








Obstetric complications and genetic risk for schizophrenia: Differential role of antenatal and perinatal events in first episode psychosis

Isabel Valli^{1,2}  | Alex Gonzalez Segura³  | Norma Verdolini⁴ |
 Clemente Garcia-Rizo^{1,5,6}  | Daniel Berge^{6,7,8} | Inmaculada Baeza^{1,6,9,10} |
 Manuel J. Cuesta^{11,12} | Ana Gonzalez-Pinto¹³ | Antonio Lobo^{6,14,15} |
 Anabel Martinez-Aran^{1,6,10,16} | Gisela Mezquida^{1,5,6,10}  |
 Laura Pina-Camacho^{6,17,18}  | Alexandra Roldan Bejarano^{6,19,20} | Sergi Mas^{1,3,6}  |
 Philip McGuire²¹ | Miquel Bernardo^{1,5,6,10*} | Eduard Vieta^{1,6,10,16*}  | PEPs group

Correspondence

Isabel Valli, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) Carrer del Rosselló 149 08004 Barcelona, Spain.

Email: isabel.valli@kcl.ac.uk

Clemente Garcia-Rizo, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.

Email: cgarcia3@clinic.cat

Funding information

Generalitat de Catalunya; Horizon 2020 Framework Programme; Instituto de Salud Carlos III; Ministerio de Economía y Competitividad; European Union; Centro de Investigación Biomédica en Red de salud Mental; CIBERSAM; ISCIII; BITRECS project; "La Caixa" Foundation, Grant/Award Number: 100010434

Abstract

Background: Obstetric complications (OCs) are key contributors to psychosis risk. However, it is unclear whether they increase psychosis vulnerability independently of genetic risk, in interaction with it, or are a manifestation of psychosis proneness. We examined the role of distinct types of OCs in terms of psychosis risk and tested whether they interact differently with genetic vulnerability, whilst accounting for other known environmental risk factors.

Study Design: 405 participants (219 first episode psychosis patients and 186 healthy volunteers) underwent a comprehensive assessment of OCs, measured using the Lewis-Murray scale and divided into complications of pregnancy, abnormalities of foetal growth and development, and complications of delivery. Participants were compared in terms of history of OCs, polygenic risk score for schizophrenia (PRS-SZ) and interactions between these.

Results: Both complications of pregnancy and abnormalities of foetal growth were significantly associated with case-control status ($p = 0.02$ and 0.03 , respectively), whereas complications of delivery were not. PRS-SZ showed a significant association with psychosis ($p = 0.04$), but there were no significant interactions between genetic risk for schizophrenia and OCs, either when these were considered globally or separated based on their timeframe.

Conclusions: We observed no significant interaction between genetic and obstetric vulnerability, yet distinct types of OCs may have a different impact

* These two authors contributed equally to this work.

For affiliations refer to page 88

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2023 The Authors. *Acta Psychiatrica Scandinavica* published by John Wiley & Sons Ltd.

on psychosis risk, based on their nature and timeframe. Examining their differential role might clarify their relative contributions to this risk.

KEYWORDS

environmental, Funding, placenta, polygenic risk score, pregnancy, utero

1 | INTRODUCTION

Environmental hazards are key contributors to psychosis risk, with a timing that extends over the prenatal and perinatal period, childhood, teenage years and early adulthood.¹ Their importance has been systematised in the Developmental Risk Factor Model of psychosis, which expands the neurodevelopmental perspective beyond the perinatal period to incorporate the impact of adverse childhood and teenage environmental exposures on brain development.² Notwithstanding, the prenatal and perinatal period are considered windows of particularly heightened vulnerability to environmental insults due to the brain maturational events ongoing at this stage.³ Obstetric complications (OCs) have thus been identified among the most robust environmental risk factors^{1,4,5} and adverse events during pregnancy, labour, delivery and the early neonatal period have been associated with the onset of psychosis in later life.⁶ A recent meta-analysis sought to summarise the evidence added in the last 20 years since the literature on the role of OCs in psychosis risk was last meta-analysed.⁷ The authors examined the magnitude of the association for different types of insults and identified several complications of pregnancy as significant risk factors for the development of psychosis. They also identified several significant associations for abnormalities in foetal growth and development. Yet, when examining labour and delivery complications, none was identified as a significant risk factor, with the exception of asphyxia, for which the authors, however, reported potential publication bias.

Despite the significant association between OCs and psychosis risk,^{6,7} several population-based studies did not identify excess exposure to OCs in individuals subsequently developing schizophrenia (SZ) compared to healthy controls.^{8–10} This discrepancy was considered to result from the combination of several potential contributing factors, including different sample sizes, severity thresholds and rating methods, but to ultimately reflect the role of heterogeneous genetic risk for SZ.¹¹ Consistent with this perspective, several population-based studies specifically assessing the incidence of OCs and the characteristics of infants born to mothers with SZ, reported a significant excess of adverse reproductive events.^{12,13}

Despite the evidence associating OCs and increased psychosis risk, little is known about the underlying

Significant outcomes

- Complications of pregnancy and abnormalities of fetal growth were associated with psychosis, whereas complications of delivery were not.
- There were no significant interactions between genetic and obstetric vulnerability, both for OCs considered globally or separated based on their timeframe.

