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Obstetric complications and psychopathology in schizophrenia: A systematic review and meta-analysis

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A R T I C L E I N F O

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A B S T R A C T

Schizophrenia (SZ) is a severe mental health condition involving gene-environment interactions, with obstetric complications (OCs) conferring an elevated risk for the disease. Current research suggests that OCs may exacerbate SZ symptoms. This study conducted a systematic review and meta-analysis to comprehensively evaluate differences in psychopathology between individuals with and without exposure to OCs in relation to SZ and related disorders. We systematically searched PubMed, PsycINFO, and SCOPUS to identify eligible studies. A total of 4091 records were retrieved through systematic and citation searches. 14 studies were included in the review, and 12 met the criteria for meta-analysis, involving 2992 patients. The analysis revealed that SZ patients who had been exposed to OCs exhibited significantly higher levels of positive symptoms (SMD=0.10, 95 % CI=0.01,0.20; p=0.03), general psychopathology (SMD=0.37, 95 %CI=0.22,0.52; p<0.001), total clinical symptomatology (SMD=0.44, 95 %CI=0.24,0.64; p<0.001) and depressive symptoms (SMD=0.47, 95 % CI=0.09,0.84; p=0.01). No significant differences were found in negative symptomatology and functioning. Our results suggest that OCs are not only associated with an increased risk of developing psychosis but with more severe symptomatology.

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1. Introduction

Schizophrenia (SZ) is a severe mental disorder characterized by complex symptomatology, including positive, negative, and cognitive symptoms, alongside neurostructural abnormalities, an increased prevalence of medical co-morbidities, and decreased life expectancy (Kirkpatrick et al., 2014). The interplay between genetics and environment has long been recognized as pivotal in SZ development (Jauhar et al., 2022). While extensive research has focused on genetic factors, there is a renewed interest in understanding the impact of environmental factors on the pathophysiology of the disease (Davies et al., 2020; Radua et al., 2018). Early environmental factors, ranging from the perinatal period to childhood and early adulthood are now known to contribute to the risk of psychosis (Arango et al., 2021). These findings align with the developmental origins of health and disease (DOHaD) paradigm, which postulates that environmental perturbations during perinatal or early life stages may lead to adverse health outcomes later in adulthood (Gluckman and Hanson, 2006).

Among environmental factors, obstetric complications (OCs) -that involve potential adverse events during gestation, pregnancy, labor, and delivery- have been historically associated with the subsequent development of psychosis (Cannon et al., 2002). However, the reliability and extent of this association have shown several inconsistencies across studies (Murray et al., 2017). To elucidate these discrepancies and shed light on this ambiguity, a recent meta-analysis has revealed the impact of various prenatal and perinatal factors on the onset of psychosis, including low birth weight, maternal infections, maternal smoking, exposure to famine or nutritional deficits during pregnancy, and premature birth, among others (Davies et al., 2020). Another important consideration is the timing of these events in relation to the heterogeneity of outcomes (Mezquida et al., 2018). Specifically, studies often categorize OCs by either focusing on detrimental prenatal events (Bernardini et al., 2015; Stathopoulou et al., 2013; Wegelius et al., 2013) delivery disturbances (Mezquida et al., 2021) or both (Verdolini et al., 2023). This temporal classification of OCs seems to have distinctive effects on the onset of the disease, as pregnancy complications and fetal growth abnormalities are associated with psychosis, while delivery complications might not be (Valli et al., 2023).

Recent years have seen significant interest in exploring the impact of OCs on SZ and related disorders, including at high risk subjects. Efforts have been made to synthesize decades of results across various domains, including neuroimaging, cognition, metabolism, and psychopathology. A systematic review of the effect of OCs on brain neuro-structure (Costas-Carrera et al., 2020) found that OCs may increase the risk of brain abnormalities (e.g., decreased grey matter volume, abnormal brain-ventricle ratios, and reduction of volume in limbic regions). Regarding cognition, a meta-analysis by Amoretti et al. (2022) indicated a moderate impact of OCs on specific cognitive domains such as working memory and verbal memory (Amoretti et al., 2022). From a metabolic standpoint, although data remain limited, some studies suggest links between birth weight (an indirect marker of the intrauterine milieu and affected by OCs) and outcomes such as antipsychotic-induced weight gain in first-episode psychosis (FEP) (García-Rizo et al., 2020; Garriga et al., 2019a), increased abdominal perimeter in treatment-resistant SZ patients (Ziauddeen et al., 2016), and glucose values in FEP (Garcia-Rizo et al., 2022) and glucose abnormalities in clozapine-treated patients (Fernandez-Egea et al., 2020). Finally, in population studies, a quadratic relationship between birth weight and Diabetes Mellitus type II in SZ patients has been described (Garriga et al., 2019b; Wium-Andersen et al., 2022).

