Obstetric complications and clinical presentation in first episode of psychosis

Norma Verdolini[1], Gisela Mezquida[2], Isabel Valli[3], Clemente Garcia-Rizo[2] , Manuel Cuesta[4], Eduard Vieta[1], Miquel Bioque[2], Antonio Lobo[5], Ana González-Pinto[6], Laura Pina-Camacho[7], Iluminada Corripio[8], Marina Garriga[1], Inmaculada Baeza[3], Laura Martínez-Sadurní[9], Byron Bitanihirwe[10], Mary Cannon[11], Miquel Bernardo[2] and PEPs GROUP[12],*

[1]Bipolar and Depressive Disorders Unit, Hospital Clinic de Barcelona, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain; [2]Barcelona Clínic Schizophrenia Unit, Hospital Clínic de Barcelona, Clinical Institute of Neuroscience, University of Barcelona, CIBERSAM, IDIBAPS, Barcelona, Spain; [3]Child and Adolescent Psychiatry and Psychology Department, Hospital Clinic of Barcelona, Institute of Neurosciences, CIBERSAM, IDIBAPS, University of Barcelona, Barcelona, Spain; [4]Department of Psychiatry, Navarre Hospital Complex, IdiSNA, Navarre Institute for Health Research, Pamplona, Spain; [5]Department of Medicine and Psychiatry, Universidad de Zaragoza; Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza; CIBERSAM, Madrid, Spain; [6]Hospital Universitario de Alava, Servicio de Psiquiatría, BIOARABA, CIBERSAM, University of the Basque Country, Spain; [7]Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, CIBERSAM, IiSGM, School of Medicine, Universidad Complutense, Madrid, Spain; [8]Department of Psychiatry, CIBERSAM, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [9]Hospital del Mar Medical Research Institute (IMIM), Autonomous University of Barcelona, CIBERSAM, Barcelona, Spain; [10]The University of Manchester Humanitarian and Conflict Response Institute, UK; [11]Department of Psychiatry, RCSI University of Medicine and Health Science, Dublin, Ireland and [12]Servicio de Psiquiatría, Hospital Universitario Doctor Peset, Universitat de València, CIBERSAM, Valencia, Spain

Abstract

Objective: Psychotic disorders exhibit a complex aetiology that combines genetic and environmental factors. Among the latter, obstetric complications (OCs) have been widely studied as risk factors, but it is not yet well understood how OCs relate to the heterogeneous presentations of psychotic disorders. We assessed the clinical phenotypes of individuals with a first episode of psychosis (FEP) in relation to the presence of OCs. *Methods:* Two-hundred seventy-seven patients with an FEP were assessed for OCs using the Lewis–Murray scale, with data stratified into three subscales depending on the timing and the characteristics of the obstetric event, namely: complications of pregnancy, abnormal foetal growth and development and difficulties in delivery. We also considered other two groups: any complications during the pregnancy period and all OCs taken altogether. Patients were clinically evaluated with the Positive and Negative Syndrome Scale for schizophrenia. *Results:* Total OCs and difficulties in delivery were related to more severe psychopathology, and this remained significant after co-varying for age, sex, traumatic experiences, antipsychotic dosage and cannabis use. *Conclusions:* Our results highlight the relevance of OCs for the clinical presentation of psychosis. Describing the timing of the OCs is essential in understanding the heterogeneity of the clinical presentation.

Significant outcomes

- OCs are associated with more severe psychopathology.
- Difficulties during delivery are specifically associated with worse psychopathology.
- OCs are heterogeneous, and timing description is essential.

Limitations

- The OCs included come from a clinical scale, so some others may be missing.
- OCs were not analysed individually but as groups according to specific characteristics.
- OCs were recorded through a familiar interview.

Introduction

First episode of psychosis (FEP) can be the initial event of a wide variety of diagnoses and eventually lead to schizophrenia, bipolar disorder, major depression disorder and other clinical entities (Salvatore *et al.*, 2009). Regardless of diagnostic heterogeneity, genetic and environmental factors interact with the risk pathway. Among the environmental factors, obstetric complications (OCs) or abnormalities during the prenatal and perinatal period have been historically described as major risk contributors (Cannon *et al.*, 2002; Davies *et al.*, 2020). However, current evidence suggests that OCs in psychosis are a risk factor not only for the later development of psychosis but also for other effects that range from neuroanatomical (Costas-Carrera *et al.*, 2020), neurocognitive (Amoretti *et al.*, 2022), metabolic abnormalities (Garcia-Rizo *et al.*, 2015) to clinical psychopathology (Mezquida *et al.*, 2021). Moreover, some specific clinical features, such as childhood attention deficit hyperactivity disorder symptoms in schizophrenia-spectrum disorders, seem to be associated with OCs (Peralta *et al.*, 2011), while higher ratings of parkinsonism, catatonia and dyskinesia have been associated with OCs in neuroleptic-naïve psychotic patients (Peralta *et al.*, 2006; Peralta & Cuesta, 2010). However, there remains much inconsistency between studies on how OCs are measured, as some authors include OCs as a discrete entity while others specify the timing and the nature of the obstetric event (Mezquida *et al.*, 2018).

The perinatal origins of psychosis model are receiving increasing attention (Garcia-Rizo & Bitanihirwe, 2020), particularly within the realm of metabolism (i.e. logic and theory). This field of enquiry in general medicine originated as the "Barker hypothesis", where the relationship between foetal growth and later type 2 diabetes mellitus (T2DM) (Hales & Barker, 1992) established a theoretical basis for the developmental origins of health and disease model (Gluckman & Hanson, 2006). This model suggests that "undesirable conditions" during the perinatal period can have long-lasting metabolic consequences. Indeed, recent research showed that birth weight (BW), an indirect measure of the intrauterine milieu, is related to weight gain (Garcia-Rizo *et al.*, 2020; Garriga *et al.*, 2019a) and glucose values in FEP (Garcia-Rizo *et al.*, 2022), with T2DM in schizophrenia (Fernandez-Egea *et al.*, 2020) and in affective disorders (Garriga *et al.*, 2019b).

However, the study of OCs and their relationship with clinical presentation in psychiatric patients has received less attention. OCs taken as a whole were associated with more prominent negative symptoms in patients with chronic schizophrenia and early onset in adolescence (Kotlicka-Antczak *et al.*, 2001). OCs were associated with negative symptoms in less affluent patients with schizophrenia (Jones *et al.*, 2011). Similar outcomes were observed in an African cohort, where OCs were associated with negative symptomatology (Mechri *et al.*, 2008). Interestingly negative symptoms were also associated with OCs in the adolescent with psychotic-like experiences (Cardno *et al.*, 2021), while also in adolescents, adverse events during early development (both prenatal and perinatal) lead to an increased risk of developing non-clinical psychosis-like symptoms (Zammit *et al.*, 2009).

When specifically evaluating the type of OCs, previously published work by Kotlicka-Antczak and colleagues has described more prominent negative symptomatology to be associated with abnormalities in delivery evaluated with the Apgar score (Kotlicka-Antczak *et al.*, 2001) while a recent cross-sectional study in patients with chronic schizophrenia with predominant negative symptomatology described an association between difficulties during delivery assessed with the Lewis–Murray scale and measures of anxiety, guilt feelings and unusual thought content (Mezquida *et al.*, 2021).