Limitations

- The Lewis-Murray scale that we employed is less detailed compared to the McNeil-Sjöström scale, and each of its subscales includes a fairly heterogeneous set of insults.
- We examined individuals with a first episode of psychosis rather than established schizophrenia, thus clinically more heterogeneous.
- The size of our sample did not allow for a separate examination of specific noxae.

mechanisms. It is still unclear whether OCs can increase psychosis vulnerability independently of genetic risk, in interaction with it, or whether obstetric hazards are a manifestation of psychosis proneness.¹⁴ Ursini et al.¹⁵ specifically examined the potential interaction between genetic risk for SZ and history of OCs in determining case-control status. The authors observed that the polygenic risk score for SZ (PRS-SZ) was significantly higher in patients with a history of OCs compared to those without, a relationship not observed in healthy control (HC) participants. The effect of genetic liability was thus significantly higher in the presence of OCs than in their absence. The intra-uterine milieu was hence proposed as a point of intersection between genetic and environmental adversity. The placenta, in particular, was indicated as a key mediator in the interaction between genetic risk and early environment on brain development.¹⁵ However, Vassos et al. reported no significant effect of PRS-SZ on the presence of OCs in cases, and no association with case control-status when stratifying participants based on OCs history.¹⁶ Discrepancies were considered to reflect methodological differences,^{17,18} particularly in

the assessment instrument used, with the McNeil-Sjöström scale¹⁹ used by Ursini et al. considered more detailed than the Lewis-Murray scale²⁰ employed by Vassos et al. In addition, Vassos et al. employed birth weight below 2.5 kg as a proxy for the presence of OCs in the absence of more detailed information. A potential contributor to these inconsistencies might be the heterogeneous nature of OCs and the specific mechanisms conferring psychosis risk. Ursini et al.¹⁵ observed that genes showing the strongest association with SZ and interacting with OCs history were overexpressed in placentae of individuals with paradigmatic ischaemic diseases, such as preeclampsia and intra uterine growth restriction (IUGR). Hence, based on their nature and timeframe, different types of OCs might play a different role in the pathophysiology of psychosis and not invariably share genomic-based mechanisms.

In this study we sought to disentangle some of the potential contributors to the aforementioned discrepancies. Our aim was to specifically assess the role of different types of OCs in determining case-control status, and then examine their relationship with PRS-SZ. We grouped OCs based on the timing of their occurrence, dividing them into complications of pregnancy, abnormalities of foetal growth and development, and complications of delivery. We also sought to take into account the potential confounding effect of other known environmental risk factors. For this purpose we employed variables identified in the Maudsley Environmental Risk score,²¹ which aggregates several measures of environmental risk for psychosis.

Consistent with the central role proposed for the placenta,¹⁵ we hypothesised that both abnormalities of pregnancy and abnormalities of foetal growth and development would be associated with psychosis risk. Whereas, considering the lack of evidence for a significant association with psychosis for complications of labour and delivery as a group,⁷ and due to their more heterogeneous nature, we hypothesised that we would observe no significant association between complications of delivery and psychosis risk. We also hypothesised that the former two types of abnormalities, more directly reflective of placental pathology, would be associated with PRS-SZ, while complications of delivery would not.

2 | METHODS

2.1 | Participants

A total of 335 patients with a first episode of psychosis (FEP) and 253 HC participants were recruited between 2009 and 2011 as part of the PEPs Project,²² a

longitudinal multicentre study conducted across 16 Spanish hospitals, members of a national network for research in mental health (CIBERSAM).²³ Patients were included if aged 7–35 years and if they had experienced psychotic symptoms for less than 12 months. HC participants were matched with patients based on age ($\pm 10\%$) and socioeconomic status of their parents (± 1 level). Exclusion criteria for the whole sample were intelligent quotient (IQ) lower than 70, history of head trauma with loss of consciousness, and presence of an organic illness with mental repercussions. HC participants had past or present psychotic disorder or major depressive disorder diagnoses as additional exclusion criteria. For the present study participants were included based on OCs data records, Caucasian ethnic background and availability of blood or saliva for the extraction of genetic information, provided that genetic data met quality control procedures described in the relevant analysis section. Based on these further inclusion criteria the subsample examined in the current study consisted of 405 participants, 219 FEP patients (diagnostic information in the supplementary material) and 186 HC subjects. All participants had to be fluent in Spanish and give written informed consent, which was obtained by parents or legal guardians for participants aged below 18 years. The study was approved by the ethics committees of all participating centres and conducted in accordance with the ethical principles of the Declaration of Helsinki of 1975, as revised in 2013.²⁴

2.2 | Clinical assessment

All participants underwent a comprehensive clinical assessment as described in detail before.²⁵ Diagnoses were established using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).²⁶

2.3 | Environmental risk measures

For this study, we considered the six environmental risk factors used to generate the Maudsley environmental risk score,²¹ which includes obstetric complications, ethnic minority status, urbanicity, high paternal age, cannabis use, and childhood adversity. Information for each risk factor was obtained using data collected during the clinical assessment as described before.²⁷ For simplicity, and due to low number of cases and controls in some of the categories proposed by Vassos et al.,²¹ we adapted the original categories of risk to dichotomous variables as described below. We also excluded ethnicity from the factors under consideration due to PRS-SZ being valid only for participants of Caucasian origin.