The impact of OCs on the clinical presentation of SZ and related disorders has been studied to a lesser extent, and the results from these studies are inconsistent. The association between OCs and positive symptom severity in patients with FEP reveal mixed findings, with two studies (Sagué-Vilavella et al., 2022; Verdolini et al., 2023) indicating a link between OCs while others have not reported such evidence (Bernardini et al., 2015; Tosato et al., 2021). In patients with established SZ, most studies did not find an association (Gallagher et al., 2014; Lezheiko et al., 2019; Mezquida et al., 2021; Onu and Ohaeri, 2020), with just one exception (Borkowska and Rybakowski, 2002). Inconsistencies also arise regarding negative symptoms, both in FEP (Sagué-Vilavella et al., 2022; Tosato et al., 2021) (Bernardini et al., 2015) and in SZ (Borkowska and Rybakowski, 2002) (Gallagher et al., 2014; Lezheiko et al., 2019; Mezquida et al., 2021; Stepniak et al., 2014). A dearth of research exists suggesting a potential link between OCs and depression in SZ (Mezquida et al., 2021), while refuting it in FEP (Sagué-Vilavella et al., 2022). Finally, findings on functional outcomes also present mixed results, with some studies showing a relation (Borkowska and Rybakowski, 2002; Sagué-Vilavella et al., 2022; Verdolini et al., 2023) while others presenting null results (Buoli et al., 2016; Smith et al., 1995; Tosato et al., 2021).

The present systematic review and meta-analysis aims to examine the association between OCs in relation to clinical psychopathology and functioning in SZ and related disorders. Our primary hypothesis lies in understanding if OCs are associated with more severe clinical manifestations (viz., symptoms) in patients with SZ and related disorders ultimately impacting functionality in these individuals.

2. Material and methods

The present systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The PRISMA checklist is reported in Appendix 1 – Supplementary materials. The protocol of this systematic review and meta-analysis was registered on PROSPERO (CRD42022316655).

2.1. Search strategy

The PICO (Patient/Population, Intervention, Comparison/Control, Outcome) framework was used to develop the search strategy: Patient/population: first episode of psychosis (FEP), SZ and related disorders; Intervention: occurrence of OCs; Comparison: patients with and without OCs; Outcome: clinical phenotypes (positive symptoms, negative symptoms, general and total symptoms from the Positive and Negative Syndrome Scale, PANSS (Kay et al., 1987), depressive symptomatology, or general functioning).

We systematically searched the PubMed, PsycINFO, and Scopus databases from inception to November 8, 2023. The search strategy is provided in the Appendix 2 - Supplementary Materials. The references of each included study, textbooks, and other materials were hand searched to identify potential additional studies not captured by the original search string.

2.2. Eligibility criteria and study outcomes

We included: i) original studies; ii) in people diagnosed with SZ and related disorders (i.e., SZ, Schizoaffective Disorder (SZA), Schizophreniform Disorder, Delusional Disorder and Brief Psychotic Disorder) according to any edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM) (American Psychiatric Association, 2022) or the International Classification of Diseases (ICD) (World Health Organization, 2019) diagnostic criteria. FEP were also included, defined as presenting with psychotic illness for the first time; iii) comparing people with and without a history of OCs (we considered OCs as encompassing various events such as pregnancy complications, abnormal fetal growth, delivery complications, and prenatal cigarette exposure); and iv) assessing clinical symptomatology or functioning according to validated instruments.

No language or age restrictions were applied. We considered both observational and interventional studies for inclusion, but in the latter case, we planned to include only baseline data. Where populations

overlapped in multiple studies, we planned to include the largest study with the most representative data relevant to our objectives.

We excluded: i) reviews and meta-analyses; ii) case reports and case series; iii) animal studies; and iv) non-peer-reviewed literature (e.g., books, book chapters, commentaries, PhD theses, conference posters).

2.3. Study selection and data extraction

Three authors (SA, GM, and MFF) independently screened studies of potential interest at both title and abstract, and full-text stages. Another author (CGR) was consulted when a consensus could not be reached. Data extraction included (where available): first author, publication year, geographical region and country, study design, diagnostic criteria and (semi)structured interview adopted, setting of the study, type of diagnosis among the SZ spectrum (e.g., SZ, SZA, FEP), type of OCs assessed, type of instrument adopted to assess the OCs (i.e., outcome), type of psychotic symptomatology explored, type of instrument adopted to explore psychotic symptomatology, number of cases and controls, mean and standard deviation (SD) of the outcome for cases and controls, mean age, duration of illness, duration of untreated illness, percentage (%) of females and percentage (%) of patients under psychotropic medication. Where necessary, numerical variables were extracted from plots. In cases where information was not available, we contacted the authors up to twice to request the necessary data.

2.4. Methodological quality appraisal

Three authors (SA, GM, and MFF) independently assessed the risk of bias in included studies, and a third author (CGR) resolved disagreements. The Newcastle-Ottawa Scale (NOS) (Stang, 2010) was adopted to grade the quality of observational studies. The NOS were converted to "Agency for Healthcare Research and Quality" (AHRQ) standards, as done elsewhere (Oliva et al., 2023).

2.5. Statistical analyses

We conducted the meta-analyses using a random-effect model (restricted maximum-likelihood estimator) (Harville, 1977) with the R-package "metafor" (Viechtbauer and Viechtbauer, 2015), using RStudio R version 4.1.2 (R Core Team, 2023). Standardized mean differences (SMD) with their confidence intervals (CI) were used as effect sizes and represented by Hedge's g. We conducted a leave-one-out sensitivity analysis by excluding one study at a time from the main analysis. Heterogeneity was assessed by using Cochran's Q test (Cochran, 1950), τ^2 and I^2 statistics (Higgins et al., 2019). Prediction intervals were calculated. Meta-regression analyses were conducted according to a-priori defined dichotomic (i.e., whether the diagnosis was SZ or FEP) and continuous predictors (i.e., mean age, and % of females) predictors whenever Cochran's Q test presented a $p<0.10$ and the I^2 statistic showed a value >50 % and when at least ten studies providing this data were available. Publication bias was explored by visual examining funnel plots and using Egger's test (Egger et al., 1997), when at least ten studies were available.