BW, an indirect marker of the prenatal environment, has been studied in a Finnish schizophrenia study sample, where both low and high BW were associated with more severe symptoms, especially in terms of "bizarre" behaviour, affective flattening and attentional impairment (Wegelius *et al.*, 2013). In addition, the same study found low BW to be associated with more severe formal thought disorder (Wegelius *et al.*, 2013). However, another study stratifying the study cohort into deficit and non-deficit schizophrenia did not find any association with low BW (Alabaf *et al.*, 2022). Maternal smoking, an indirect marker of an adverse intrauterine environment, has been correlated with lower BW (Abraham *et al.*, 2017) and also with more negative symptomatology (Stathopoulou *et al.*, 2013). Indeed, a later study found that maternal smoking was associated with more severe deficit symptoms (Bernardini *et al.*, 2015). Additionally, recent research evaluating the effect of maternal cortisol during pregnancy highlights the importance not only of timing but also of foetal sex (Ellman *et al.*, 2019). Indeed, in a large schizophrenia hospital cohort, OCs were associated with negative symptomatology only in females (Gallagher *et al.*, 2014).

Nevertheless, negative findings have also been described. No association was described between OCs and clinical psychopathology neither in a Nigerian cohort of patients diagnosed with schizophrenia (Onu & Ohaeri, 2020) nor in a cohort of severely ill schizophrenia patients (Smith *et al.*, 1995).

OCs have been related to clinical symptomatology not only in schizophrenia but also in affective disorders (Serati *et al.*, 2020; Solé *et al.*, 2020; Sagué-Vilavella *et al.*, 2022). In a longitudinal study, hypomania with previous psychotic experiences was initially associated with gestational influenza; however, later analysis did not confirm the association (Anderson *et al.*, 2016). Nevertheless, in the general population, a study evaluating a wide range of psychopathology measures in offspring suggested that the association between prenatal and postnatal factors and psychopathology of offspring during adulthood was mediated by familial factors (Essau *et al.*, 2018). Beyond this, recent research focussing on FEP highlights the effect of other environmental factors in later life related to psychopathological profile at onset of psychiatric illness, such as childhood adversity (Butjosa *et al.*, 2022) and cannabis use (González-Blanco *et al.*, 2021; Safont *et al.*, 2022).

Built on the rationale described above, in this paper, we aimed to evaluate the clinical presentation and characteristics of a cohort of FEP according to their profile of OCs.

Material and methods

Study setting

This study is part of the multicentre Project 'Phenotype–genotype interaction: application of a predictive model in first psychotic episodes', the PEPs study, which is a longitudinal cohort study examining gene–environment (G×E) interactions on the pathway to psychosis. A complete description of the PEPs protocol has been published previously (Bernardo *et al.*, 2019, 2013).

The PEPs Project incorporates clinical parameters from various assessments/visits: baseline, 2-month, 6-month, 1-year and 2-year follow-up. For the present study, we have focussed on baseline visits.

Subjects

Three-hundred thirty-five FEP patients were included in the PEPs Project, running between 2009 and 2011 at 16 Spanish hospitals that participated in the Biomedical Research Networking Center for Mental Health (CIBERSAM) (Salagre *et al.*, 2019), which is following up a cohort of patients with FEP (Fraguas & Díaz-Caneja, 2021). From those 335 patients recruited initially, due to missing data required for the analyses, only 277 were included in the study.

Patients were included if they met the following inclusion criteria: aged between 7 and 35 years old at recruitment; presence of psychotic symptoms of less than 12-month duration; the ability to speak Spanish correctly and providing written informed consent. The exclusion criteria were an Intelligent Quotient (IQ) lower than 70 and with significant difficulties or malfunctioning with adaptive processes, history of head trauma with loss of consciousness and the presence of an organic disease. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Ethics committees of all participating centres approved the current study. As inclusion criteria, informed consent was obtained from all participants or from parents or legal guardians of under-age subjects.

Antipsychotic treatment

As most of the participating centers were tertiary university hospitals, a large majority of the patients included in the study were recruited during their first hospitalisation, when the first anti-psychotic treatment was initiated. In the whole sample recruited, the majority of the patients ($n = 304$, 90.7%) were taking antipsychotic treatment by the time they were included in the study, with a mean 54.08 days of treatment (Bioque *et al.*, 2016). Only a small proportion ($n = 49$, 14.6% of the sample) had been taking antipsychotic for more than 3 months before the inclusion. A previous report gave a full description of the psychopharmacological treatment used in this study (Bioque *et al.*, 2016). The prescribed daily dose (PDD) for a drug was defined as the daily dose of a drug formulation, oral or injectable, calculated separately for each treatment day of an individual patient who was treated with this drug formulation for at least three consecutive days (irrespective of the dose). To compare the different antipsychotics, the PDDs doses of antipsychotics were converted to an estimated daily equivalent doses of chlorpromazine (CPZ) following the international consensus (Gardner *et al.*, 2010).

Clinical assessments

At baseline, a complete psychiatric personal and family history was performed in a systematic interview, including OCs registration, substance use and traumatic experiences.

Clinical symptomatology was assessed using the Spanish-validated version of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Peralta & Cuesta, 1994), a semi-structured interview with 30 items rated on a seven-point scale.

Drug use was evaluated by a part of the European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence (EuropAsi) (Kokkevi & Hartgers, 1995). In the inclusion visit, a systematic register of drug misuse habits was performed. For the present study, we focussed on cannabis consumption, and we registered its use as dichotomous exposure or no exposure. The number of traumatic experiences was collected from the list of events that appear in the Traumatic Experiences in Psychiatric Outpatients Questionary (TQ) (Davidson & Smith, 1990). This tool is an 18-item self-reported questionnaire that assesses the presence of stressful events across the lifespan. As Mas *et al.* (2020) highlighted, due to the high heterogeneity of traumatic experiences on the item list, we only recorded the total number of experiences. These data were encoded and registered as 'No exposure' (non-traumatic experiences during childhood) and 'Any exposure' (one or more traumatic experiences during childhood) (Vassos *et al.*, 2019; Mas *et al.*, 2020).

Obstetric complications

OCs were assessed using the Lewis–Murray scale through familiar interviews (Lewis *et al.*, 1989). This approach has proved accurate in previous samples (Borrajo *et al.*, 2011). The Lewis–Murray scale allows describing adverse events as absent, equivocal or definite. We only included definite scores as present ones. The scale also groups OCs into three categories, A, B and C (Cannon *et al.*, 2002; Mezquida *et al.*, 2018) according to the type of complication defined as follows:

A. Complications of pregnancy (syphilis or rubella, rhesus iso-immunisation/Rh incompatibility, severe preeclampsia, requiring hospitalisation or induction of labour and bleeding before delivery of threatened abortion);
B. Abnormal foetal growth and development (twin delivery, preterm birth week less than 37 weeks or long-term birth week of more than 42 weeks, weight at birth less than 2500 g and any important physical abnormality);
C. Difficulties in delivery (including premature rupture of membranes, duration of delivery more than 36 h or less than 3 h, umbilical cord prolapse, complicated caesarean delivery, abnormal foetal presentation, use of forceps and being in an incubator for more than 4 weeks).

