Gender differences in symptomatology in people with psychotic spectrum disorders: protocol for a systematic review and pairwise meta-analysis of observational studies

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Abstract

Introduction: Gender differences in symptomatology in people with psychosis have been studied extensively in last decades. Previous narrative reviews have shown some evidence of gender differences in depressive, negative and paranoid symptoms, but yielding inconclusive findings. These reviews are limited by not doing systematic searches nor performing quantitative synthesis of the evidence. Therefore, we aimed to systematically investigate if there are gender differences in symptoms in people with psychosis. We describe the protocol for a systematic review and pairwise meta-analysis comparing a range of symptomatic outcome measures between men and women diagnosed with a psychotic spectrum disorder at different stages of the disorder (ultra-high risk for psychosis, early psychosis and established psychosis) in observational studies.

Methods and analysis: We will conduct systematic searches in PsychInfo, PubMed, Web of Science, Scopus and Dialnet to identify observational studies that compare gender differences or provide results separated by the gender of the participant in measures of symptomatology. Literature searches, study selection, data extraction, risk of bias assessment and outcome quality assessment will be undertaken by two independent reviewers. A series of pairwise meta-analyses will be conducted in R using random-effects models to assess the effect size of all outcome measures that are assessed in at least two studies. The quality of studies will be evaluated using the XXX tool, and the confidence in the results will be evaluated using the XX. Meta-regression and sensitivity analyses will be conducted to assess the robustness of the findings.

Ethics and dissemination: No ethical issues are foreseen. Results from this study will be published in peer-reviewed journals and presented at relevant conferences.

PROSPERO registration number: CRD42021264942.

Keywords: sex differences, schizophrenia, first episode psychosis, ultra-high risk for psychosis, symptoms, clinical presentation

Article Summary

Strengths and limitations of this study

- This will be the first systematic review and meta-analysis examining the role of gender in the clinical expression of symptomatology in people with psychosis. The findings of this study have the potential to enhance our knowledge of psychosis characterization and treatment by taking a gender and phase-specific approach.
- There is risk of heterogeneity, given the different study designs and measurements that will be included; however, we will try to control variability by several meta-regression analyses.
- The limitations of individual studies will be addressed with the XXX tool, and the credibility of the results will be evaluated using the GRADE framework.

Word count: 2689 words

Background

Psychotic spectrum disorders present considerable heterogeneity in several of their core features. Since the first conceptualisations of psychotic disorders, researchers have noticed that the clinical presentation and course of the disorder seems to be different in males and females. Evidence suggests that females have a later age of onset and better prognosis [1][2], but whether males and females with psychosis present differences in symptoms is not yet clear.

Several narrative reviews published in recent years have examined the characterization of gender differences in a broad array of outcomes in people with psychosis, and have linked these differences to the contribution of sex hormones and molecular mechanisms [3]. Although narrative reviews suggest that women tend to express more depressive symptomatology and men experience more negative symptoms [4] [5], the results of different studies are still heterogeneous and do not permit establishing sound conclusions. In patients considered at ultra-high risk for psychosis, a review concluded that men had more severe negative symptoms prior to the onset of illness, however the methodological limitations of the studies did not allow to establish clear conclusions [6]. In contrast, a more recent review argues that the differences found could be explained by comorbidities and illness behaviors, such as substance abuse, that is more frequent in men and not controlled in all studies [1].

Therefore, evidence is still fragmentary and inconclusive, and thus a comprehensive statistical synthesis to detect true differences in clinical symptoms between women and men with psychosis is lacking. These reviews therefore provide a limited information on which symptoms do women and men have differences, not providing a systematic and methodologically sound comparison among studies. Despite several systematic reviews and meta-analysis examining the role of gender in aspects of psychosis such as age at onset of the disorder, duration of untreated psychosis, or cognitive functioning have been published [2,7,8], none of them focused on gender differences in symptomatology.

As a result of these inconsistencies, it is still unclear in which domain/s of clinical symptoms do men and women have a different expression, nor in which they do not have true differences. However, given that gender differences in psychosis have been described in all aspects of the disease, understanding how the disorder is expressed in males and females could not only clarify etiological aspects of psychosis, but also to

identify therapeutic targets and develop accurate and directed interventions.

