if they did not align with the inclusion criteria, such as focusing on non-primary psychotic disorders, lacking gender-disaggregated data, or evaluating variables outside the review's scope. To ensure transparency and consistency in study selection, all exclusion reasons were recorded in a study selection log, and any discrepancies between reviewers were

resolved through discussion. The double-blind selection process was conducted independently by two reviewers (G.S. and M.G.), and disagreements were adjudicated by a third reviewer when necessary.

2.4. Data extraction

V.B., M.G., and G.S. extracted the data. These data were systematically collected from the included studies using a structured and pre-piloted extraction form. Two researchers independently conducted the extraction process to ensure accuracy and minimize bias; any discrepancies were resolved through discussion or consultation with a third researcher. Key details include general information such as study authors, publication year, and country of origin. Study characteristics, including study design, sample size, and demographic characteristics of participants (such as age, gender distribution, and clinical features), will also be extracted. The focus of the data extraction will be on identifying gender differences in clinical features (such as symptom severity, onset, and presentation), demographic factors (including socio-economic status and family history), and long-term outcomes (such as treatment response and prognosis). This data will enable a comprehensive analysis of the gendered aspects of psychosis onset in young individuals. Clinical symptom severity and functional outcomes were assessed using the instruments reported in each original study, most commonly the Positive and Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF). Still, these tools were not used consistently across all included studies. No formal harmonization or statistical adjustment for instrument variance was performed, as the aim of the review was not to pool symptom scores across studies quantitatively, but to synthesize gender-related patterns within each study using its respective assessment framework. Comparisons between males and females were therefore interpreted within individual studies rather than across studies employing different instruments.

2.5. Critical appraisal assessment

The included studies were evaluated using the Newcastle-Ottawa Scale (NOS), which assesses the risk of bias in observational studies across three domains: selection, comparability, and exposure. A critical appraisal was conducted with established tools to evaluate the quality and validity of the studies. NOS was employed to assess observational studies, focusing on aspects such as participant selection, group comparability, and outcome measurement.

This scale provided an overall score ranging from 1 (indicating the highest risk of bias) to 9 (indicating the lowest risk of bias) (Hartling et al., 2013). Additional tools were used for experimental studies where applicable. To minimize selection bias and ensure consistency in quality ratings, these procedures were conducted independently by two authors (V.B. and M.G.). Any discrepancies were resolved through joint consensus following independent evaluations.

The critical appraisal focused on assessing potential biases in study design, group comparability, and data reporting quality. Studies with methodological flaws, such as high risks of bias or inadequate reporting of gender differences, were approached with caution. The goal was to ensure that the studies included in the review met sufficient quality standards to support meaningful conclusions about gender differences in FEP among adolescents and young adults.

3. Results

3.1. Flow chart of included studies

The Prisma Flow Chart in Fig. 1 summarizes the search results. The search strategy initially identified 314 studies from the databases. After removing duplicates, 312 studies remained. Following the title and abstract screening, 162 studies were assessed for eligibility. Ultimately, we included six studies in the systematic review (Arranz et al., 2015; Ceskova et al., 2015; Comacchio et al., 2019; Pang et al., 2016; Thorup et al., 2014; Tseliou et al., 2017).

3.2. Ratings of study quality and risk of bias

According to the quality ratings of the study, four studies were rated as good quality (Arranz et al., 2015; Ceskova et al., 2015; Pang et al., 2016; Tseliou et al., 2017), one as moderate quality (Comacchio et al., 2019), and one as poor quality (Thorup et al., 2014). Since most of the studies included in this review were of moderate or good quality, the risk of bias from them was low.

3.3. Characteristics of the included studies

The six studies included in this systematic review employed a variety of methodological designs, including prospective cohort studies, retrospective analyses, and secondary analyses of clinical trial data. Sample sizes ranged from small clinical cohorts to larger multicenter datasets. While all studies included individuals aged 13–24 or allowed age-stratified extraction within this range, there was variability in recruitment settings (inpatient vs outpatient) and diagnostic tools. Most studies reported findings disaggregated by gender but did not always clarify whether “sex” or “gender” was used, reflecting a limitation in the primary literature.