2.3.1 | Obstetric complications

The Maudsley environmental risk score employed birth weight below 2.5 kg as a proxy measure of OCs. We employed the Lewis-Murray scale,²⁰ which groups OCs into different categories: complications of pregnancy (Lewis A), abnormal foetal growth and development (Lewis B), and difficulties in delivery (Lewis C). We also considered a measure combining antepartum complications (Lewis AB) and a measure comprehensive of all complications regardless of their timeframe (Lewis T), all categorised as dichotomous variables (yes/no).

Studies employing a different scale, the McNeil-Sjöström scale,¹⁹ include measures of severity. In the Lewis-Murray scale, severity is not assessed and scoring is rather given on the quality of the recall, classified as either dubious or certain.²⁰ We defined a positive OCs history based on the presence of at least one certain complication.

2.3.2 | Urbanicity

For this item the place of birth was categorised into 'rural' (including rural areas and towns up to 10,000 inhabitants) and 'urban' (for towns and cities with more than 10,000 inhabitants).^{21,27}

2.3.3 | Paternal age

Paternal age was divided in 2 categories: less than 40 years, and equal or more than 40 years.^{21,27}

2.3.4 | Cannabis use

Cannabis use was assessed using the European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence (EuropAsi)²⁸ and categorised into 'no exposure' and 'any exposure'.

2.3.5 | Childhood adversity

Traumatic experiences were assessed using the Traumatic Experiences in Psychiatric Outpatients Questionnaire (TQ),²⁹ an 18-item self-report questionnaire. Data were coded as 'no exposure' (no traumatic experiences during childhood) and 'any exposure' (1 or more traumatic experiences during childhood).

2.4 | Biological samples collection and storage

Blood samples were collected using BD Vacutainer[®] tubes, with K2 EDTA (Becton Dickinson, Franklin Lakes, New Jersey). Genomic DNA was extracted with the MagNA Pure LC DNA isolation Kit using an LC MagNA Pure system (Roche Diagnostics GmbH, Mannheim, Germany). Saliva samples were collected using the Ora-gene DNA Sample collection Kit (OG-500, DNA Self-Collection Kit, Genotek, Ottawa, Ontario, Canada) and DNA was extracted according to the manufacturer's protocol. Both samples were stored at -80°C . DNA concentration and quality were measured spectrophotometrically using a NanoDrop[®] 2000 (Thermo Fisher Scientific, Epsom, Surrey, UK). For each participant, 2.5 μg of genomic DNA were sent for genotyping at the Spanish National Genotyping Centre (CeGen) using the Axiom Spain Biobank Array (developed at the University of Santiago de Compostela, Spain).

2.5 | Genetic data processing

Genotyping data were submitted to the Michigan Imputation Server³⁰ employing the standard Minimac4 software pipeline and setting a European Population reference from build GRCh37/hg19 and Eagle v2.4 phasing. For the PRS-SZ calculation, we employed as reference GWAS summary results derived from 76,755 cases and 243,649 controls.³¹ Duplicated and unknown strand GWAS summary SNPs were excluded. Quality control was performed with PLINK v1.07.³² Inclusion criteria for SNPs were minor allele frequency (MAF) > 0.01 , Hardy-Weinberg equilibrium $p > 10^{-6}$, marker missingness < 0.01 and imputation INFO > 0.8 . Pruning was done using a window/step size of 200/50 kb and $r^2 > 0.25$. Sample quality control included individuals with heterozygosity values within three standard deviations (SD) from the mean, a missingness rate < 0.01 , matching chromosomal and database-labelled sex and self-reported European ancestry. PRS were constructed using the PRSice-2 v2.3.3 software.³³ Clumping for the SNPs in the reference data was set at 250 kb and $r^2 > 0.1$ and the effect values of the SNP's risk alleles were added to create the individual score. For the analyses we employed 2 normalised PRS-SZ, constructed from SNPs with $P < 5 \times 10^{-8}$ (PRS-SZ 10^{-8}) and $P < 1 \times 10^{-6}$ (PRS-SZ 10^{-6}) in the reference GWAS, which in the work of Ursini et al. were the only ones interacting with OCs on case-control status.¹⁵ However, both Ursini et al.¹⁵ and Vassos et al.¹⁶ employed reference data from the study of Ripke et al.³⁴ to construct the PRS-SZ, while we employed

data from the most recent GWAS study,³¹ as the reference sample included was larger and thus the statistical power increased.

2.6 | Statistical Analyses

We first assessed the difference between cases and controls in terms of demographic variables and environmental risk exposures²¹ using binary logistic regression models.

Binary logistic regression models were then fitted with case-control status as dependent variable, assessing the role of OCs, for each of the Lewis-Murray subscales, for antepartum complications (Lewis AB) and for the total score (Lewis T), covarying for the environmental exposures found to be significantly different between cases and controls in the previous analysis. Similarly we assessed the association of PRS-SZ at the 10^{-6} and 10^{-8} thresholds¹⁵ with case-control status. A genetic principal component analysis (PCA) was performed to control for population stratification by means of the *SNPRelate* package, and the first 10 principal components (PC) were used as covariates in all statistical analyses examining PRS-SZ.

We then examined the potential interaction between OCs and PRS-SZ on case-control status, covarying initially only for the first 10 genetic PC, using PRS-SZ as a continuous and also as a dichotomous variable (5th quintile vs. the other quintiles).¹⁵ We then performed a

sensitivity analysis with the 10 principal components as well as age, sex and significant environmental risk exposures.