Statistical analysis

Socio-demographic and other descriptive variables were assessed through univariate analyses. As for OCs, both the total numbers as well as their subtypes (A, B and C) were considered as dichotomic variables (yes/no). The Total-T group comprehended all the OCs. Particularly, as we were interested in evaluating the effect of OCs according to their timing of appearance, we created another group for analysis purposes, viz., any OC during gestation AB (from the combination of groups A and B).

To assess differences among patients with or without OCs in terms of psychopathology, independent *t*-test analyses of the PANSS and its subscales between the groups studied (OCs and their subtypes) were performed. Then, analyses of covariance (one-way ANCOVA) were performed to remove possible confounding factors in the association between OCs and psychopathology. In the model, PANSS subscales (positive, negative or general psychopathology) or total PANSS score were included as the dependent variable, OCs and their subtypes, age, sex, cannabis use (yes/no), childhood adversity (yes/no) and CPZ dosage were included as the independent variables.

The Statistical Package for Social Science (SPSS) version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. All statistical tests were two-tailed, and significance was determined at the 0.05 level.

Table 1. Clinical and socio-demographic characteristics of the sample

	First-Episode Psychosis ($n = 277$)
Age (years) mean ± SD	23.09 ± 5.9
Sex (female): n (%)	93 (33.6)
Childhood adversity yes/no (%)	138 (51.5)/130 (48.5)
Daily equivalent doses of chlorpromazine (mean ± SD)	564.29 ± 431.8
Cannabis Use yes/no (%)	125 (45.5%)/150 (54.5%)
PANSS positive subscale score (mean ± SD)	18.49 ± 7.9
PANSS negative subscale score (mean ± SD)	18.68 ± 8.3
PANSS general subscale score (mean ± SD)	37.71 ± 13.1
PANSS total score (mean ± SD)	74.89 ± 24.9
Lewis-Murray A: Complications of pregnancy yes (%)/ n	15 (5.5%)/ 272
Lewis-Murray B: Abnormal fetal growth and development yes(%)/n	24 (9.4%)/ 256
Lewis-Murray C: Difficulties in delivery yes (%)/n	40 (17.2%)/ 233
Lewis-Murray AB: Any obstetric complication during pregnancy yes (%)/n	35 (13.8%)/ 253
Lewis-Murray T: Total yes (%)/n	63 (27.3%)/ 231

PANSS, positive and negative syndrome scale SD, standard deviation.

Results

Clinical and socio-demographic characteristics of the sample are described in Table 1.

As outlined in the Methods section, the Lewis–Murray scale items are described as present only if the definite value was confirmed. The description represents the proportion of patients with abnormalities in each group out of the total evaluated. The reduction in the number of subjects is due to the consideration of missing data when at least one of the abnormalities accounting in a group was missing, and at the same time, none of them was present.

In Table 2, there is a description of the clinical differences measured by the PANSS subscales/total scale scores between groups in relation to the presence (yes) or absence (no) of the described events. Overall, patients who were exposed to stressful events during the perinatal period displayed a more severe psychopathological profile than patients who did not experience them (except for negative symptomatology in A-complications in pregnancy). Besides the significant outcomes in Table 2, subjects with difficulties during the whole pregnancy period (AB) presented with differences which showed a trend towards significance in positive subscale ($p = 0.064$) and total score ($p = 0.053$). For difficulties in delivery, the positive subscale also showed differences with a trend towards significance ($p = 0.083$). However, neither of them displayed a significant association when included in the regression analyses.

We then performed a regression analyses (one-way ANCOVA). Only models in which PANSS and its subscales were significantly different among OCs groups are reported.

For difficulties during the whole pregnancy period, when we considered the PANSS general subscale as the dependent variable, the following independent variables, that is, LewisAB ($F = 4.054$; $p = 0.045$) and daily equivalent doses of CPZ ($F = 7.362$; $p = 0.007$) were significantly associated, while age ($F = 0.702$; $p = 0.403$), sex ($F = 0.211$; $p = 0.646$), cannabis use ($F = 0.839$; $p = 0.361$) and childhood adversity ($F = 0.588$; $p = 0.444$) were not associated.

For difficulties during delivery, when we considered the PANSS general subscale as the dependent variable, the following independent variables, Lewis C ($F = 6.826$; $p = 0.010$) and daily equivalent doses of CPZ ($F = 7.885$; $p = 0.005$) were significantly associated, while age ($F = 0.791$; $p = 0.375$), sex ($F = 0.565$; $p = 0.453$), cannabis use ($F = 1.306$; $p = 0.255$) and childhood adversity ($F = 0.415$; $p = 0.520$) were not associated. When considering the PANSS total scale as the dependent variable, Lewis C ($F = 4.795$; $p = 0.030$) and daily equivalent doses of CPZ ($F = 10.119$; $p = 0.002$), were significantly associated, while age ($F = 0.968$; $p = 0.326$), sex ($F = 0.080$; $p = 0.778$) cannabis use ($F = 0.997$; $p = 0.319$) and childhood adversity ($F = 0.878$; $p = 0.350$) were not.

For OCs taken all together, when considering the PANSS positive subscale as the dependent variable, LewisT ($F = 6.950$; $p = 0.009$) was significantly associated, while daily equivalent doses of CPZ ($F = 3.384$; $p = 0.067$), age ($F = 0.466$; $p = 0.496$), sex ($F = 2.027$; $p = 0.156$), cannabis use ($F = 3.113$; $p = 0.079$) and childhood adversity ($F = 0.050$; $p = 0.824$) were not associated. When considering the PANSS general subscale as the dependent variable, the following independent variables, Lewis T ($F = 7.755$; $p = 0.006$) and daily equivalent doses of CPZ ($F = 6.818$; $p = 0.010$) were significantly associated, while age ($F = 1.185$; $p = 0.278$), sex ($F = 0.947$; $p = 0.332$), cannabis use ($F = 0.1.065$; $p = 0.303$) and childhood adversity ($F = 0.754$; $p = 0.386$) were not associated. Finally, when considering the PANSS total scale as the dependent variable, the independent variables Lewis T (F = 6.608 $p = 0.011$) and daily equivalent doses of CPZ ($F = 9.053$; $p = 0.003$) were significantly associated, while age ($F = 1.434$; $p = 0.232$), sex ($F = 0.193$; $p = 0.661$), cannabis Use ($F = 0.682$; $p = 0.410$) and childhood adversity ($F = 1.375$; $p = 0.242$) were not associated.

Discussion

The findings from our study show a worse psychopathological profile among people with FEP that experienced difficulties during the perinatal period compared with patients who were not exposed to them. These results confirm the association between OCs and the presentation of clinical symptomatology in a cohort of FEP. Notably, our results were not confounded by other known risk factors such as age, sex, cannabis use or stressful childhood events.