3.4. Age of onset and diagnosis

Four of the included studies provided data on age of onset or age at diagnosis. Across these, a consistent trend emerged: females experienced the first episode of psychosis at a later age compared to males. The difference, typically around 2–4 years, aligns with the estrogen protection hypothesis and is in line with previous findings in the literature. However, the operational definitions of “onset” (e.g., first contact with services vs symptom onset) varied across studies, which may have influenced comparability.

3.5. Symptom presentation

Five studies examined gender differences in symptomatology at onset. Females tended to present more frequently with affective symptoms such as mood disturbances, anxiety, and somatic complaints, whereas males more commonly exhibited prominent positive symptoms (e.g., hallucinations, delusions) and negative symptoms (e.g., affective flattening, avolition). Some studies also reported higher rates of dissociative features and internalizing symptoms among females, potentially contributing to higher rates of initial misdiagnosis with mood or personality disorders.

3.6. Substance use

Substance use patterns were examined in four studies and consistently showed higher rates of use among males. Males were more likely to use alcohol, cannabis, and stimulants such as cocaine. Where reported, initiation of cannabis use occurred earlier in males, although one study noted no significant gender difference in age of initiation. The presence of substance use disorders was more frequent among male participants and was linked to poorer functional outcomes.

3.7. Treatment response

Three studies assessed response to treatment, using indicators such as changes in PANSS scores and remission rates. Females tended to show greater improvement in positive symptoms and higher short-term remission rates. These findings were often interpreted in light of better treatment adherence, stronger social support, and greater insight among female participants. However, long-term outcomes were more variable,

and hormonal fluctuations (e.g., peripartum, menstrual cycle) were noted as potential risk periods for relapse among females.

4. Discussion

This systematic review examined gender differences in FEP among adolescents and young adults (ages 13–24), analyzing clinical, demographic, and outcome characteristics across six studies. The findings consistently emphasize gender disparities in the age of onset, symptom presentation, misdiagnosis rates, treatment response, and long-term outcomes. These results align with a growing body of research indicating that biological, psychological, and sociocultural factors shape the experience of psychotic disorders differently for males and females (Ochoa et al., 2012; Seeman et al., 2019). A consistent finding across studies is that women tend to experience FEP at a later age compared to men. This aligns with the estrogen protection hypothesis, which suggests that estrogen has neuroprotective effects that may delay the onset of psychosis in females (Carter et al., 2022; Abel et al., 2010). This later onset in females is often accompanied by a more affective and atypical presentation, including prominent mood symptoms (e.g., depression, anxiety, somatic complaints) rather than the classic psychotic symptoms (hallucinations, delusions) that are more commonly seen in men (Køster et al., 2008). The documented gender disparities in the clinical presentation and trajectory of FEP underscore a critical issue affecting diagnosis and treatment: the under-recognition and misdiagnosis of FEP in women. This variation in symptomatology contributes to higher rates of misdiagnosis among women, who are more likely to be diagnosed with bipolar disorder, major depressive disorder, or borderline personality disorder before receiving a correct psychotic disorder diagnosis (Tseliou et al., 2017). Divergence from the typical presentation makes it challenging for clinicians to accurately identify FEP in women, resulting in delayed or missed diagnoses. The consequences of such delays are substantial. Untreated or later-treated FEP in women can lead to a prolonged duration of untreated psychosis (DUP), potentially worsening the severity of the illness and hindering recovery. Moreover, a delayed diagnosis can prevent women from receiving appropriate and timely treatment, resulting in increased disability, poorer social functioning, and a compromised quality of life. Addressing this gender disparity requires a shift toward more nuanced diagnostic criteria and assessment tools. Clinicians need enhanced training to recognize atypical presentations in women, ensuring that all individuals experiencing FEP receive prompt, appropriate, and gender-sensitive care to achieve the best possible outcomes.

The diagnostic overshadowing effect, where mood symptoms in women are overemphasized while psychotic features are underrecognized, has been reported in several studies (Arranz et al., 2015; Comacchio et al., 2019). In contrast, men with FEP often present with more severe negative symptoms, such as blunted affect, social withdrawal, and cognitive impairments, which may be linked to greater neurodevelopmental disruptions and higher genetic vulnerability to schizophrenia (Ceskova et al., 2015). These negative symptoms contribute to greater functional impairment and lower baseline social functioning in men compared to women (Pang et al., 2016).