3. Results

3.1. Characteristics of included studies

A total of 4091 records were identified from systematic search, and after duplicate removal 2683 studies were screened. Among these, 2597 were excluded at the title/abstract level and 75 after the full-text evaluation. After full-text evaluation, 8 authors were contacted to request unpublished data and additional information, and three of them provided unpublished data from their publications (Buoli et al., 2016; Sagué-Vilavella et al., 2022; Tosato et al., 2021). Finally, 11 studies meeting our inclusion criteria were identified from the systematic search, and three more studies were identified through citation screening. Of the 14 studies included in the systematic review, 12 of them provided enough data to perform a meta-analysis. The PRISMA flowchart is depicted in Fig. 1, additional information on the studies included in the systematic review and meta-analysis is presented in Table 1, and a list of excluded studies with reasons of exclusion is presented in the Appendix 3 - Supplementary Materials.

A total of 2992 patients with SZ and related disorders were included in the meta-analysis. One study (Stepniak et al., 2014) reported the sample as a range, for the analysis we used the smaller sample size. The mean age of participants was 30.5 years old (SD=7.7, range of means=22.7–43.5). 1477 (49.4 %) were males, 825 (27.6 %) were females; sex data was not available for the other 690 (23 %). Ten studies included 2007 (67.1 %) people diagnosed with SZ (Borkowska and Rybakowski, 2002; Buoli et al., 2016; Gallagher et al., 2014; Lezheiko et al., 2019; Mezquida et al., 2021; Onu and Ohaeri, 2020; Smith et al., 1995; Stathopoulou et al., 2013; Tosato et al., 2021; Wegelius et al., 2013), three studies included 361 (12.1 %) people experiencing FEP (Bernardini et al., 2015; Sagué-Vilavella et al., 2022; Verdolini et al., 2023), and one study included 624 (20.8 %) people diagnosed with SZ and schizoaffective disorder (Stepniak et al., 2014). The total number of people with SZ and related disorders and a lifetime history of OCs was 909 (30.4 %, range=13–251), compared to 2083 (69.6 %, range=18–632) people with the same diagnosis and without a history of OCs. All studies were cross-sectional and were published between 1995 and 2023.

The quality of the included studies was good for 5 (35.8 %) studies (Buoli et al., 2016; Mezquida et al., 2021; Onu and Ohaeri, 2020; Sagué-Vilavella et al., 2022; Verdolini et al., 2023), fair for 6 (42.8 %) studies (Borkowska and Rybakowski, 2002; Lezheiko et al., 2019; Smith et al., 1995; Stathopoulou et al., 2013; Wegelius et al., 2013; Tosato et al., 2021), and poor for 3 (21.4 %) studies (Bernardini et al., 2015; Gallagher et al., 2014; Stepniak et al., 2014) (see the agreed quality grades of each study in Table 1 and a report of each general score in the Appendix 4 - Supplementary materials).

A qualitative description of the results for specific domains (i.e. positive symptoms, negative symptoms, general and total symptoms from the PANSS subscales, depressive symptoms, and functioning) from the 12 studies included in the meta-analyses is available in the Appendix 5- Supplementary materials.

3.2. Main analyses

The main results of the meta-analyses conducted are displayed in Table 2 and Fig. 2.

Patients with SZ and related disorders with a positive lifetime history of OCs presented higher total scores at psychotic symptoms scales (SMD=0.44, 95 %CI=0.24,0.64; $p<0.001$) when compared to patients without a history of OCs. When looking at different subscales, the first showed higher scores at positive (SMD=0.10, 95 %CI=0.01,0.20; $p=0.03$) and general (SMD=0.37, 95 %CI=0.22,0.52; $p<0.001$) symptoms scales. No differences were found between the two groups in terms of negative symptom scales (SMD=0.19, 95 %CI=-0.01,0.38; $p=0.05$).

Patients with SZ and related disorders who had a positive lifetime history of OCs also presented with worse depressive symptoms (SMD=0.47, 95 %CI=0.09, 0.84; $p=0.01$). No differences were found between the 2 groups in terms of functioning (SMD=-0.01, 95 %CI=-0.35, 0.34; $p=0.95$).

Additional details on the main analyses are presented in the Appendix 6 - Supplementary Materials.

3.3. Meta-regression analyses

We conducted meta-regression analyses to explore the role of dichotomous and continuous predictors of negative symptomatology and functioning, as these were the comparisons that reached a high level of heterogeneity (I^2=67 %, Qp-value=<0.01; and I^2=58 %, Qp-