Compared with patients who were not exposed to perinatal stress, patients that experienced difficulties during delivery displayed a more severe psychopathological profile in relation to total PANSS score but also for the three subscales, positive, negative and general psychopathology. All were statistically significant except for the positive symptom subscale, which only showed a trend towards significance. However, when co-varied by all the potential confounders, only PANSS general psychopathology and total score maintained significant associations. Similar findings were observed when all the OC variables were considered. In this case, patients who presented OCs displayed a statistically significant difference in clinical profile. However, when the covariates were included in the analysis, the PANSS negative subscale did not retain its significant association, while the rest did (positive, general subscale,

Table 2. Comparisons between groups depending on the presence (yes) or absence (no) of obstetric complications

PANSS	Positive Subscale		Negative Subscale		General Subscale		Total scale	
	No mean (SD)	Yes mean (SD)	No mean (SD)	Yes mean (SD)	No mean (SD)	Yes mean (SD)	No mean (SD)	Yes mean (SD)
Lewis A	18.44 (8.0)	21.27 (6.9)	18.84 (8.4)	16.53 (7.4)	37.72 (13.2)	39.20 (12.4)	74.99 (25.3)	77.00 (20.0)
Lewis B	18.77 (7.9)	20.04 (9.4)	18.47 (8.0)	21.25 (10.9)	37.69 (12.6)	44.42 (17.1)	74.92 (24.1)	85.71 (32.6)
Lewis C	17.81 (7.9)^	20.23 (8.2)	18.25 (8.2)*	21.28 (9.0)	36.65 (12.5) *	43.68 (15.4)	72.72 (24.2)*	85.18 (28.4)
Lewis AB	18.58 (7.9)^	21.29 (8.4)	18.66 (8.1)	19.60 (9.9)	37.67 (12.7)*	42.86 (15.5)	74.90 (24.5) ^	83.74 (28.0)
Lewis T	17.59 (7.7)*	21.03 (8.2)	18.31 (8.0)*	20.25 (9.5)	36.50 (12.1)*	42.59 (15.1)	72.40 (23.6)*	83.87 (27.8)

Lewis A, complications of pregnancy; Lewis AB, any obstetric complication during pregnancy; Lewis B, abnormal fetal growth and development; Lewis C, difficulties in delivery; Lewis T, total; PANSS, positive and negative syndrome scale; SD, standard deviation.
*$p < 0.05$, ^$p < 0.10$.

and total scale score). Patients with difficulties during the whole pregnancy period also displayed a worse clinical profile, which proved significant in the general psychopathology subscale and maintained its association when covariates were included in the statistical model. Thus, in our sample, perinatal risk factors are associated with the general psychopathology subscale and the total PANSS score.

Our results are in line with previous findings; in chronic schizophrenia patients, difficulties in delivery have been associated with more severe symptomatology from the general psychopathological subscale from the PANSS (Mezquida et al., 2021), while the lower Apgar score, which is a simple and objective method evaluating the degree of birth asphyxia, was associated with negative symptoms in early-onset schizophrenia (Kotlicka-Antczak et al., 2001). Although other similar results were described, they considered OCs as a unique construct and did not differentiate between pregnancy and delivery periods (Kotlicka-Antczak et al., 2001; Borkowska & Rybakowski, 2002; Jones et al., 2011). Although Mechri and associates (Mechri et al., 2008) reported that higher sub-scores were observed during the period of childbirth, no further specification was obtained in relation with psychopathology besides more severe negative symptomatology. In contrast to other studies, we did not find any difference in relation to sex (Gallagher et al., 2014). As expected, the antipsychotic dose evaluated in CPZ equivalents was also associated with the clinical psychopathology. Indeed, one study suggested that the use of risperidone resulted in better compensation of psychopathological deficits (negative symptoms) in patients who had OCs (Borkowska & Rybakowski, 2002).

Our results rely mostly on an increased effect of OCs in the general psychopathology score and not in relation to negative symptomatology, as emphasised in previous studies. An important issue that needs to be taken into account, particularly in this study, is the 'type of psychotic patient' included, because only one previous study described symptomatology in non-affective FEP (Bernardini et al., 2015). Notably, around 17% of individuals with first-episode non-affective psychosis 'shift' to affective psychosis over time (Kim et al., 2011) and OCs have been related to clinical presentation in affective disorders (Mackay et al., 2017). The general psychopathology score captures a wide array of symptoms of psychopathology, which could be referred to as transdiagnostic and OCs have been associated with a wide psychopathological presentation in childhood and adolescence (Roffman et al., 2021). As previously described in metabolism (Garcia-Rizo et al., 2016), our results do not suggest a specific association between perinatal events and psychosis but with serious mental disorders.

Difficulties during delivery are often related to birth asphyxia, a condition with potentially fatal consequences (Graham et al., 2008). In psychosis, birth asphyxia has been described as a risk factor for developing psychosis (Radua et al., 2018; Pugliese et al., 2019; Davies et al., 2020) with long-term implications. Recent studies have shown its effect in neuroanatomy in schizophrenia (Wortinger et al., 2020) and also in bipolar disorder (Haukvik et al., 2014). Indeed research in animal models has studied the interaction between perinatal asphyxia and schizophrenia risk genes (Wakuda et al., 2015; Paparelli et al., 2017). In the general population, birth asphyxia has been associated with unspecific psychopathology such as hyperexcitability, irritability, timidity, aggressiveness, reduced activity, concentration and motivation (Nabieva, 2009). Furthermore, birth asphyxia is a risk factor widely described not only for schizophrenia (Dalman et al., 2001; Pugliese et al., 2019) but also for other pathologies such as personality disorder (Fazel et al., 2012) and pervasive developmental disorders (Van Handel et al., 2007).

Several limitations need to be highlighted when considering our findings. OCs were not recorded at birth but retrospectively in a familiar interview, which has been accepted as valid in a psychosis sample (Borrajo et al., 2011). OCs were categorised from a clinical scale and further information regarding the timing and duration of the insult is required (Ellman et al., 2019). The heterogeneity of methods evaluating OCs should be considered. While our approach is based on the Lewis–Murray scale, other authors evaluated OCs with the McNeil–Sjostrom questionnaire (Mechri et al., 2008) while others directly obtained OCs from the "social history" section of the hospital records (Jones et al., 2011).

When considering all the results, we note that difficulties during delivery are more related to psychopathology than difficulties during the pregnancy period, suggesting an important effect of labour complications on patient outcomes later in life. Our results have interesting implications in terms of early intervention services/strategies in psychosis, as patients at initial stages with a background of OCs and unspecified symptomatology shall be closely monitored due to the heterogeneity of the clinical presentation of psychosis.

Conclusions

Our results confirm that the presence of difficulties during the perinatal period is associated with a more severe clinical presentation at onset and in the first stages of the illness. Our approach to differentiating the events according to the timing of the event distinguished the effect of difficulties during pregnancy and during

delivery into different clinical areas. Our results highlight the need of describing the timing of the event during the perinatal period to better understand its impact on the clinical presentation at onset. This might help to have a greater understanding of its impact on the clinical and functional outcome, giving way to the design and the implementation of early and personalised interventions with the potential to modulate the outcome of schizophrenia following a first episode of the disease.