Thorup and colleagues suggest that women generally show better short-term remission rates and higher functional recovery following FEP compared to men (Thorup et al., 2014). This is likely due to greater social support networks, higher treatment adherence, and better insight into their condition. However, these advantages do not necessarily translate into better long-term outcomes. Despite their higher remission rates, women are at greater risk of relapse when hormonal fluctuations occur, such as during menstruation, pregnancy, or menopause (Thorup et al., 2014). The impact of reproductive hormones on psychotic symptoms is a crucial but often overlooked aspect of gender disparities in psychosis. Some studies indicate that postpartum psychosis, which affects women shortly after childbirth, may represent an extremely vulnerable period for women with a history of FEP, necessitating specialized interventions tailored to the hormonal cycle (Jones, 2020). Another important factor influencing treatment response is gender-specific sensitivity to antipsychotic medications. Studies have found that women require lower doses of antipsychotics to achieve the same therapeutic effect as men, yet they also experience higher rates of metabolic side effects such as weight gain, insulin resistance, and dyslipidemia (Castellani et al., 2019). This suggests that current pharmacological guidelines, which are largely based on male-centric clinical trials, may not be optimal for female patients.

Despite the biological basis for gender differences in psychosis, sociocultural and environmental factors also play a significant role. Several studies have shown that women with psychosis experience higher rates of childhood trauma, interpersonal violence, and social stress compared to men, which may contribute to variations in symptomatology and illness trajectory (Pruessner et al., 2019). The influence of early-life stress and trauma on psychosis risk seems to be more pronounced in women, resulting in higher levels of dissociative symptoms, mood instability, and PTSD comorbidity (Seeman et al., 2019). Furthermore, societal stigma and gender norms influence help-seeking behaviors. Men are less likely to seek professional help early in the course of their illness, potentially contributing to delays in treatment and poorer outcomes (Pang et al., 2016). Conversely, women may be more likely to seek psychiatric care but are at risk of being misdiagnosed with mood disorders rather than psychotic disorders (Thorup et al., 2014). The role of social support systems also differs between genders. Women tend to receive a diagnosis at a later age compared to men; however, this finding should be interpreted in light of the consistently reported later age of onset in females. A later diagnosis does not necessarily imply a diagnostic delay per se, but may partly reflect the natural temporal shift associated with later onset (Arranz et al., 2015). Nevertheless, some evidence suggests that, beyond later onset, diagnostic challenges in women may arise from difficulties in symptom recognition after onset, particularly when presentations are predominantly affective or atypical. These challenges may contribute to longer pathways to care and, in some cases, to a prolonged duration of untreated psychosis, although DUP was not consistently reported across the included studies. In contrast, men with psychosis are more likely to experience social isolation, which has been linked to higher rates of treatment noncompliance and relapse (Køster et al., 2008).

Despite the strengths of this systematic review, several limitations must be considered when interpreting the findings. The small number of studies included restricts the statistical power of the analysis, making it challenging to draw definitive conclusions regarding gender differences in first-episode psychosis. Additionally, heterogeneity in study designs, assessment tools, and diagnostic criteria complicates direct comparisons across studies, potentially introducing variability in the reported findings. This heterogeneity also included the use of different clinical assessment instruments, which further limited direct cross-study comparisons of symptom severity.

Cultural and regional differences across the included studies also present a challenge, as variations in healthcare systems, diagnostic practices, and sociocultural attitudes toward gender and mental health may influence both symptom presentation and access to care. The impact of gender norms and stigma surrounding psychotic disorders may differ across societies, further complicating the generalizability of the results. However, cultural and ethnic variables were inconsistently reported across the included studies and were rarely operationalized in a way that allowed meaningful comparisons. As a result, it was not possible to conduct formal subgroup analyses based on culture or ethnicity. Given the limited number of eligible studies and the heterogeneity in study designs, assessment tools, and outcome measures, we adopted a pooled narrative synthesis as the most appropriate approach to identify recurring gender-related patterns across different clinical and geographical contexts. Nevertheless, we acknowledge that cultural factors may interact with gender in shaping symptom expression, help-seeking behaviors, and diagnostic pathways, and this interaction

Table 1
Overview of included studies on gender differences in FEP. NA=Not applicable.