Analyses were performed using the IBM SPSS Statistics version 26 and R v4.1.2 (R Core Team 2017). All tests were two-tailed and statistical significance considered for p -values <0.05 .

3 | RESULTS

Patients and HC participants did not differ in terms of age or sex. When examining the exposure to environmental risk factors only cannabis use appeared as significantly associated with case-control status (Table 1).

Further analyses were therefore covaried only for this environmental factor.

When examining all OCs taken together (Lewis T) we observed that they significantly differed between cases and controls (Table 2, Figure 1). When examining separately each of the Lewis-Murray subscales we found significant associations with psychosis for complications of pregnancy (Lewis A), for abnormalities of foetal growth and development (Lewis B), and for both antepartum abnormalities combined (Lewis AB), while we found no significant association with complications of delivery (Lewis C) (Table 2, Figure 1).

We then tested whether the PRS-SZ was associated with case-control status in this sample, and found that PRS-SZ was significantly higher in patients relative to

TABLE 1 Demographic and environmental exposure information.

	HC (n = 186)	FEP (n = 219)	OR (95% C.I.)	p-value
Age mean (SD)	23.88 (6.37)	23.38 (5.87)	0.99 (0.95–1.02)	0.41
<i>Sex</i>				
Male	66.1%	67.6%		
Female	33.9%	32.4%	1.07 (0.71–1.62)	0.76
<i>Urbanicity</i>				
Rural	9.7%	8.7%		
Urban	90.3%	91.3%	1.28 (0.57–2.22)	0.73
<i>Paternal age</i>				
<40	92.9%	88.1%		
≥ 40	7.1%	11.9%	1.77 (0.85–3.69)	0.13
<i>Cannabis</i>				
No	87.1%	55.3%		
Yes	12.9%	44.7%	5.47 (3.30–9.06)	<0.001
<i>Childhood adversity</i>				
No	55.4%	49.8%		
Yes	44.6%	50.2%	1.25 (0.84–1.87)	0.27

TABLE 2 Odds ratio estimation for case control status adjusted by cannabis use for Lewis Murray subscales and total score.

OC	OR (95% C.I)	p-value
Lewis A	5.85 (1.26–17.08)	0.02
Lewis B	2.51 (1.07–5.86)	0.03
Lewis C	1.51 (0.78–2.93)	0.22
Lewis AB	2.97 (1.40–6.31)	0.005
Lewis Total	2.12 (1.21–3.73)	0.01

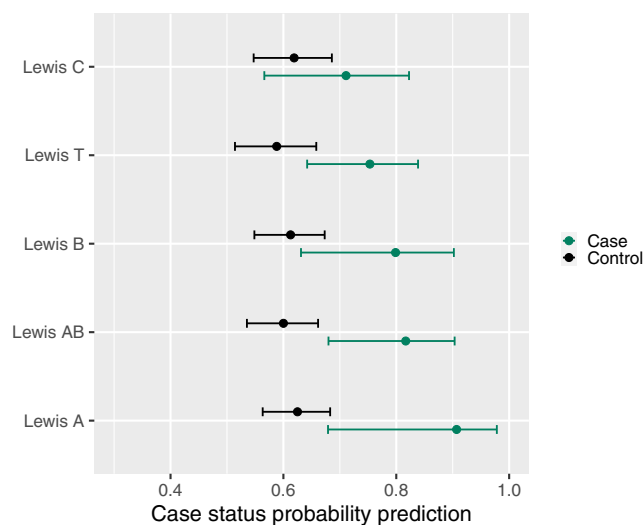


FIGURE 1 Association of different types of OCs with case controls status: for complications of pregnancy (Lewis A), complications of foetal growth and development (Lewis B), antenatal complications (Lewis AB), complications of delivery (Lewis C) and all OCs regardless of their timeframe (Lewis T).

controls when employing PRS-SZ 10^{-6} [OR 1.24 (95% CI 1.01 to 1.52), $p = 0.041$] (Figure 2), but not when employing PRS-SZ 10^{-8} [OR 1.14 (95% CI 0.93–1.40), $p = 0.20$].

We also analysed the relationship between PRS-SZ and case control-status separately for participants with and without OCs history and found that the association did not reach significance at either threshold for both the former [PRS-SZ 10^{-6} : OR 1.5 (95% CI 0.76–2.96, $p = 0.25$), PRS-SZ 10^{-8} : OR 1.04 (95% CI 0.75–1.43, $p = 0.83$)] or the latter subsample [PRS-SZ 10^{-6} : OR 1.1 (95% CI 0.81–1.5, $p = 0.53$), PRS-SZ 10^{-8} : OR 1.06 (95% CI 0.52–2.15, $p = 0.88$)].