References

Abraham M, Alramadhan S, Iniguez C, Duijts L, Jaddoe VWV, Dekker HT, Den Crozier S, Godfrey KM, Hindmarsh P, Vik T, Jacobsen GW, Hanke W, Sobala W, Devereux G and Turner S (2017) A systematic review of maternal smoking during pregnancy and fetal measurements with meta-analysis. *PLoS One* **12**, e0170946. https://doi.org/10.1371/JOURNAL.PONE.0170946

Alabaf S, Kirkpatrick B, Chen S, Cardinal RN and Fernandez-Egea E (2022) Early versus late risk factors for deficit and nondeficit schizophrenia. *Revista de Psiquiatría y Salud Mental* **15**, 38–46. https://doi.org/10.1016/j.rpsm.2021.03.002

Amoretti S, Rabelo-da-Ponte FD, Garriga M, Forte MF, Penadés R, Vieta E, Parellada E, Ramos-Quiroga JA, Gama CS, Verdolini N, Bitanihirwe B and Garcia-Rizo C (2022) Obstetric complications and cognition in schizophrenia: a systematic review and meta-analysis. *Psychological Medicine*, 1–11. https://doi.org/10.1017/s0033291722002409

Anderson JJ, Hoath S, Zammit S, Meyer TD, Pell JP, Mackay D and Smith DJ (2016) Gestational influenza and risk of hypomania in young adulthood: prospective birth cohort study. *Journal of Affective Disorders* **200**, 182–188. https://doi.org/10.1016/j.jad.2016.04.048

Bernardini F, Wan CR, Crisafio A, Massey SH and Compton MT (2015) Prenatal exposure to maternal smoking and symptom severity among offspring with first-episode nonaffective psychosis. *Schizophrenia Research* **164**, 277–278. https://doi.org/10.1016/J.SCHRES.2015.02.012

Bernardo M, Bioque M, Parellada M, Ruiz JS, Cuesta MJ, Llerena A, Sanjuán J, Castro-Fornieles J, Arango C and Cabrera B (2013) Assessing clinical and functional outcomes in a gene–environment interaction study in first episode of psychosis (PEPs). *Revista de Psiquiatría y Salud Mental (English Edition)* **6**, 4–16. https://doi.org/10.1016/j.rpsmen.2012.11.001

Bernardo M, Cabrera B, Arango C, Bioque M, Castro-Fornieles J, Cuesta MJ, Lafuente A, Parellada M, Saiz-Ruiz J and Vieta E (2019) One decade of the first episodes project (PEPs): advancing towards a precision psychiatry. *Revista de Psiquiatría y Salud Mental (English Edition)* **12**, 135–140. https://doi.org/10.1016/j.rpsm.2019.03.001

Bioque M, Llerena A, Cabrera B, Mezquida G, Lobo A, González-Pinto A, Díaz-Caneja CM, Corripio I, Aguilar EJ, Bulbena A, Castro-Fornieles J, Vieta E, Lafuente A, Mas S, Parellada M, Saiz-Ruiz J, Cuesta MJ, Bernardo M, Gassó P, Amoretti S, García Bernardo E, Tapia-Casellas C, Alonso-Solís A, Grasa E, Hernández M, González I, Ruiz P, Modrego F, Escartí MJ, Mané A, Torrent C, Baeza I, Contreras F, Albacete A, Bobes J, García-Portilla MP, Zabala Rabadán A, Segarra Echevarría R, Rodriguez-Jimenez R, Morales-Muñoz I, Butjosa A, Landin-Romero R, Sarró S, Ibáñez Á, Sánchez-Torres AM and Balanzá-Martínez V (2016) A pharmacovigilance study in first episode of psychosis: psychopharmacological interventions and safety profiles in the PEPs project. *International Journal of Neuropsychopharmacology* **19**. https://doi.org/10.1093/ijnp/pyv121

Borkowska A and Rybakowski JK (2002) Does risperidone act better in schizophrenic patients who have a family or obstetric history? *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **26**, 1349–1353.

Borrajo RH, Zandio M, Zarzuela A, Serrano JF, Rosa A, Fañanás L, Peralta V and Cuesta MJ (2011) Hidalgo Borrajo R., *et al.*, Validity of maternal recall of obstetric complications in mothers of patients with schizophrenia spectrum disorders and their healthy siblings. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2010.09.017

Butjosa A, Usall J, Vila-Badia R, Mezquida G, Cuesta MJ, Rodríguez-Toscano E, Amoretti S, Lobo A, González-Pinto A, Espliego A, Corripio I, Vieta E, Baeza I, Bergé D, Bernardo M, Bioque M, García-Rizo C, Mayoral M, Merchan J, Alonso-Solís A, Rabella M, López P, Zorrilla I, De-la-Cámara C, Barcones F, Sanjuan J, Dolores Moltó M, Morro L, Monserrat C, Verdolini N, Salagre E, de la Serna E, Castro-Fornieles J, Contreras Fernández F, Saiz Masvidal C,

Paz Garcia-Portilla M, Bousoño M, Gutiérrez Fraile M, Zabala Rabadán A, Dompablo M, Rodriguez-Jimenez R, Rubio-Abadal E, Pardo M, Sarró S, Pomarol-Clotet E, Ibanez A, Sánchez-Torres AM and Selva-Vera G (2022) Impact of traumatic life events on clinical variables of individuals with first-episode psychosis and healthy controls. International *Journal of Social Psychiatry.* https://doi.org/10.1177/00207640211070398

Cannon M, Jones PB and Murray RM (2002) Obstetric complications and schizophrenia: historical and meta-analytic review. *American Journal of Psychiatry* 159, 1080–1092. https://doi.org/10.1176/APPI.AJP.159.7.1080

Cardno AG, Selzam S, Freeman D and Ronald A (2021) Psychotic-like experiences in adolescence occurring in combination or isolation: associations with Schizophrenia risk factors. *Psychiatric Research and Clinical Practice* 3, 67–75. https://doi.org/10.1176/APPI.PRCP.20200010

Costas-Carrera A, Garcia-Rizo C, Bitanihirwe B and Penadés R (2020) Obstetric complications and brain imaging in Schizophrenia: a systematic review. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.* https://doi.org/10.1016/j.bpsc.2020.07.018

Dalman C, Thomas HV, David AS, Gentz J, Lewis G and Allebeck P (2001) Signs of asphyxia at birth and risk of schizophrenia: population-based case-control study. *British Journal of Psychiatry* 179, 403–408. https://doi.org/10.1192/bjp.179.5.403

Davidson J and Smith R (1990) Traumatic experiences in psychiatric outpatients. *Journal of Traumatic Stress* 33(3), 459–475. https://doi.org/10.1007/BF00974785

Davies C, Segre G, Estradé A, Radua J, De Micheli A, Provenzani U, Oliver D, Salazar de Pablo G, Ramella-Cravaro V, Besozzi M, Dazzan P, Miele M, Caputo G, Spallarossa C, Crossland G, Ilyas A, Spada G, Politi P, Murray RM, McGuire P and Fusar-Poli P (2020) Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. *The Lancet Psychiatry* 7, 399–410. https://doi.org/10.1016/S2215-0366(20)30057-2

Ellman LM, Murphy SK, Maxwell SD, Calvo EM, Cooper T, Schaefer CA, Bresnahan MA, Susser ES and Brown AS (2019) Maternal cortisol during pregnancy and offspring schizophrenia: influence of fetal sex and timing of exposure. *Schizophrenia Research.* https://doi.org/10.1016/j.schres.2019.07.002

Essau CA, Sasagawa S, Lewinsohn PM and Rohde P (2018) The impact of pre- and perinatal factors on psychopathology in adulthood. *Journal of Affective Disorders* 236, 52–59. https://doi.org/10.1016/j.jad.2018.04.088