Author, year	Country	Study Design	Mean age (n± SD)	Sex (%)	Sample size	Main results
Arranz, 2015	Spain	Sub-analysis of a randomized, open clinical trial	Men: 24.1 ± 5.9 years (n = 85) Women: 30.1 ± 11.2 years (n = 29)	Men: 74.6 % Women: 25.4 %	114 patients (85 men, 29 women)	A significantly higher percentage of men (89.4 %) reported current substance use compared to women (55.2 %). This difference was statistically significant ($p < 0.001$). While there was no significant difference in the age of first alcohol or cocaine use between genders, men started using cannabis significantly younger than women ($p < 0.02$). The number of substances used predicted an earlier age of psychosis onset in men, but not in women. Being male itself was also a significant predictor of an earlier age of psychosis onset.
Ceskova, 2015	Multicenter study across 14 European countries	Analysis of data from the European First-Episode Schizophrenia Trial (EUFEST), a one-year, pragmatic, multicenter, randomized, open-label trial	Men: 26.0 (25.5–26.5) years Women: 26.5 (25.7–27.3) years	Men: 60 % Women: 40 %	498 patients (298 men, 200 women)	There were no significant differences between men and women at baseline in age or in the proportion of patients assigned to different antipsychotic medications, except for ziprasidone (significantly fewer men received ziprasidone). Baseline PANSS (Positive and Negative Syndrome Scale) scores were similar between groups. Women showed significantly greater improvement in Positive PANSS (PPANSS) and total PANSS (TPANSS) scores over the course of the one-year study compared to men. Using generalized estimating equations (GEE), a significant interaction between time and gender was found for PPANSS and TPANSS, indicating a more robust improvement in women over time. Only olanzapine showed a significantly greater improvement in total PANSS scores for women compared to men over the course of treatment.
Comacchio, 2019	Italy (multicenter study)	Secondary analysis of data from the GET UP PIANO trial, a pragmatic cluster randomized controlled trial	NA	NA	444 FEP patients (260 males, 184 females)	Childhood sexual abuse was significantly more prevalent in women (22.6 %) than in men (11.6 %). The prevalence of childhood physical abuse did not differ significantly between genders (29.0 % in women vs. 31.7 % in men). Childhood abuse was associated with higher levels of negative symptoms in both men and women. There were some gender differences in positive symptoms with women scoring higher on excitement and men on grandiosity. Men also displayed higher levels of several negative symptoms than women. Childhood abuse was associated with a significantly lower age of psychosis onset in women only. Women, overall, reported significantly higher total, met, and unmet needs for care compared to men; however these differences were not statistically significant. Abuse had little impact on overall needs for care, but both groups showed higher levels of unmet needs in the functioning domain.
Pang, 2016	Singapore	Retrospective cohort study analyzing data from the Singapore Early Psychosis Intervention Programme (EPIP)	Women: 28.8 ± 6.5 years (n = 258) Men: 26.8 ± 6.2 years (n = 275)	Women: 48.4 % Men: 51.6 %	533 patients (258 women, 275 men)	Women were older at service entry. While there were few baseline differences, female participants showed significantly better improvement over one year across several measures, including PANSS scores (positive, negative, and total) and GAF scores (disability and total). At 1 year, a higher percentage of females achieved symptomatic and functional remission, and overall recovery.
Thorup, 2014	Denmark	Analysis of data from the Danish OPUS study, a 2-year randomized controlled	NA	NA	578 patients with first-	Males consistently showed significantly higher levels of negative symptoms than

(*continued on next page*)

Table 1 (*continued*)

Author, year	Country	Study Design	Mean age (n± SD)	Sex (%)	Sample size	Main results
		trial comparing intensive early intervention with standard treatment for first-episode psychosis. This analysis specifically focused on the 5-year follow-up data.			episode psychosis	females. Males also showed higher scores on other measures of psychopathology than women across all time points. Females demonstrated better social functioning at 5-year follow-up, showing a greater likelihood of being employed or in education compared to males. A larger percentage of women also lived with children. Significantly more women than men reached recovery status at the 5-year follow-up. Women also exhibited greater compliance with medication compared to men. A significantly larger proportion of men had a second diagnosis of substance abuse. Significantly more males than females died during the 5-year follow-up, and there was a trend for more males to commit suicide (although not statistically significant in the provided excerpt).
Tseliou, 2017	United Kingdom (inner-city London)	Retrospective cohort study using audit data from seven Early Intervention Services (EIS) across London.	NA	Men: 65.1 % Women: 34.9 %	1098 patients (713 men, 385 women)	Men presented with significantly more violent behavior prior to referral, while women had significantly more suicide attempts. After one year of EIS care, men remained significantly more violent. Women were significantly more likely to have been admitted to a psychiatric ward. There were no significant gender differences in GAF (Global Assessment of Functioning) scores after adjusting for confounders.

warrants dedicated investigation in future research.