Furthermore, these achievements will contribute to reduce the still present gender bias in mental health research [9].

To overcome this gap in the current knowledge, we will perform a pairwise meta-analysis comparing data of a broad array of symptoms relevant to the expression of psychosis between men and women with a psychotic spectrum disorder at different stages of the illness.

Personalized treatment approaches in other fields of psychiatry are proving to be successful, and tailoring the treatment symptom targets of psychosis for each person, considering the gender of the individual, will be a crucial step forward [1].

Aim and Objectives

Our aim is to statistically synthesize and estimate whether males and females at different stages of a psychotic disorder (ultra-high risk mental state, first-episode psychosis and established illness) present differences in symptoms. These will include:

- a) Psychotic symptomatology, including positive, negative and disorganised symptoms.
- b) Depressive symptomatology and other symptoms relevant to the functioning of people with psychosis, including mania and anxiety symptoms. However, those symptoms relevant to psychosis that can be identified will also be collected and analysed.
- c) Control for relevant variations in methodology of the studies, and for those variables that may influence the clinical expression of psychosis.

Methods

Design

We have developed the methods for this systematic review and meta-analysis following the guidelines of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist [10]. This systematic review and meta-analysis is registered in the PROSPERO database (registration number:

[CRD42021264942](#)). We will update the record in PROSPERO if any changes are made to the protocol.

Eligibility criteria

Types of participants

This meta-analysis will include individuals aged 16-65 with a diagnosis of a psychotic spectrum disorder (schizophrenia, schizophreniform, schizoaffective disorders, delusional disorder, brief psychotic disorder, recent-onset psychosis, ultra-high risk for psychosis) irrespective of the diagnostic criteria used, following the strategy of the Cochrane Schizophrenia Group. The Cochrane Schizophrenia Group suggests that specific diagnostic criteria - such as ICD-11 or DSM-5- are not accurately used in clinical routine. Therefore, including studies that do not use these systems should increase generalizability and representativeness [11].

Studies with participants with other diagnoses out of the psychotic spectrum will be included only if individuals with a diagnosis of a psychotic spectrum disorder represent more than 80% of the sample.

We will exclude studies in which all participants, by study inclusion criteria, 1) are acutely ill, 2) have a comorbid pathology or psychosis secondary to another psychiatric or medical diagnosis (eg. Dual pathology, bipolar disorder with psychotic symptoms, psychotic depression, OCT comorbid to psychosis), 3) have a concomitant medical illness, 4) have dementia or intellectual disability (premorbid IQ < 70).

For the purposes of the review we define recent-onset psychosis as a first diagnosis of a psychotic spectrum disorder within the last five years, according to the research done in our group [12] and established operational definitions [13].

Types of studies

We will include both cross-sectional and longitudinal observational studies. To be included, we require that a study presents data about outcomes separately for males and females. For the case of longitudinal studies or clinical trials, we will only include their baseline data.

To reduce the risk of “language bias” [14] the included languages will be English, Spanish, Italian, German and Chinese. We will consider studies irrespective of setting (inpatients and outpatients), nationality and ethnicity. Grey literature will be included where identified.

Types of outcomes

Primary outcomes. Measures of positive, negative, depressive, disorganized symptomatology, and general psychopathology accordingly to published and validated scales such as the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS), the Scales for Assessment of Positive Symptoms (SAPS), the Scales of Negative Symptoms (SANS), the Beck Depression Inventory (BDI), the Calgary Depression Inventory (CDI) or any other scale.

Secondary outcomes. As secondary outcomes, we will consider data on other symptoms of interest in the study of psychosis (e.g., mania, anxiety). As with primary outcomes, we will include secondary outcomes measured with rating scales published in peer-reviewed journals, such as the Beck Anxiety Inventory (BAI) or the Young Mania Rating Scale (YMRS).

Search strategy and information sources

Electronic searches

Electronic databases will be searched without restrictions for publication period, including PsychInfo, PubMed, Web of Science, Scopus and Dialnet. The final search strategy of PubMed appears in table 1. The date of the last search update will be provided in the final publication.