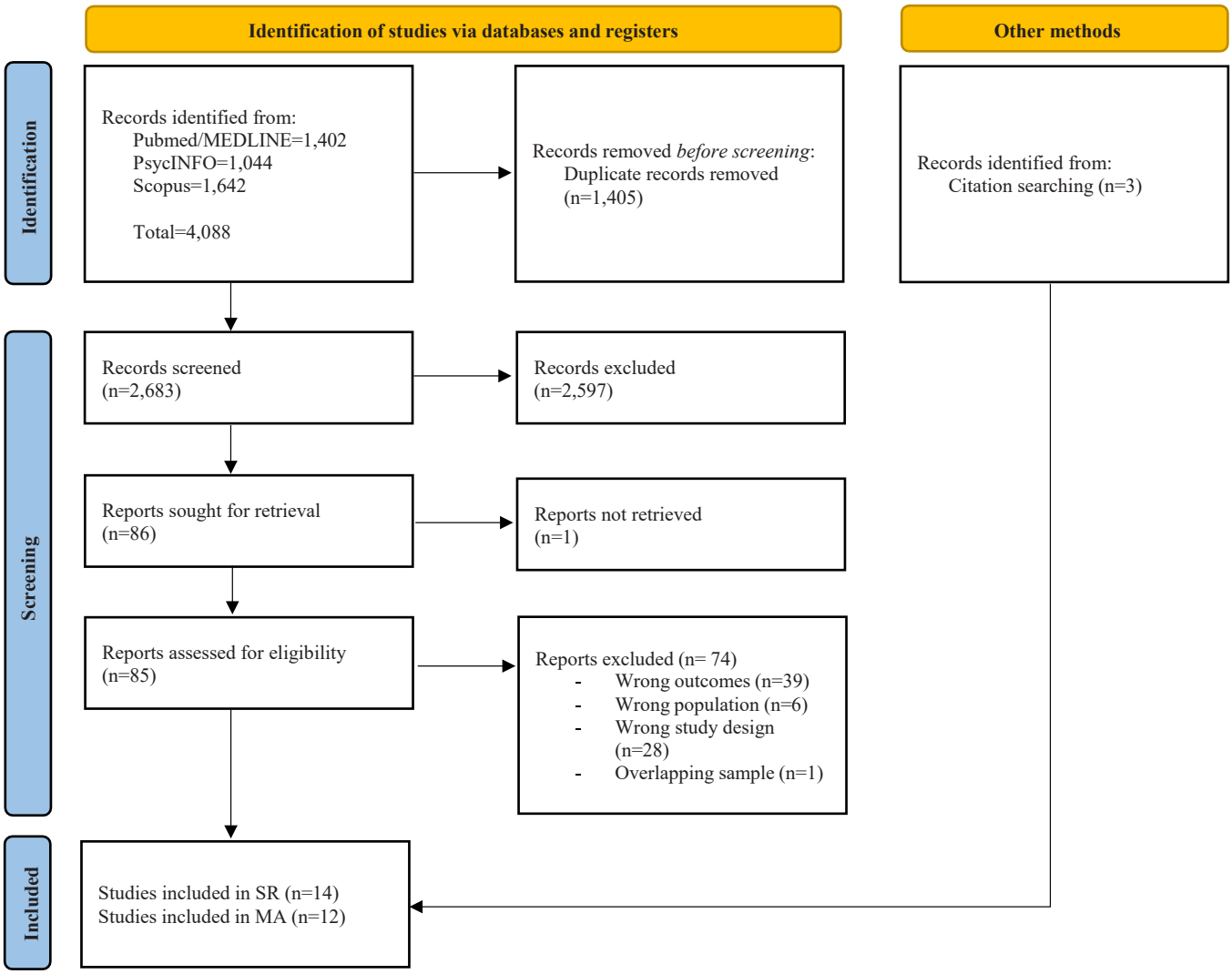

Fig. 1. PRISMA 2020 flow diagram.
Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

value=0.04, respectively). In addition, we conducted a meta-regression for positive symptomatology to explore the role of the diagnosis of SZ or FEP, as for this comparison we had at least 10 studies providing data. None of them was significantly associated with our outcomes.

Additional details on the meta-regression analyses are presented in the Appendix 7 - Supplementary Materials.

3.4. Sensitivity analyses

Leave-one-out sensitivity analyses were conducted.

By removing Borkowska et al. (2002), Verdolini et al. (2023), Onu et al. 2020, Stepniak et al. (2014), Mezquida et al. (2021), and Sagué-Vilavella et al. (2022) from the comparison exploring positive symptomatology, the overall effect became non-significant. By removing Bernardini et al. (2015), Stepniak et al. (2014), and Lezheiko et al. (2019) from the comparison exploring negative symptomatology, the overall effect became significant.

Additional details on the sensitivity analyses are presented in the Appendix 8 - Supplementary Materials.

3.5. Publication bias

The visual inspection of the funnel plots and the Egger tests did not suggest publication bias for the associations with at least 10 studies (i.e., positive psychotic symptomatology and negative psychotic symptomatology). Additional details on the publication bias are presented in the Appendix 9 - Supplementary Materials.

3.6. Studies included only in the qualitative synthesis

Two studies were not included in the meta-analysis (Gallagher et al., 2014; Wegelius et al., 2013). Gallagher et al. (2014) explored sex differences by examining the varying effects of OCs on symptomatology in both men (579) and women (207), however, it did not analyze clinical differences between patients with and without OCs. Wegelius et al. (2013) focused on the study of the relationship between birth weight and symptomatology in SZ, in a group of 178 patients, but included only specific items from the Scales for the Assessment of Positive Symptoms, SAPS (hallucinations, delusions, bizarre behavior, positive formal thought) and the Scales for the Assessment of Negative Symptoms, SANS (affective flattening, alogia, avolition/apathy anhedonia/asociality attention) (Wegelius et al., 2013).

4. Discussion

The present systematic review and meta-analysis aimed to examine

Table 1
Characteristics of included studies.