We then employed multiple logistic regressions to examine the interaction between genetic risk for schizophrenia and OCs history in determining case-control status, adjusted by the first 10 genetic PC. We observed no significant interaction between Lewis T and PRS-SZ as a continuous variable at either the 10^{-6} (Figure 3) or 10^{-8} threshold. Equally we observed no

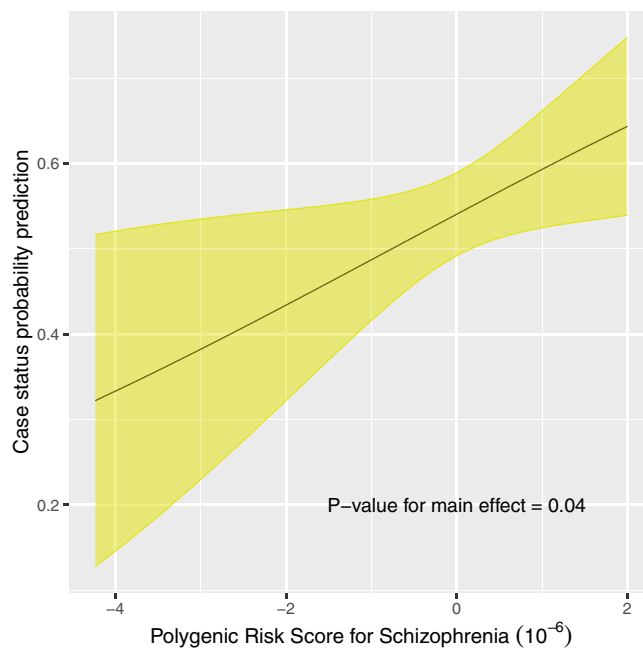


FIGURE 2 Association between polygenic risk for schizophrenia and case control status.

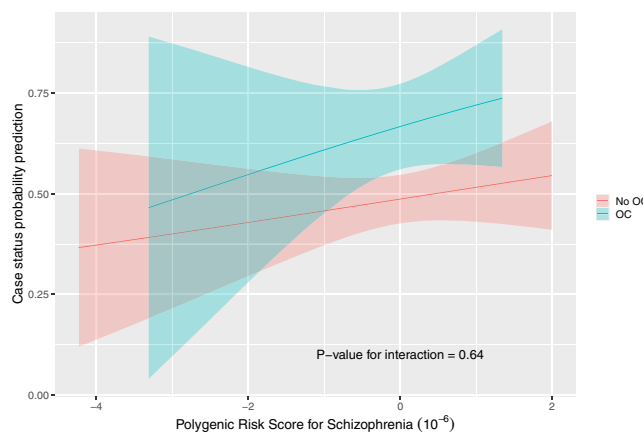


FIGURE 3 Interaction between polygenic risk for schizophrenia and OCs on case control status: OC considered together regardless of their timeframe (Lewis T).

significant interaction when repeating the analysis for each of the Lewis-Murray subscales and for Lewis AB. We also employed multiple logistic regressions to examine the interaction between OCs and PRS on determining case-control status using PRS-SZ for both thresholds as a dichotomous variable (5th quintile vs. the other quintiles) adjusted by the first 10 genetic PC. Again we found no significant interaction between genetic risk for SZ and OCs history in the likelihood that a subject is a patient or a control (Tables S1 and S2, supplementary material).

We also observed no significant difference in the risk of experiencing OCs, either for total scores or any of the subscales, based on PRS-SZ, in the whole sample (Table S3, supplementary material) or when HC and patients with FEP were examined separately (Tables S4 and S5, supplementary material).

Finally we performed sensitivity analyses including sex, age and cannabis use as covariates and identified no significant difference in terms of any of the results.

4 | DISCUSSION

In this study we examined whether different types of OCs are differentially associated with psychosis risk. We grouped OCs based on the timing of their occurrence according to the Lewis-Murray scale,²⁰ which subdivides them into complications of pregnancy (group A), abnormalities of foetal growth and development (group B) and difficulties in delivery (group C). We also examined whether grouping OCs based on the timeframe of exposure could contribute to clarify their relationship with genetic risk for SZ. In addition we took into account the potential role of other known environmental risk factors for psychosis, examining the impact of variables included in the Maudsley Environmental Risk Score.²¹ Among these variables, in our multicentre FEP sample, we observed a significant association with case-control status only for cannabis use, while we found no significant associations with measures of urbanicity and childhood adversity, nor with paternal age. We hence took into account the potential confounding effect of cannabis use in subsequent analyses.

Consistent with our first hypothesis, we observed a significant association between OCs and case-control status, with a differential role based on the timeframe of exposure (Figure 1). We observed a significant effect for the total score (Lewis T) and for both complications of pregnancy (Lewis A) and for abnormalities of foetal growth and development (Lewis B). The finding was further strengthened when combining the two subcategories of antenatal complications (Lewis AB), whilst we observed no significant relationship between abnormalities of delivery and psychosis risk (Lewis C). Our results are consistent with those of the latest meta-analysis on the role of OCs,⁷ which identified significant associations with psychosis for several antenatal complications and only weaker evidence for asphyxia at birth but no other complications of delivery. Taken together these findings might further emphasise the potential important impact of intrauterine vascular deficits on brain development compared to more heterogeneous perinatal events, with the exception of acute hypoxia with ischaemic damage

during birth. The former can be the result of several noxae, including preeclampsia, placental inflammatory changes secondary to maternal infection, placentation abnormalities or haemorrhages during pregnancy, and can manifest in terms of IUGR, which can reflect different placental difficulties in supporting foetal growth. We hence hypothesised that these antenatal complications would be interacting with genetic risk for schizophrenia in determining case control status.