Fazel S, Bakiyeva L, Cnattingius S, Grann M, Hultman CM, Lichtenstein P and Geddes JR (2012) Perinatal risk factors in offenders with severe personality disorder: a population-based investigation. *Journal of Personality Disorders* 26, 737–750. https://doi.org/10.1521/pedi.2012.26.5.737

Fernandez-Egea E, Walker R, Ziauddeen H, Cardinal RN and Bullmore ET (2020) Birth weight, family history of diabetes and diabetes onset in schizophrenia. *BMJ Open Diabetes Research & Care* 8. https://doi.org/10.1136/bmjdrc-2019-001036

Fraguas D and Díaz-Caneja CM (2021) First episode psychosis longitudinal cohort studies: the CIBERSAM FEP cohort. *European Neuropsychopharmacology* 51, 132–133. https://doi.org/10.1016/J.EURONEURO.2021.06.011

Gallagher BJ, Jones BJ and Eaton KE (2014) A sex-specified effect of obstetrical complications in symptoms of schizophrenia. *Clinical Schizophrenia & Related Psychoses* 8, 143–148A. https://doi.org/10.3371/CSRP.GAJO.030113

Garcia-Rizo C, Bioque M, Mezquida G, Amoretti S, Cuesta MJ, Díaz-Caneja CM, Mas S, Lobo A, González-Pinto A, Fraguas D, Corripio I, Vieta E, Baeza I, Bergé D, Fernandez-Egea E, Garriga M, Bernardo M, Parellada E, Meseguer A, Moreno C, Pina-Camacho L, Alonso-Solís A, Rabella M, Zorrilla I, López P, Barcones MF, De-la-Cámara C, Sanjuan J, Cañete C, Mané A, Morro L, Salagre E, Hidalgo-Matezzi D, Castro-Fornielles J, de la Serna E, Contreras F, Saiz-Masvidal C, Bobes J, García-Portilla MP, Gutiérrez-Fraile M, Segarra R, Fares-Otero NE, Rodriguez-Jimenez R, Butjosa A, Usall J, Sarró S, Pomarol-Clotet E, Ibañez Á, Sánchez-Torres AM and Selva-Vera G (2020) Birth weight and antipsychotic induced weight gain: a prenatal programming approach in the PEPs study. *Schizophrenia Research* 218, 292–294. https://doi.org/10.1016/j.schres.2019.12.030

Garcia-Rizo C and Bitanihirwe BKY (2020) Implications of early life stress on fetal metabolic programming of schizophrenia: a focus on epiphenomena underlying morbidity and early mortality. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* https://doi.org/10.1016/j.pnpbp.2020.109910

Garcia-Rizo C, Cabrera B, Bioque M, Mezquida G, Lobo A, Gonzalez-Pinto A, Diaz-Caneja CM, Corripio I, Vieta E, Baeza I, Garcia-Portilla MP, Gutierrez-Fraile M, Rodriguez-Jimenez R, Garriga M, Fernandez-Egea E, Bernardo M and GROUP, Pep. (2022) The effect of early life events on glucose levels in first-episode psychosis. *Frontiers in Endocrinology (Lausanne)* 13, 2696. https://doi.org/10.3389/FENDO.2022.983792

Garcia-Rizo C, Fernandez-Egea E, Bernardo M and Kirkpatrick B (2015) The thrifty psychiatric phenotype. *Acta psychiatrica Scandinavica* 131, 18–20. https://doi.org/10.1111/acps.12309

Garcia-Rizo C, Kirkpatrick B, Fernandez-Egea E, Oliveira C and Bernardo M (2016) Abnormal glycemic homeostasis at the onset of serious mental illnesses: a common pathway. *Psychoneuroendocrinology* 67. https://doi.org/10.1016/j.psyneuen.2016.02.001

Gardner DM, Murphy AL, O'Donnell H, Centorrino F and Baldessarini RJ (2010) International consensus study of antipsychotic dosing. *American Journal of Psychiatry* 167. https://doi.org/10.1176/appi.ajp.2009.09060802

Garriga M, Fernandez-Egea E, Mallorqui A, Serrano L, Oliveira C, Parellada E, Kirkpatrick B, Vieta E, Bernardo M and Garcia-Rizo C (2019a) Antipsychotic-induced weight gain and birth weight in psychosis: a fetal programming model. *Journal of Psychiatric Research* 115, 29–35. https://doi.org/10.1016/j.jpsychires.2019.05.004

Garriga M, Wium-Andersen MK, Wium-Andersen IK, Nordentoft M and Osler M (2019b) Birth dimensions, severe mental illness and risk of type 2 diabetes in a cohort of Danish men born in 1953. *European Psychiatry* 62, 1–9. https://doi.org/10.1016/j.eurpsy.2019.08.015

Gluckman P and Hanson M (2006) Developmental Origins of Health and Disease, Developmental Origins of Health and Disease. New York: Cambridge University Press. https://doi.org/10.1017/CBO9780511544699

González-Blanco L, García-Portilla MP, Gutiérrez M, Mezquida G, Cuesta MJ, Urbiola E, Amoretti S, Barcones F, González-Pinto A, Pina-Camacho L, Corripio I, Vieta E, Baeza I, Toll A, Sáiz PA, Bobes J, Bernardo M, Bioque M, Sagué M, Alonso-Solís A, Grasa E, González-Ortega I, Zorrilla I, Santabárbara J, De-la-Cámara C, Aguilar EJ, Nacher J, Bergé D, Mané A, Montejo L, Anmella G, Castro-Fornieles J, de la Serna E, Contreras F, Sáiz-Masvidal C, García-Álvarez L, Bobes-Bascarán T, Zabala-Rabadán A, Segarra-Echevarría R, Sanchez-Pastor L, Rodriguez-Jimenez R, Usall J, Butjosa A, Sarró S, Guerrero-Pedraza A, Ibañez Á, Ribeiro M and Balanzá-Martínez V (2021) Impact of previous tobacco use with or without cannabis on first psychotic experiences in patients with first-episode psychosis. *Schizophrenia Research* 236, 19–28. https://doi.org/10.1016/j.schres.2021.07.017

Graham EM, Ruis KA, Hartman AL, Northington FJ and Fox HE (2008) A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. *American Journal of Obstetrics and Gynecology* 199, 587–595. https://doi.org/10.1016/j.ajog.2008.06.094

Hales CN and Barker DJP (1992) Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia.* https://doi.org/10.1007/BF00400248

Haukvik UK, McNeil T, Lange EH, Melle I, Dale AM, Andreassen OA and Agartz I (2014) Pre- and perinatal hypoxia associated with hippocampus/amygdala volume in bipolar disorder. *Psychological Medicine* 44, 975–985. https://doi.org/10.1017/S0033291713001529

Jones BJ, Gallagher BJ, Moss DM and McFalls JA (2011) Obstetrical complications, social class and type of schizophrenia. *Clinical Schizophrenia & Related Psychoses* 5, 33–39. https://doi.org/10.3371/CSRP.5.1.5