Study	Country/ Region	n. total (with/ without obstetric complications)	Mean Age (SD)	% Female	Diagnosis	Criteria used for diagnosis	Instrument to assess obstetric complications	Outcome explored (scale)	Quality of the study (NOS)
Bernardini et al. (2015)	Italy/Europe	93 (19/74)	22.7 (3.7)	25	FEP	DSM-IV	Mothers completed a questionnaire detailing tobacco smoking during pregnancy	Psychotic symptomatology (PANSS)	Poor (5)
Borkowska et al. (2002)	Poland/Europe	50 (32/18)	28 (12)	42	Schizophrenia	DSM-IV ICD−10	Semi structured questionnaire about history of OCs not specified	Psychotic symptomatology (PANSS)	Fair (7)
Buoli et al. (2016)	Italy/Europe	51(13/38)	40.25 (10.9)	48	Schizophrenia	DSM-IV-TR and DSM−5	Lewis-Murray scale	Functioning (GAF)	Good (9)
Gallagher et al. (2014)	Pennsylvania/ United States	786 (154/632)	-	26	Schizophrenia	DSM-III	Clinical history and questionnaire about history of OCs not specified	Clinical subtypes of schizophrenia: positive and negative	Poor (5)
Lezheiko et al. (2019)	Russia	369 (111/258)	29.7 (10.1)	55	Schizophrenia	ICD−10	Clinical history and questionnaire about history of OCs not specified	Psychotic symptomatology (PANSS)	Fair (7)
Mezquida et al. (2021)	Spain/Europe	98 (26/72)	33.75 (9.2)	36	Schizophrenia	DSM-IV-TR	Lewis-Murray scale	Psychotic symptomatology (PANSS), Negative symptomatology (BNSS), Depressive symptomatology (CDSS)	Good (8)
Onu et al. 2020	Nigeria/Africa	136 (30/106)	31.76 (10.4)	47	Schizophrenia	ICD−10	Lewis-Murray scale	Psychotic symptomatology (BPRS)	Good (9)
Sagué-Vilavella et al. (2022)	Spain/Europe	37 (16/21)	27.1 (6.7)	49	Non-affective FEP	DSM-IV-TR	Lewis-Murray scale	Psychotic symptomatology (PANSS) and Functioning (FAST), Depressive symptomatology (MADRS)	Good (8)
Smith et al. (1995)	Canada /North America	66 (39/27)	-	26	Schizophrenia	DSM-III-R	Lewis-Murray scale	Functioning (GAF)	Fair (5)
Stathopoulou et al. (2013)	Greece/Europe	212 (92/120)	-	40	Schizophrenia	DSM-IV-TR	Parent's smoking status: smoker/ non-smoker father/ mother; Questionnaire not specified	Psychotic symptomatology (PANSS)	Fair (6)
Stepniak et al. (2014)	Germany/ Europe	750 (398/352)	-	0	Schizophrenia and schizoaffective disorder	DSM-IV-TR	Clinical history and questionnaire about history of OCs not specified	Psychotic symptomatology (PANSS)	Poor (6)
Tosato et al. (2021)	Italy/Europe	61 (21/40)	-	30	First Episode Schizophrenia	ICD−10	Lewis-Murray scale	Psychotic symptomatology (PANSS)	Fair (7)
Verdolini et al. (2023)	Spain/Europe	231 (63/168)	23.09 (5.9)	34	FEP	DSM-IV-TR	Lewis-Murray scale	Psychotic symptomatology (PANSS)	Good (8)
Wegelius et al. (2013)	Finland/ Europe	178 (42/136)	43.5 (6.77)	30	Schizophrenia	DSM-IV-TR	Low and High birth weight	Psychotic symptomatology (SAPS and SANS)	Fair (6)

Legend: OCs- Obstetric complications; DSM - Diagnostic and Statistical Manual of Mental Disorders; ICD- International Statistical Classification of Diseases; FEP - First Episode Psychosis; PANSS - Positive and Negative Syndrome Scale; BNSS-Brief Negative Symptom Scale; CDSS-Calgary Depression Severity Scale; FAST- Functioning Assessment Short Test; GAF- Global Assessment of Functioning; MADRS- Montgomery Asberg Depression Rating Scale; SANS- Scale for the Assessment of Negative Symptoms; SAPS- Scale for the Assessment of Positive Symptoms.

the association between OCs and clinical psychopathology in SZ and related disorders. Our results highlight that individuals with SZ and related conditions who have a history of OCs exhibit a greater burden of clinical symptoms, including positive symptoms, general psychopathology, depressive symptoms, and total clinical symptomatology compared to those without such a history. To the best of our knowledge, this is the first systematic review and meta-analysis examining the relationship between OCs and clinical symptomatology in individuals with SZ and associated disorders.

Aside from being linked to the risk of developing psychosis, current evidence suggests that OCs pose a risk also for their association with clinical outcomes related to earlier age at illness onset (Baeza et al., 2021), and various neuroanatomical (Costas-Carrera et al., 2020), neurocognitive (Amoretti et al., 2022), and metabolic abnormalities

Table 2
Results of the meta-analyses in detail.

Outcome	Studies, n	Individuals included (cases/controls), n	SMD	95 % CI	p-value	95 % PI	I^2 (%)	tau^2	Qp
Psychotic Symptomatology									
Total	5	477 (159/319)	**0.44**	**0.24, 0.64**	**1.45e−05**	**0.24, 0.64**	0	0	0.44
Positive	10	1911* (661/1250)	**0.10**	**0.01, 0.20**	**0.03**	**0.01, 0.20**	0	0	0.44
Negative	10	1911* (661/1250)	0.19	−0.01, 0.38	0.05	−0.31, 0.69	67	0.05	<0.01
General	6	846 (269/577)	**0.37**	**0.22, 0.52**	**1.29e−06**	**0.22, 0.52**	0	0	0.55
Global Functioning									
Total	5	446 (151/294)	−0.01	−0.36, 0.34	0.95	−0.69, 0.67	58	0.09	0.04
Depressive Symptomatology									
Total	2	135 (42/93)	**0.47**	**0.09, 0.84**	**0.01**	**0.09, 0.84**	0	0	0.54

Notes: CI – Confidence Intervals; I^2 – Higgin and Thompson's I^2 estimating of the total heterogeneity; PI – Prediction Intervals; Qp – p-value for the Cochran's Q-test of (residual) heterogeneity; SMD – Standardized mean difference; tau^2 – between-study variance.
Bold values represent significant results.
*As the study by Stepniak et al., 2014 reported n. as a range, we considered the smaller sample size.