Reference lists and other sources

We will inspect a) previous narrative reviews concerning gender differences in psychotic disorders in a broad array of outcomes, and b) the reference list of our included studies, to check for additional studies that could meet our inclusion criteria not found by the electronic search.

Identification and selection of studies

Studies identified using electronic and manual searches will be exported and listed in Picoportal software [15]; duplicates will be excluded. The eligibility for the inclusion process will comprise two stages:

- 1) Screening: two authors (MFQ and ME) will independently check title and abstracts identified in the literature searches, and exclude those not pertinent. Disagreement will be resolved by discussion. If there is remaining doubt, we will obtain the full article for further inspection.
- 2) Eligibility: in the inspection of full articles, the same two reviewers of the screening stage will independently assess them for eligibility. Disagreements will be resolved with a third reviewer (HGM) or, when this is not possible, by contacting the study authors.

Data extraction

Data will be independently extracted by two authors using a standard data collection form. Results will be compared and inconsistencies resolved by discussing with a third author acting as an arbitrator or, when this is not possible, by contacting the study authors. Collected data will include:

- Study citation, year of study, year of publication, setting and country.
- Sample characteristics (diagnosis, diagnostic system, number of males, number of females, age, ethnicity, stage of disorder, sample source, location). When available, we will collect other sociodemographic and descriptive variables of interest, such as age of onset, premorbid adjustment or working status.
- Study design
- Outcome measures

We will contact study authors asking for additional data of their studies missing in the reports.

Study quality assessment

We will use the tool for observational cohort and cross-sectional studies of the National Heart, Lung and Blood Institute Study Quality Assessment Tool [16]. Users of this tool

must focus on key attributes relevant to the internal validity of the studies, rather than on numerical scores. Here we illustrate some of the domains considered by the tool:

- Was the research question or objective in this paper clearly stated?
- Was the study population clearly specified and defined?
- Was the participation rate of eligible persons at least 50%?
- Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
- Was a sample size justification, power description, or variance and effect estimates provided?
- Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
- Were the outcome assessors not involved in the care of the patient?
- Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

A judgment on the study quality is made based on the following three categories: “Good methodological quality”, “Fair methodological quality”, and “Poor methodological quality”. Two independent review authors will assess the quality in the selected studies and any disagreement will be resolved through discussion. If necessary, the senior author (HGM) will act as an arbitrator. Our group has extensive experience using this tool for assessing risk of bias in previous systematic reviews [17]. Effects of studies with a given rating of “Poor” in the overall domain will be analyzed by excluding them in sensitivity analyses.

Assessing overall quality of evidence: adaptation of GRADE

We will use an adaptation of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (GRADE) approach [18] to evaluate the quality of evidence at the outcome level for observational studies following previous procedures of other authors [19]. Observational studies are usually rated down for quality using GRADE. However, as all our included studies will be observational, we

will initially rate all outcomes as high quality and then downgrade them based on five main criteria: risk of bias, imprecision, indirectness, heterogeneity and publication bias. Two authors will evaluate the confidence in the outcome independently, and a senior author will act as an arbitrator. The authors involved will complete the GRADE online learning modules before starting the evaluation (<https://cebgrade.mcmaster.ca/>).

Data analysis

Characteristics of the included studies

We will generate descriptive statistics and study sample characteristics across all eligible observational studies, describing clinical and methodological variables, such as sample distribution (number of males and females), age, diagnoses, duration of the disorder, country, setting, or scales used to measure symptomatology.

Pairwise meta-analysis: data synthesis

As we expect most studies to report means and standard deviations, we will calculate standardized mean differences (SMD) with 95% confidence intervals for each outcome [20]. In case of adding a negative valence scale to an asset-based outcome, we will recode the means (multiplied by minus one) so that the valences coincided. For studies with more than one scale in the same outcome group, we will convert mean values for each of these measures to a single mean value for the intervention and control groups respectively. We will compute the variance of the mean among scales enclosed within the same outcome grouping using Borenstein, Hedges, Higgins, and Rothstein's [21] method. If means or standard deviations are not available to calculate effect size and associated standard error we will estimate it/them from other reported statistics (for example, t , f) or authors will be contacted for this information. If we find studies in which symptomatology is treated as a binary variable, odds ratios (OR) will be calculated as an index of effect size.