Kim JS, Baek JH, Choi JS, Lee D, Kwon JS and Hong KS (2011) Diagnostic stability of first-episode psychosis and predictors of diagnostic shift from non-affective psychosis to bipolar disorder: a retrospective evaluation after recurrence. *Psychiatry Research* 188, 29–33. https://doi.org/10.1016/J.PSYCHRES.2010.09.017

Kokkevi A and Hartgers C (1995) EuropASI: European adaptation of a multi-dimensional assessment instrument for drug and alcohol dependence. *European Addiction Research* 1, 208–210. https://doi.org/10.1159/000259089

Kotlicka-Antczak M, Gmitrowicz A, Sobów TM, Rabe-Jabłonska J and Rabe-Jabłońska J (2001) Obstetric complications and Apgar score in early-onset schizophrenic patients with prominent positive and prominent negative symptoms. *Journal of Psychiatric Research* **35**, 249–57. https://doi.org/10.1016/S0022-3956(01)00022-X

Lewis S, Owen M and Murray R (1989) Obstetric complications and schizophrenia: Methodology and mechanisms. In Schulz S and Tamminga C (eds), Schizophrenia: Scientific Progress. New York, NY: Oxford University Press, pp. 56–68.

Mackay DF, Anderson JJ, Pell JP, Zammit S and Smith DJ (2017) Exposure to tobacco smoke in utero or during early childhood and risk of hypomania: prospective birth cohort study. *European Psychiatry* **39**, 33–39. https://doi.org/10.1016/j.eurpsy.2016.06.001

Mas S, Boloc D, Rodríguez N, Mezquida G, Amoretti S, Cuesta MJ, González-Peñas J, García-Alcón A, Lobo A, González-Pinto A, Corripio I, Vieta E, Castro-Fornieles J, Mané A, Saiz-Ruiz J, Gassó P, Bioque M and Bernardo M (2020) Examining gene-environment interactions using aggregate scores in a first-episode psychosis cohort. *Schizophrenia Bulletin* **46**, 1019–1025. https://doi.org/10.1093/schbul/sbaa012

Mechri A, Mrad A, Mokni S, Gaddour N, Letaif M and Gaha L (2008) Complications obstétricales dans la schizophrénie : étude comparative en population tunisienne. *Annales Medico-Psychologiques (Paris)* **166**, 646–652. https://doi.org/10.1016/j.amp.2006.01.021

Mezquida G, Fernandez-Egea E, Treen D, Mane A, Berge D, Savulich G, Garcia-Alvarez L, Garcia-Portilla MP, Bobes J, Bernardo M, Garcia-Rizo C, Mané A, Bergé D, Savulich G, Garcia-Alvarez L, García-Portilla P, Bobes J, Bernardo M and Garcia-Rizo C (2018) Obstetric phenotypes in the heterogeneity of schizophrenia. *Journal of Nervous and Mental Disease* **206**, 882–886. https://doi.org/10.1097/NMD.0000000000000897

Mezquida G, Fernández-Egea E, Treen D, Mané A, Bergé D, Savulich G, García-Álvarez L, García-Portilla MP, Bobes J, Bernardo M and García-Rizo C (2021) Difficulties in delivery and depressive symptomatology in schizophrenia. *Revista de Psiquiatria y Salud Mental* **14**, 66–68. https://doi.org/10.1016/j.rpsm.2019.12.002

Nabieva TN (2009) Neurological consequences following perinatal asphyxia in preschool age children. *Uspekhi Fiziologicheskikh Nauk* **40**, 72–77.

Onu JU and Ohaeri JU (2020) Association of family history of schizophrenia and history of obstetric complications at birth: relationship with age at onset and psychopathology dimensions in a Nigerian cohort. *African Health Sciences* **20**, 697–708. https://doi.org/10.4314/ahs.v20i2.21

Paparelli A, Iwata K, Wakuda T, Iyegbe C, Murray RM and Takei N (2017) Perinatal asphyxia in rat alters expression of novel schizophrenia risk genes. *Frontiers in Molecular Neuroscience* **10**. https://doi.org/10.3389/fnmol.2017.00341

Peralta V and Cuesta MJ (1994) Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. *Psychiatry Research* **53**, 31–40. https://doi.org/10.1016/0165-1781(94)90093-0

Peralta V and Cuesta MJ (2010) Neuromotor abnormalities in neuroleptic-naive psychotic patients: antecedents, clinical correlates, and prediction of treatment response. *Comprehensive Psychiatry* **52**, 139–145. https://doi.org/10.1016/j.comppsych.2010.05.009

Peralta V, Cuesta MJ and Serrano JF (2006) Obstetric complications and neurological abnormalities in neuroleptic-naive psychotic patients. *European Archives of Psychiatry and Clinical Neuroscience* **256**, 407–413. https://doi.org/10.1007/s00406-006-0653-7

Peralta V, de Jalón EG Campos MS, Zandio M, Sanchez-Torres A and Cuesta MJ (2011) The meaning of childhood attention-deficit hyperactivity symptoms in patients with a first-episode of schizophrenia-spectrum psychosis. *Schizophrenia Research* **126**, 28–35. https://doi.org/10.1016/J.SCHRES.2010.09.010

Pugliese V, Bruni A, Carbone EA, Calabrò G, Cerminara G, Sampogna G, Luciano M, Steardo L, Fiorillo A, Garcia CS and De Fazio P (2019) Maternal stress, prenatal medical illnesses and obstetric complications: risk factors for schizophrenia spectrum disorder, bipolar disorder and major depressive disorder. *Psychiatry Research*. https://doi.org/10.1016/j.psychres.2018.11.023

Radua J, Ramella-Cravaro V, Ioannidis JPA, Reichenberg A, Phiphopthatsanee N, Amir T, Yenn Thoo H, Oliver D, Davies C, Morgan C, McGuire P, Murray RM and Fusar-Poli P (2018) What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry*. https://doi.org/10.1002/wps.20490

Roffman JL, Sipahi ED, Dowling KF, Hughes DE, Hopkinson CE, Lee H, Eryilmaz H, Cohen LS, Gilman J, Doyle AE and Dunn EC (2021) Association of adverse prenatal exposure burden with child psychopathology in the Adolescent Brain Cognitive Development (ABCD) study. *PLoS One* **16**, e0250235. https://doi.org/10.1371/journal.pone.0250235

Safont G, Garriga M, Amoretti S, Cuesta MJ, Parellada M, González-Pinto A, Bergé D, Rodriguez-Jimenez R, Bejarano AR, Sarró S, Ibáñez Á, Usall J, Gutiérrez M, Vieta E, Arranz B, Berrocoso E, Verdolini N and Bernardo M (2022) Sex and substance use in first episode psychosis: impact on clinical symptoms, psychosocial functioning and cognitive performance. *Revista de Psiquiatría y Salud Mental*. https://doi.org/10.1016/j.rpsm.2022.03.002

Sagué-Vilavella M, Amoretti S, Garriga M, Mezquida G, Williams E, Serra-Navarro M, Forte MF, Varo C, Montejo L, Palacios-Garran R, Madero S, Sparacino G, Anmella G, Fico G, Giménez-Palomo A, Pons-Cabrera MT, Salgado-Pineda P, Montoro Salvatierra I, Sánchez Gistau V, Pomarol-Clotet E, Ramos-Quiroga JA, Undurraga J, Reinares M, Martínez-Arán A, Pacchiarotti I, Valli I, Bernardo M, Garcia-Rizo C, Vieta E and Verdolini N (2022) Shaped before birth: obstetric complications identify a more severe clinical phenotype among patients presenting a first affective or non-affective episode of psychosis. *Journal of Psychiatric Research* **151**, 461–468. https://doi.org/10.1016/j.jpsychires.2022.05.005