Our decision to focus on individuals aged 13 to 24 aimed to ensure developmental homogeneity; however, this may have led to the exclusion of relevant studies on older individuals, particularly females, who tend to experience later onset. While contemporary early intervention services increasingly extend their upper age limits into the late 20 s or early 30 s, our age restriction was chosen to prioritize developmental specificity rather than service-based definitions of early psychosis.

Moreover, although we targeted this specific age range, a few included studies reported mean ages slightly above it. These were retained when age-relevant data could be extracted, but may have introduced some age-related heterogeneity.

Another significant limitation is the insufficient reporting on psychosocial variables such as socioeconomic status, social support, and environmental stressors. These factors are known to influence the course of psychotic disorders and may partially explain the observed gender differences. Without this contextual information, our understanding of the interaction between biological and social determinants remains incomplete.

Moreover, while some biological mechanisms, like hormonal influences, are mentioned, most of the studies reviewed did not investigate potential gender differences at the genetic, inflammatory, or immunological levels. This represents an important limitation, as emerging evidence suggests that immunological and genetic mechanisms may contribute to sex-based vulnerability in psychosis (e.g., differences in cytokine profiles, neuroinflammatory responses, or gene-environment interactions), which remain largely unexplored in current clinical studies.

This highlights a significant gap in the existing literature, and future research should include these biological areas to provide a more integrated and mechanistic understanding of gender disparities in FEP.

Although we conducted a methodological quality appraisal using NOS, the limited number of included studies and significant heterogeneity in design and outcome reporting restricted our ability to systematically compare findings across quality levels. No consistent differences emerged between studies of higher and lower methodological quality.

Lastly, while concentrating on the 13–24 age range has facilitated a more developmentally targeted analysis, significant differences still exist between adolescents and young adults regarding symptom expression and treatment response. Future studies should explore how age and gender interact in early psychosis to inform more personalized and effective interventions (Tables 1 and 2).

5. Conclusion

This systematic review provides strong evidence for significant gender differences in the presentation, progression, and outcomes of FEP in adolescents and young adults. Women often present with atypical or affective symptoms, increasing the likelihood of misdiagnosis and potentially delaying access to effective care. While some studies suggest a possible advantage for women regarding short-term outcomes, such as remission and treatment response, other findings highlight more complex interactions that warrant further exploration, particularly concerning hormonal fluctuations, diagnostic biases, and social determinants of health.

We focused on the 13–24 age range to capture the neurodevelopmental transition from adolescence to young adulthood, a period of significant clinical vulnerability. However, we acknowledge that this cutoff may have excluded relevant studies involving older individuals, particularly females with later onset, which limits the generalizability of our findings. Furthermore, although we conducted a quality appraisal, the small number of studies and methodological heterogeneity prevented us from identifying consistent differences between higher- and lower-quality studies.

Future research should address these gaps by including a wider age range, clarifying the use of sex and gender constructs, and incorporating both psychosocial and biological moderators, such as inflammation,

Table 2
Gender-specific clinical features reported in selected studies on FEP.