When examining the role of PRS-SZ we considered the two thresholds that had been identified by Ursini et al. to interact with OCs history.¹⁵ We identified a significant positive association with psychosis risk for the 10^{-6} threshold (Figure 2) but not for the 10^{-8} threshold. However, when examining the relationship between genetic risk for SZ and OCs history, we identified no significant interaction between PRS-SZ at both thresholds and OCs, either when considering the total score or any of the Lewis-Murray subscales. In particular, contrary to our hypothesis, we did not identify a significant interaction between antepartum abnormalities (Lewis A, Lewis B or Lewis AB) and PRS-SZ, both when considering it as a continuous or a dichotomous variable for either threshold. We also found no significant interaction with complications of delivery (Lewis C). Ursini et al. also examined the relationship between PRS-SZ and case-control status within two subgroups of participants, those with and those without a history of OCs, and found that the role of PRS-SZ was highly significant in the former group but not in the absence of OCs¹⁵. We examined the same relationship and observed no significant association in either subgroup. We also examined whether a higher PRS-SZ was associated with a higher likelihood of experiencing OCs for each of the subscales and found no significant association in the whole sample, or separately within patients and controls. Our results are therefore consistent with those of Vassos et al., who identified no significant interaction between PRS-SZ and OCs¹⁶, though equally limited by employing the same rating scale. Compared to Vassos et al., we used a more stringent threshold to define a positive OCs history, including only participants with definite rather than dubious exposure.¹⁷ However, the Lewis-Murray scale²⁰ is less detailed in recording pre- and perinatal hazards compared to the McNeil-Sjöström scale¹⁹ used by Ursini et al.,¹⁵ and the difference in the assessment instrument employed has been considered a key contributor to discrepant findings.¹⁷

Yet, not all OCs are sustained by insults that could be hypothesised to have a genetic basis and their heterogeneous nature might be an important factor underlying inconsistent results. Jablensky et al.¹¹ identified excess of two specific pregnancy complications in mothers with SZ and BP compared to mothers with major depression and

HC mothers: placentation abnormalities and antepartum haemorrhages. Hence, based on the reported differential expression of SZ risk genes in placentae from complicated pregnancies,¹⁵ genetic mechanisms might be most relevant for noxae directly reflective of placental pathology. However, the relationship with genetic risk for SZ is considered to go beyond just paradigmatic placental disorders. It is rather suggested that genetic risk for SZ might confer increased susceptibility to a wider array of OCs¹⁴, with variable genetic loadings translating into different thresholds of vulnerability for the developing brain.¹¹ Maternal infections, for instance, are considered to injure neurons and neural progenitor cells either directly or through the activation of astrocytes and microglia with release of inflammatory cytokines.³⁵ They normally operate via inflammatory pathways activating oxidative stress, but it is suggested that higher genetic risk for SZ can upregulate placental transcriptional programs involved in oxidative stress responses,^{15,35} rendering the foetal brain more susceptible to neurodevelopmental abnormalities if an infection occurs. Jablensky et al.¹¹ also observed that, among labour and delivery complications, only foetal distress occurred more frequently in women with SZ or affective disorders compared to healthy control mothers. Resilience mechanisms to hypoxia and ischaemic damage, such as oxytocin driven changes in GABAergic neurotransmission, are physiologically activated during childbirth.³⁶ However it has been suggested that they might be impaired in those with a more pronounced genetic predisposition to SZ, increasing the vulnerability to asphyxia of the neonatal brain.³

To clarify the relationship between OCs and genetic risk for SZ it might thus be necessary to focus on the specific subset of complications that have been significantly associated with case-control status,⁷ or to select OCs based on the underlying pathophysiological mechanisms. Our attempt in this direction was limited by the assessment instrument employed, the Lewis-Murray scale, and by our inability to select specific noxae due to the size of the sample. The latter was larger compared to one of the samples in which Ursini et al.¹⁵ had replicated their original finding, thus theoretically sufficiently powered. However participants to our study had a first episode of psychosis rather than a SZ diagnosis and were therefore more heterogeneous. In addition, Ursini et al.¹⁵ examined OCs globally, whereas we also sought to test the possible interaction of PRS-SZ with different OC subcategories. The size of our sample might have hampered our ability to answer this further question. Finally, each of the Lewis-Murray subscales that we employed includes a fairly diverse set of insults, sustained by different pathophysiological mechanisms.

Hence, future efforts in this direction might need to examine specific noxae to further clarify how pre and perinatal risk factors interact with genetic liability for psychosis and pave the way for antenatal and post-natal risk reduction interventions.

AFFILIATIONS

¹Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

²Institute of Psychiatry Psychology and Neuroscience, King's College London, London, UK

³Department of Clinical Foundations, Pharmacology Unit, University of Barcelona, Barcelona, Spain

⁴Department of Mental Health, Umbria 1 Mental Health Center, Perugia, Italy

⁵Barcelona Clínic Schizophrenia Unit (BCSU), Hospital Clínic de Barcelona, University of Barcelona, Barcelona, Spain

⁶Centro de Investigación Biomédica en red de salud Mental (CIBERSAM), Spain

⁷Hospital del Mar Medical Research Institute, Barcelona, Spain

⁸Universitat Pompeu Fabra, MELIS Department, Barcelona, Spain

⁹Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clínic de Barcelona, Barcelona, Spain

¹⁰Institute of Neurosciences, University of Barcelona, Spain

¹¹Department of Psychiatry, Navarra University Hospital, Pamplona, Spain

¹²Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain

¹³Department of Psychiatry, Hospital Universitario de Alava, UPV/EHU, BIOARABA, Vitoria, Spain