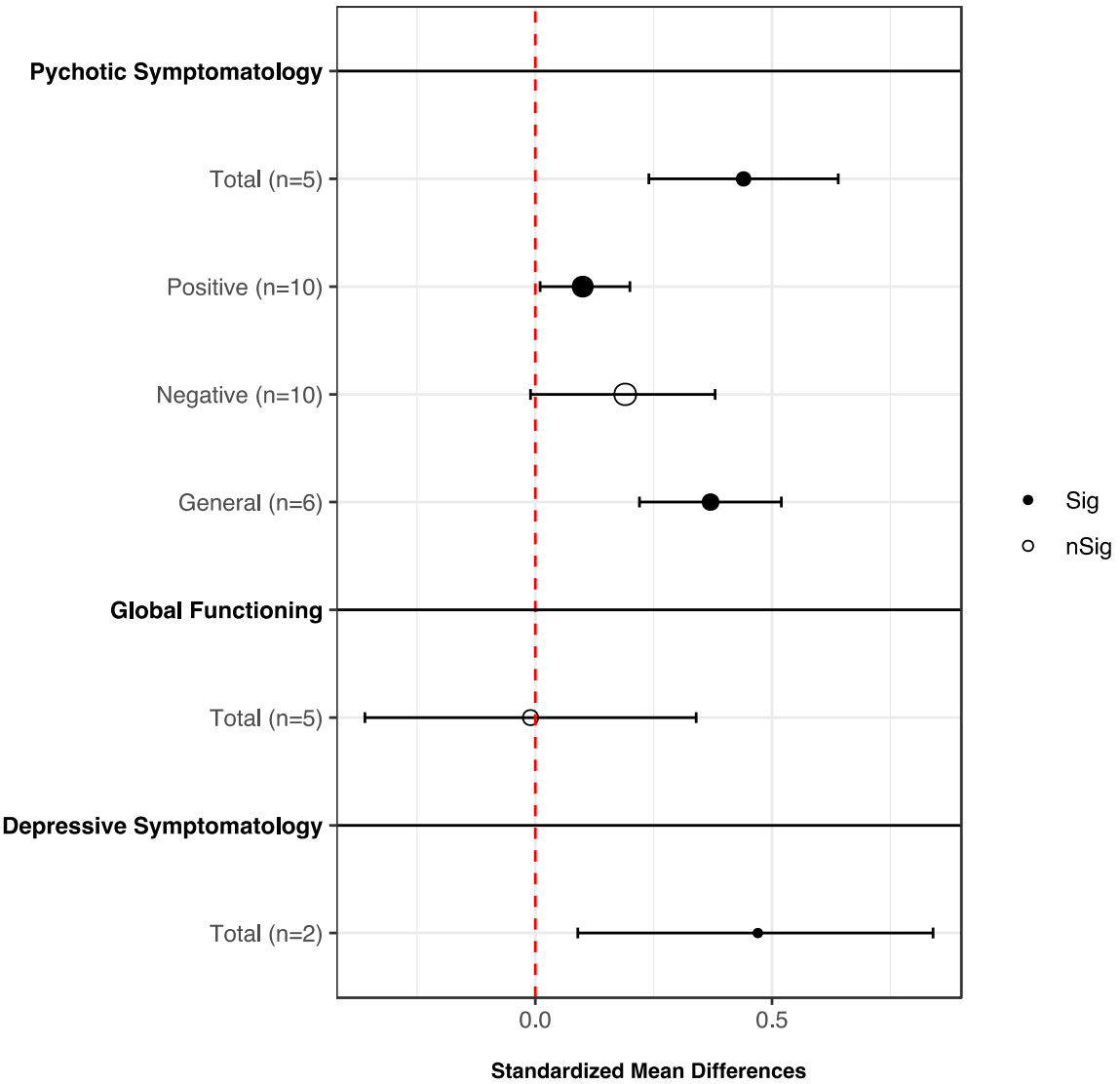

Fig. 2. Overall results regarding psychotic symptomatology, depressive symptomatology, and global functioning of the comparisons included in the meta-analysis. n – number of studies included in the meta-analysis; Sig – significant; nSig – not significant. Point size is proportional to the number of patients included in that specific comparison.

(Garcia-Rizo et al., 2015) as epiphenomena (Garcia-Rizo and Bitanihirwe, 2020, 2024). The present results confirm that OCs also exert an effect on psychopathology.

Patients with a history of OCs exhibited higher total scores on psychotic symptom scales. Different OCs might exert their deleterious effect through different pathways implying a worse clinical profile. Events during gestation or delivery promote different risks (Valli et al., 2023). Hypoxia-regulated/vascular-expression genes (such as *AKT1* or

BDNF) interact with OCs related to fetal asphyxia (Nicodemus et al., 2008) and may subsequently affect brain structure and cognition (Costas-Carrera et al., 2023). Birth weight, an indirect marker of the intrauterine milieu, is influenced by growth events during pregnancy and is associated with cortical morphology across the psychosis spectrum (Haukvik et al., 2014) and cognitive impairment (Torniainen et al., 2013).