Author, year	Clinical Features in Women	Clinical Features in Men
Arranz, 2015	• They were less likely to use any substance overall (55.2 % vs 89.4 % in men). • They were less likely to use alcohol (51.7 % vs 84.7 % in men), cannabis (31 % vs 64.7 % in men), and cocaine (0 % vs 28.2 % in men). • Among those who used cannabis, a smaller proportion also used alcohol (55.6 % vs 92.7 % in men). • A larger percentage of women reported no substance use (44.8 % vs 10.6 % in men). • There was no significant difference between men and women regarding the age of first use of alcohol or cocaine. However, women began using cannabis at a significantly later age (18.0 years vs 16.08 years in men). • The number of substances used did not influence the age at onset of psychosis in women.	• Men had a significantly higher rate of overall substance use (89.4 % vs 55.2 % in women). • They were significantly more likely to use alcohol, cannabis, and cocaine than women. • Among those who used cannabis, a much higher percentage also used alcohol (92.7 % vs 55.6 % in women). • A much smaller percentage of men reported no substance use (10.6 % vs 44.8 % in women). • Men began using cannabis significantly younger than women (16.08 years vs 18.0 years in women). • The number of substances used significantly predicted an earlier age at onset of psychosis in men (consuming multiple substances was associated with earlier onset).
Ceskova, 2015	• Women in the EUFEST trial demonstrated a more robust improvement in Positive and Total PANSS (Positive and Negative Syndrome Scale) scores over the course of treatment compared to men. This was statistically significant after three, six, and nine months of treatment, even after accounting for multiple testing using the Bonferroni correction. The improvement was particularly pronounced in the Positive PANSS subscale. • When considering responses to individual antipsychotics, women receiving olanzapine showed significantly greater improvement in total PANSS scores than men. • The main outcome measure in the original EUFEST trial was all-cause treatment discontinuation. While not detailed in the excerpt you've given, the study found no statistically significant differences between men and women regarding treatment discontinuation.	• Men showed less robust improvement in Positive and Total PANSS scores compared to women, though baseline scores were similar. • Men receiving olanzapine showed less improvement in total PANSS scores compared to women receiving the same medication. • Significantly fewer men were prescribed ziprasidone than women. • Similar to women, the provided text does not detail the findings on treatment discontinuation, though this was a primary outcome measure for the overall EUFEST trial.
Comacchio, 2019	• Women experienced childhood sexual abuse significantly more often than men (22.6 % vs. 11.6 %). • Childhood abuse (both physical and sexual) was associated with higher levels of negative symptoms in women. • Childhood abuse was associated with a significantly earlier age of psychosis onset specifically in women. This effect was not observed in men. • Women generally reported higher overall needs for care (though not statistically significant after adjusting for multiple comparisons), especially in the areas of functioning and services, compared to men. This difference was more pronounced in those who had experienced childhood abuse.	• Men reported childhood sexual abuse less frequently than women (11.6 % vs 22.6 %). • Similar to women, childhood abuse (both physical and sexual) was associated with higher levels of negative symptoms in men. • Childhood abuse did not significantly impact the age of psychosis onset in men. • Men reported similar overall needs for care as women (though not statistically significant after adjusting for multiple comparisons), and the impact of childhood abuse on needs for care was less pronounced than in women.
Pang, 2016	• Older at service entry • More likely married • More often referred from primary care • Better improvement in PANSS scores over time • Higher rates of remission and recovery	• Younger at service entry • More likely unmarried/single • More often referred from National Service • Worse improvement in PANSS scores over time • Lower rates of remission and recovery
Thorup, 2014	• Better social functioning (employment, education) • Higher likelihood of living with children • Higher rates of recovery • Better medication compliance • Lower rates of substance abuse	• Higher levels of negative symptoms • Higher likelihood of living alone • Lower rates of recovery • Poorer medication compliance • Higher rates of substance abuse • Higher mortality and suicide attempts
Tseliou, 2017	• More suicide attempts prior to EIS. • Higher likelihood of psychiatric admission during the first year of EIS care.	• More violent behavior prior to and during the first year of EIS care. • Poorer social and vocational functioning at 1 year (although not significant after adjusting for confounders).

genetics, and hormonal influences. Developing standardized and gender-sensitive diagnostic tools and treatment strategies is essential to reduce diagnostic delays and improve long-term outcomes in FEP, ensuring equitable and timely care for all individuals affected.

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Giulia Santangelo: Writing – original draft, Investigation, Data curation, Conceptualization. **Martina Gnazzo:** Writing – original draft, Methodology, Investigation. **Valentina Baldini:** Writing – original draft, Methodology, Investigation. **Diana De Ronchi:** Writing – original draft, Validation, Methodology. **Marco Carotenuto:** Writing – original draft, Supervision. **Andrea Fiorillo:** Writing – original draft, Validation. **Armando D'Agostino:** Writing – review & editing, Supervision, Methodology, Investigation.

Declaration of competing interest

The authors have no conflict to declare.

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