¹⁴Department of Medicine and Psychiatry, University of Zaragoza, Zaragoza, Spain

¹⁵Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza, Spain

¹⁶Bipolar and Depressive Unit, Hospital Clínic de Barcelona, Institute of Neurosciences, Barcelona, Spain

¹⁷Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Madrid, Spain

¹⁸School of Medicine, Complutense University, Madrid, Spain

¹⁹Department of Psychiatry, Institut d'Investigació Biomèdica Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

²⁰Department of Psychiatry, Autònoma University of Barcelona, Barcelona, Spain

²¹Department of Psychiatry, University of Oxford, Oxford, UK

ACKNOWLEDGMENTS

We acknowledge all participants for their contribution.

FUNDING INFORMATION

This work was supported by the Ministerio de Economía y Competitividad (PI08/0208, PI11/00325, PI14/00612, PI20/00661); Instituto de Salud Carlos III – Fondo Europeo de Desarrollo Regional co-funded by the European Union; Centro de Investigación Biomédica en Red de salud Mental, CIBERSAM, ISCIII; by the CERCA Programme/Generalitat de Catalunya AND Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017SGR1355). IV and NV were supported by the BITRECS project, which received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 754550 and from "La Caixa" Foundation (ID 100010434), under the agreement LCF/PR/GN18/50310006.

CONFLICT OF INTEREST STATEMENT

Norma Verdolini received financial support for CME activities and travel funds from Angelini, Janssen-Cilag, Lundbeck, Otsuka. Clemente Garcia-Rizo received honoraria/travel support from Abbott, Adamed, Angelini, Cassen-Recordati, Janssen-Cilag and Lundbeck. Inmaculada Baeza received honoraria and travel support from Angelini, Otsuka-Lundbeck and Janssen. Ana Gonzalez-Pinto received grants and served as consultant, advisor or CME speaker for Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Sanofi-Aventis, Angelini, Exeltis, Novartis, Takeda, Rovi. Antonio Lobo received financial support to attend scientific meetings from Janssen. Alexandra Roldan Bejarano served as advisor or speaker for Otsuka and Angelini. Miquel Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Rovi and Takeda. Eduard Vieta received grants and served as consultant, advisor or CME speaker for AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Galenica, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sage, Sanofi-Aventis, Servier, Shire, Sunovion and Takeda. CD-C received financial support to attend scientific meetings from Janssen, Ammirall, Lilly, Lundbeck, Rovi, Esteve, Novartis, Astrazeneca, Pfizer and Casen Recordati. MPG-P has been a consultant to and/or has received honoraria/grants from Alter, Angelini, Cassen-Recordati, Janssen-Cilag, Idorsia, Lundbeck, Otsuka, and SAGE Therapeutics. LGB received honoraria for lecturing and/or research

or travel grants for attending conferences from Otsuka, Lundbeck, Janssen-Cilag, Casen Recordati, Angelini and Pfizer. AI received research support from or served as speaker or advisor for Janssen-Cilag, Lundbeck and Otsuka. RR-J has been a consultant for and/or received lecturing honoraria from JanssenCilag, Lundbeck, Otsuka, Pfizer, Ferrer, Juste, Takeda, Exeltis, Casen-Recordati, Angelini, Rovi. All other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Isabel Valli  <https://orcid.org/0000-0003-3052-7383>

Alex Gonzalez Segura  <https://orcid.org/0000-0002-9398-2183>

Clemente Garcia-Rizo  <https://orcid.org/0000-0002-4855-1608>

Gisela Mezquida  <https://orcid.org/0000-0002-6080-2203>

Laura Pina-Camacho  <https://orcid.org/0000-0003-1960-6443>

Sergi Mas  <https://orcid.org/0000-0003-3336-6298>

Eduard Vieta  <https://orcid.org/0000-0002-0548-0053>

REFERENCES

1. Arango C, Dragioti E, Solmi M, et al. Risk and protective factors for mental disorders beyond genetics: an evidence-based atlas. *World Psychiatry*. 2021;20(3):417-436.
2. Murray RM, Bhavsar V, Tripoli G, Howes O. 30 years on: how the neurodevelopmental hypothesis of schizophrenia morphed into the developmental risk factor model of psychosis. *Schizophr Bull*. 2017;43(6):1190-1196.
3. Marin O. Developmental timing and critical windows for the treatment of psychiatric disorders. *Nat Med*. 2016;22(11):1229-1238.
4. Sague-Vilavella M, Amoretti S, Garriga M, et al. Shaped before birth: obstetric complications identify a more severe clinical phenotype among patients presenting a first affective or non-affective episode of psychosis. *J Psychiatr Res*. 2022;151:461-468.
5. Tosato S, Bonetto C, Vassos E, et al. Obstetric complications and polygenic risk score: which role in predicting a severe short-term outcome in psychosis? *Genes (Basel)*. 2021;12(12):1895.
6. Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. *Am J Psychiatry*. 2002;159(7):1080-1092.
7. Davies C, Segre G, Estrade A, et al. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. *Lancet Psychiatry*. 2020;7(5):399-410.
8. Done DJ, Johnstone EC, Frith CD, Golding J, Shepherd PM, Crow TJ. Complications of pregnancy and