Regarding positive symptomatology, our results revealed an increased severity in patients with OCs. However, the significance of the meta-analysis frequently varies when performing a leave-one-out sensitivity analysis, indicating the potential influence of individual studies on the overall results. There appear to be no characteristics of the included studies that justify this variability; rather, it is likely attributable to sample size, as combining all studies together attained statistical significance. In addition, antipsychotic treatment heterogeneity could be a contributing factor. Since the studies included patients receiving various medications, the different antipsychotic profiles and subsequent adverse events may have influenced the positive symptom severity observed. Beyond traditional antipsychotic treatments, recent advancements in psychoceutical therapies represent a promising frontier in the management of severe psychopathological phenotypes in schizophrenia (for instance, N-acetylcysteine for improving cognition, or N-dimethyltryptamine for psychotic symptoms); however, they are not without risks, depending on the compound used (Cano et al., 2022). Among the adverse events most frequently reported after the use of typical antipsychotics are motor effects such as dystonia (Mohamed et al., 2024). These adverse events could interact with the neurodevelopmental disruptions associated with OCs, potentially contributing to the increased symptom severity and variability observed across studies. Additionally, given the heterogeneity in antipsychotic treatment regimens and the varied timing of assessments in psychosis evolution (FEP against stablished SZ in terms of treatment), the relationship between OCs and symptom severity remains complex and multifaceted.

Regarding general symptomatology, our results display a more severe profile in patients with OCs. It is worth mentioning that this general score may underlie and capture a wide array of symptoms of psychopathology which could be referred to as transdiagnostic and more prevalent in FEP (Verdolini et al., 2023). From the present results it is feasible to defend the notion that general and total symptomatology scores may be a representation of the overall severity of the illness, thus confirming the hypothesis that the presence of OCs is associated with more severe clinical phenotypes. Moreover, as previously noted regarding positive symptomatology, the heterogeneity in antipsychotic treatments, varying medication side-effect profiles, and the timing of assessments (early versus chronic phases of the illness) further complicate the relationship between OCs and symptom severity. This highlights the need for additional research to disentangle the combined effects of neurodevelopmental factors, medication regimens, and patient-specific characteristics on clinical outcomes, particularly through studies in both early and chronic schizophrenia samples, as well as investigations considering pregnancy status, where antipsychotic use may have influenced clinical symptom severity (Galbally et al., 2014).

No differences were found between patients with and without OCs in terms of negative symptomatology severity. Despite this, some aspects must be considered to interpret this finding, taking into account that negative symptoms have traditionally been considered a unique domain (Galderisi and Mucci, 2023). Even so, mounting evidence indicates that this symptomatology consists of distinct domains or clusters that exhibit varying behavior over time and may possess distinct underlying pathophysiology. Specifically, it may be divided into two clusters: motivation/pleasure and emotional expression dimensions, or subdivided into five constructs: anhedonia, asociality, avolition, blunted affect, and alogia (Strauss et al., 2019; Wolpe and Fernandez-Egea, 2023). Along the same line, another point that could explain the lack of consistent findings between studies is that negative symptomatology can be either primary, intrinsic to the underlying pathophysiology of SZ, or secondary, arising from treatment side effects, other psychiatric or medical comorbidities, or environmental factors, such as social hypoestimulation (Correll and Schooler, 2020). For this reason, as negative symptom concepts and rating methods have co-evolved, studies employing next-generation negative symptom scales, such as the Brief Negative Symptom Scale (Mané et al., 2014) or the Clinical Assessment Interview for Negative Symptoms (Valiente-Gómez et al., 2015), might yield more precise evaluations to detect primary negative symptoms and could provide further insight of the subtleties of this symptomatology (Kirkpatrick and Fernandez-Egea, 2024). However, after excluding Bernardini et al. (2015), Stepniak et al. (2014), and Lezheiko et al. (2019) from the meta-analysis exploring negative symptomatology, the overall effect became significant. Interestingly, these three studies do not use a validated scale (e.g., the Lewis-Murray Obstetric Complication Scale) to assess the presence of OCs, but instead evaluate them based on medical history or general questionnaires. This may have influenced the results, and studies using reproducible and validated instruments may be better able to detect a significant association between OCs and negative symptoms. It is therefore possible that a better assessment of both negative symptoms and OCs could demonstrate that negative symptoms are also more severe in patients with OCs.

In people with SZ and related disorders, affective symptomatology, specifically depressive symptoms, have traditionally been overlooked because they are not considered as fundamental as positive and negative symptoms, despite their high prevalence (Fiorillo et al. 2024) and their high impact on poorer outcomes, lower quality of life, and diminished treatment response (Wang et al. 2024). In particular, it has been reported that psychotic patients with depressive symptoms have earlier and more relapses, more hospitalizations, a worse functional outcome, and higher incidence of suicide, even after controlling for positive, negative, and cognitive symptomatology (Bergé et al., 2016; Bornheimer et al., 2022), including an increased risk of suicide after the FEP (Toll et al., 2023). Thus, given the prevalence of depressive symptoms in SZ and their potential link to worse outcomes, in the present study, additional analyses explored the relationship between OCs and the affective domain. Meta-analyses results derived from the inclusion of two studies (Mezquida et al., 2021; Sagué-Vilavella et al., 2022) showed that SZ spectrum disorder patients with a positive lifetime history of OCs presented higher severity of depressive symptoms.