We will perform series of pair-wise meta-analyses by separating studies according to the stage of the disorder (ultra-high risk for psychosis, recent-onset psychosis, and established psychosis) and separated by domains of symptoms. If there are not enough studies available for meta-analysis into a certain domain of symptomatology in one of the stages of the disorders, these studies will be presented narratively in the form of systematic review. As heterogeneity is likely, we will use a random-effects model.

Assessment of heterogeneity

The statistical heterogeneity will be assessed with the Cochran's Q , I^2 and the τ^2 statistics. Cochran's Q is a Chi-squared distributed measure of weighted squared deviations. It can be converted into a p value and is the usual heterogeneity test statistic. Meanwhile, the principal advantage of the I^2 parameter, the proportion of the observed variance reflecting real differences in effect size, is that it can be calculated and compared across meta-analyses of different sizes, of different types of study, and using different types of outcome data [22]. Finally, τ^2 is the random effects variance of the true effect sizes.

Investigation of heterogeneity: meta-regression and sensitivity analysis

As we expect some degree of heterogeneity in our outcomes to be present, we will explore the following potential effect modifiers of our symptomatology outcomes by meta-regression (for continuous variables) and subgroup analyses (for dichotomous variables) if there are 10 or more studies that include these factors:

1. Year of publication of the study
2. Country of the study: developed vs developing countries
3. Setting: inpatients vs outpatients (at enrolment in the study)
4. The sample size of the study
5. Diagnostic system criteria (eg. DSM vs ICD, specific diagnostic criteria vs unspecified diagnostic criteria).
6. Relevant sociodemographic characteristics that may impact symptom presentation. These may include age of onset, duration of illness, duration of untreated psychosis, premorbid adjustment, substance abuse, marital status, work status, dose of antipsychotic treatment.

We will perform sensitivity analyses by exclusion of studies characterized as pertaining to poor methodological quality as assessed with the NHLBI assessment tool.

Publication bias

To assess small study effects and publication bias, we will use contour-enhanced funnel plots and Begg and Mazumdar [23] tests by outcome valence if 10 or more studies are included.

Statistical software

All analyses will be done using the meta package [24] for the R software [25]. The procedures described here follow similar steps as previous meta-analyses done by the first author [26].

Strengths and limitations of the review

Our main strength is that this study would be the first systematic review and meta-analytic quantification of the role of gender in the expression of symptomatology in people with psychosis, overcoming the limitations of previous narrative reviews on the topic, thus providing the most reliable approach to evidence synthesis.

However, this review also has limitations. First, meta-analyses are not bias-free: reviewer selection bias and publication bias need to be considered. We will attempt to limit such biases by conducting an exhaustive systematic literature search, by including studies published in many languages with no limit on date and state of publication, and by empirically examining publication bias. Second, as our meta-analysis will depend on data previously assessed on our included studies, it is possible that not all our outcome variables of interest will be examined. Third, we will combine data from multiple observational studies with differing inclusion criteria, target populations, countries, settings, and domains of symptoms. However, the generalizability of the findings might still be limited to individuals who voluntarily participate in clinical studies.

Patient and public involvement

There is no patient or public involvement in this study.

Ethics and dissemination

Ethics approval is not required as data were sourced from previously reported studies. Findings will be published in peer-reviewed scientific journals, and the data set will be made publicly available on the Open Science Framework (Identifier: DOI 10.17605/OSF.IO/82YS6, <https://osf.io/82ys6/>).

Table 1 legend

Final search strategy for PubMed

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Author Contributions

HGM and MF designed the study protocol, with input from JU, SO, IB, MV and ME.

HGM and MFQ wrote the draft and the final version of the manuscript.

All authors critically reviewed the report for important intellectual content and approved the final submitted version.

HGM is the guarantor of the review.

Data availability statement

Data availability is not applicable to this article as no new data were created or analysed in this study.

Declaration of interest

All authors declare no competing interests.

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Collaborators

We thank Marcos Catalan Vega for assisting in the construction of the search terms for the electronic literature search.

Patient consent for publication: not required

Ethics approval: This review does not require ethical approval

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