- delivery in relation to psychosis in adult life: data from the British perinatal mortality survey sample. *BMJ*. 1991;302(6792):1576-1580.
9. Byrne M, Browne R, Mulryan N, et al. Labour and delivery complications and schizophrenia. Case-control study using contemporaneous labour ward records. *Br J Psychiatry*. 2000;176:531-536.
 10. Kendell RE, McInnery K, Juszczak E, Bain M. Obstetric complications and schizophrenia. Two case-control studies based on structured obstetric records. *Br J Psychiatry*. 2000;176:516-522.
 11. Jablensky AV, Morgan V, Zubrick SR, Bower C, Yellachich LA. Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. *Am J Psychiatry*. 2005;162(1):79-91.
 12. Nilsson E, Lichtenstein P, Cnattingius S, Murray RM, Hultman CM. Women with schizophrenia: pregnancy outcome and infant death among their offspring. *Schizophr Res*. 2002;58(2-3):221-229.
 13. Bennedsen BE, Mortensen PB, Olesen AV, Henriksen TB, Frydenberg M. Obstetric complications in women with schizophrenia. *Schizophr Res*. 2001;47(2-3):167-175.
 14. Cannon TD, Rosso IM, Hollister JM, Bearden CE, Sanchez LE, Hadley T. A prospective cohort study of genetic and perinatal influences in the etiology of schizophrenia. *Schizophr Bull*. 2000;26(2):351-366.
 15. Ursini G, Punzi G, Chen Q, et al. Convergence of placenta biology and genetic risk for schizophrenia. *Nat Med*. 2018;24(6):792-801.
 16. Vassos E, Kou J, Tosato S, et al. Lack of support for the genes by early environment interaction hypothesis in the pathogenesis of schizophrenia. *Schizophr Bull*. 2022;48(1):20-26.
 17. Ursini G, Weinberger DR. Replicating G x E: the devil and the details. *Schizophr Bull*. 2022;48(1):4.
 18. Vassos E, Murray RM. The jury is still out on placental genes and obstetric complications. *Schizophr Bull*. 2022;48(1):55.
 19. McNeil TF, Cantor-Graae E, Torrey EF, et al. Obstetric complications in histories of monozygotic twins discordant and concordant for schizophrenia. *Acta Psychiatr Scand*. 1994;89(3):196-204.
 20. Lewis SW, Owen MJ, Murray RM. Obstetric complications and schizophrenia: methodology and mechanisms. In: Schulz SC, Tamminga CA, eds. *Schizophrenia: A Scientific Focus*. Oxford University Press; 1989:56-68.
 21. Vassos E, Sham P, Kempton M, et al. The Maudsley environmental risk score for psychosis. *Psychol Med*. 2020;50(13):2213-2220.
 22. Bernardo M, Bioque M, Parellada M, et al. Assessing clinical and functional outcomes in a gene-environment interaction study in first episode of psychosis (PEPs). *Rev Psiquiatr Salud Ment*. 2013;6(1):4-16.
 23. Salagre E, Arango C, Artigas F, et al. CIBERSAM: ten years of collaborative translational research in mental disorders. *Rev Psiquiatr Salud Ment (Engl Ed)*. 2019;12(1):1-8.
 24. World MA. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.
 25. Cuesta MJ, Sanchez-Torres AM, Cabrera B, et al. Premorbid adjustment and clinical correlates of cognitive impairment in first-episode psychosis. The PEPsCog Study. *Schizophr Res*. 2015;164(1-3):65-73.
 26. First M, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)*. American Psychiatric Press; 1997.
 27. Mas S, Boloc D, Rodriguez N, et al. Examining gene-environment interactions using aggregate scores in a First-episode psychosis cohort. *Schizophr Bull*. 2020;46(4):1019-1025.
 28. Kokkevi A, Hartgers C. EuroPASI: European adaptation of a multidimensional assessment instrument for drug and alcohol dependence. *Eur Addict Res*. 1995;1:208-210.
 29. Davidson J, Smith R. Traumatic experiences in psychiatric outpatients. *J Trauma Stress*. 1990;3:459-475.
 30. Das S, Forer L, Schonherr S, et al. Next-generation genotype imputation service and methods. *Nat Genet*. 2016;48(10):1284-1287.
 31. Trubetskoy V, Pardinas AF, Qi T, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*. 2022;604(7906):502-508.
 32. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81(3):559-575.
 33. Choi SW, O'Reilly PF. PRSice-2: polygenic risk score software for biobank-scale data. *Gigascience*. 2019;8(7):giz082.
 34. Ripke S, Walters JT, O'Donovan MC. Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia. medRxiv 2020. doi:10.1101/2020.09.12.20192922
 35. Al-Haddad BJS, Oler E, Armistead B, et al. The fetal origins of mental illness. *Am J Obstet Gynecol*. 2019;221(6):549-562.
 36. Tyzio R, Cossart R, Khalilov I, et al. Maternal oxytocin triggers a transient inhibitory switch in GABA signaling in the fetal brain during delivery. *Science*. 2006;314(5806):1788-1792.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Valli I, Gonzalez Segura A, Verdolini N, et al. Obstetric complications and genetic risk for schizophrenia: Differential role of antenatal and perinatal events in first episode psychosis. *Acta Psychiatr Scand*. 2023;148(1):81-90. doi:10.1111/acps.13546