In SZ management, achieving not only symptomatic remission but also functional remission is a major goal of both pharmacological and non-pharmacological interventions, particularly in the early stages (Amoretti et al., 2023; Bernardo et al., 2021; Bioque and Parellada, 2023). Thus, we also considered analyzing this parameter to elucidate potential differences in this outcome taking into consideration the presence of OCs. Contrary to our expectations, no differences were found between the two groups in terms of functioning. A feasible rationale for this statement might be the heterogeneity of the scales used to assess functioning. While both the GAF and FAST aim to assess functioning in individuals with mental health disorders, GAF scores primarily reflect symptom severity based on clinical judgment, whereas the FAST scale is a clinician-administered assessment scale that, in addition to clinical judgement, also incorporates self-report or informant reports to evaluate the main functioning problems experienced by psychiatric patients (Rosa et al., 2007). For instance, a GAF score of 51–60 indicates moderate symptoms (e.g., flat affect and circumlocutory speech, occasional panic attacks) or moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflicts with peers or co-workers). In contrast, a FAST score indicating moderate impairment (35−45) reflects moderate difficulties in most areas of functioning, particularly social and occupational activities (e.g., patients with no friends, unable to keep a job, maintain interpersonal relationships, and/or live independently).

Overall, our results confirm that OCs impact numerous outcomes in SZ and related disorders, including psychopathology, leading to a more severe clinical profile. These findings align with both the neurodevelopmental and sociodevelopmental models of schizophrenia, which

emphasize the impact of early-life factors in the risk and progression of the disease (Murray et al., 2017), suggesting that risk factors, even when they occur early in life, can not only affect the risk of developing the disease but also exacerbate clinical outcomes.

4.1. Limitations

Several limitations warrant consideration in interpreting our findings. Firstly, we included both patients with chronic disorders, as well as those with FEP. However, the meta-regressions conducted to explore the potential influence of diagnosis and illness chronicity did not show significant differences (De Prisco and Vieta, 2024). In addition, regarding the point about chronicity, our team is preparing a systematic review on OCs in individuals at clinical high risk for psychosis to shed more light on this topic. Second, the small sample sizes of some of the included studies and the limited number of studies conducted in the field might have limited statistical power. Third, the different (and sometimes poor) conceptualization of OCs. While some studies group OCs together, there is a growing consensus in the literature suggesting the need to differentiate between OCs in terms of their nature and timeframe (such as early or late prenatal or perinatal period), as they could lead to varied neurodevelopmental and clinical outcomes (Cannon et al., 2002). Along with this, OCs are not unique to schizophrenia; they are commonly linked to a variety of other neurodevelopmental disorders, including intellectual disabilities, attention deficit disorder, and autism spectrum disorders (Carter et al., 2024; Chen et al., 2023). In addition, this potential epidemiology does not allow for assertions of causality but only for associations between OCs and SZ, which could be bidirectional. It is plausible that genes implicated in schizophrenia, such as *FURIN* or *MAN2A1,* increase the risk of OCs, as they are associated with higher susceptibility to infections (Trubetskoy et al., 2022). Similarly, the *AKT3* gene, known for its role in hippocampal neurogenesis deficits in SZ, might also increase the risk of intrauterine growth retardation (Trubetskoy et al., 2022). Also, the method of gathering information concerning OCs (as a dichotomous variable -presence/absence- or also considering the type and severity of the OC based on their nature and timeframe) was different across studies. Fourth, several different rating scales were used to assess SZ symptoms. However, we used the SMD to minimize these differences.

These limitations, while important, should not hinder the strengths of the present study. The results from this pioneering meta-analysis contribute significantly to the current literature on a clinically relevant topic, namely, elucidating the association between early-life risk factors such as OCs and the severity of clinical phenotypes in individuals with SZ and related disorders. The study offers a comprehensive synthesis of findings across multiple studies, employing rigorous meta-analytic techniques to quantitatively assess and consolidate results. It also suggests potential moderators influencing these associations, providing nuanced insights into the impact of OCs on both chonic and FEP outcomes, supporting the neuro and sociodevelopmental hypothesis in SZ, and reaffirming that clinicians should systematically assess the presence of OCs, as this could significantly impact diagnosis and treatment planning. Overall, the study enhances understanding of the complex interplay between OCs and SZ, informing future research directions and clinical practices aimed at improving outcomes in affected individuals.

5. Conclusions

The findings of the present meta-analysis suggest a consistent correlation between OCs and more severe psychopathological phenotypes in SZ spectrum disorders. Specifically, in comparison to patients without OCs, those with a history of OCs presented greater severity in positive, depressive, and general symptomatology, but not in the negative and functional outcomes.

These results confirm the influence of the pre-and perinatal period on the subsequent development of clinical trajectories in SZ, even at the first stages of the illness. Given the limited number of studies available for comparison, additional research focusing on the characteristics of perinatal stressful events, also considering the nature and the timing of the obstetric events, is necessary to comprehensively elucidate their impact on the clinical statement of individuals affected by psychosis. Therefore, the clustering of early life complications can serve as an early warning sign of difficulties and challenges ahead and herald the opportunity for tailoring and personalizing interventions to enhance both clinical and functional outcomes.

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Availability of data and materials

Requests to see any data that are not included in the Article or the appendix should be directed to the corresponding author.

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PROSPERO registration

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105913.

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