Salagre E, Arango C, Artigas F, Ayuso-Mateos JL, Bernardo M, Castro-Fornieles J, Bobes J, Desco M, Fañanás L, González-Pinto A, Haro JM, Leza JC, Mckenna PJ, Meana JJ, Menchón JM, Micó JA, Palomo T, Pazos Á, Pérez V, Saiz-Ruiz J, Sanjuán J, Tabarés-Seisdedos R, Crespo-Facorro B, Casas M, Vilella E, Palao D, Olivares JM, Rodriguez-Jimenez R and Vieta E (2019) CIBERSAM: ten years of collaborative translational research in mental disorders. *Revista de Psiquiatria y Salud Mental* **12**, 1–8. https://doi.org/10.1016/j.rpsm.2018.10.001

Salvatore P, Baldessarini RJ, Tohen M, Khalsa H-MMK, Perez Sanchez-Toledo J, Zarate CA, Vieta E and Maggini C (2009) McLean-Harvard International First-Episode Project: two-year stability of DSM-IV diagnoses in 500 first-episode psychotic disorder patients. *Journal of Clinical Psychiatry* **70**, 458–466. https://doi.org/10.4088/JCP.08m04227

Serati M, Bertino V, Malerba MR, Mucci F, Barkin JL, Grassi S, Altamura AC and Buoli M (2020) Obstetric complications and subsequent risk of mood disorders for offspring in adulthood: a comprehensive overview. *Nordic Journal of Psychiatry*. https://doi.org/10.1080/08039488.2020.1751878

Smith GN, Honer WG, Kopala L, MacEwan GW, Altman S and Smith A (1995) Obstetric complications and severity of illness in schizophrenia. *Schizophrenia Research* **14**, 113–120. https://doi.org/10.1016/0920-9964(94)00017-3

Solé E, Roca A, Torres A, Hernández AS, Fernández N, Díaz CN, Vieta E and Garcia-Esteve L (2020) Obstetric complications in bipolar disorder: psychiatric factors and the risk of caesarean section. *European Neuropsychopharmacology* **32**, 47–55. https://doi.org/10.1016/J.EURONEURO.2019.12.115

Stathopoulou A, Beratis IN and Beratis S (2013) Prenatal tobacco smoke exposure, risk of schizophrenia, and severity of positive/negative symptoms. *Schizophrenia Research* **148**, 105–110. https://doi.org/10.1016/j.schres.2013.04.031

Van Handel M, Swaab H, De Vries LS and Jongmans MJ (2007) Long-term cognitive and behavioral consequences of neonatal encephalopathy following perinatal asphyxia: a review. *European Journal of Pediatrics*. https://doi.org/10.1007/s00431-007-0437-8

Vassos E, Sham P, Kempton M, Trotta A, Stilo SA, Gayer-Anderson C, Di Forti M, Lewis CM, Murray RM and Morgan C (2019) The Maudsley environmental risk score for psychosis. *Psychological Medicine*, 1–8. https://doi.org/10.1017/S0033291719002319

Wakuda T, Iwata K, Iwata Y, Anitha A, Takahashi T, Yamada K, Vasu MM, Matsuzaki H, Suzuki K and Mori N (2015) Perinatal asphyxia alters neuregulin-1 and COMT gene expression in the medial prefrontal cortex in rats.

Progress in Neuro-Psychopharmacology and Biological Psychiatry **56**, 149–154. https://doi.org/10.1016/j.pnpbp.2014.08.002

Wegelius A, Pankakoski M, Lehto U, Suokas J, Häkkinen L, Tuulio-Henriksson A, Lönnqvist J, Paunio T and Suvisaari J (2013) An association between both low and high birth weight and increased disorganized and negative symptom severity in schizophrenia and other psychoses. *Psychiatry Research* **205**, 18–24. https://doi.org/10.1016/j.psychres.2012.08.026

Wortinger LA, Engen K, Barth C, Andreassen OA, Nordbø Jørgensen K and Agartz I (2020) Asphyxia at birth affects brain structure in patients on the schizophrenia-bipolar disorder spectrum and healthy participants. *Psychological Medicine*. https://doi.org/10.1017/S0033291720002779

Zammit S, Odd D, Horwood J, Thompson A, Thomas K, Menezes P, Gunnell D, Hollis C, Wolke D, Lewis G and Harrison G (2009) Investigating whether adverse prenatal and perinatal events are associated with non-clinical psychotic symptoms at age 12 years in the ALSPAC birth cohort. *Psychological Medicine* **39**, 1457–1467. https://doi.org/10.1017/S0033291708005126

Appendix

*PEPs group: Silvia Amoretti [1,21], Florencia Forte [1,2], Jessica Merchán-Naranjo[7], Elena Urbiola[7], Anna Alonso-Solís[8], Eva Grasa[8], Iñaki Zorrilla[6], Edurne García Corres[6], Concepcion De la Camara[5], Pedro M Ruiz-Lazaro[5], Maria Jose Escarti[12], Olga Rivero[12], Amira Trabsa[9], Teresa Legido[9], Maria Serra[3], Maria Sague-Vilella[3], Elena de la Serna[3], J Castro-Fornielles[3], Fernando Contreras[13], Mª Paz García-Portilla[14], Pilar Saiz[14], Rafael Segarra [15], Arantzazu Zabala[15], Luis Sanchez-Pastor[16], Roberto Rodriguez-Jimenez[16], Judith Usall[17], Anna Butjosa[17], Salvador Sarró[18], Edith Pomarol-Clotet[18], Angela Ibañez[19], AM Sanchez-Torres[4], Vicent Balanzá-Martínez[20]

[1]Bipolar and Depressives Disorder Unit, Hospital Clinic de Barcelona, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain.

[2] Barcelona Clínic Schizophrenia Unit, Hospital Clínic de Barcelona, Clinical Institute of Neuroscience, University of Barcelona, CIBERSAM, IDIBAPS, Barcelona, Spain.

[3]Child and Adolescent Psychiatry and Psychology Department, Hospital Clinic of Barcelona, Institute of Neurosciences, CIBERSAM, IDIBAPS, University of Barcelona, Barcelona, Spain.

[4] Department of Psychiatry, Navarre Hospital Complex, IdiSNA, Navarre Institute for Health Research, Pamplona, Spain.

[5] Department of Medicine and Psychiatry, Universidad de Zaragoza; Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza; CIBERSAM, Madrid, Spain.

[6] Hospital Universitario de Alava, Servicio de Psiquiatría, BIOARABA, CIBERSAM,University of the Basque Country, Spain.

[7]Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, CIBERSAM, IiSGM, School of Medicine, Universidad Complutense, Madrid, Spain.

[8] Department of Psychiatry, CIBERSAM, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

[9] Hospital del Mar Medical Research Institute (IMIM), Autonomous University of Barcelona, CIBERSAM, Barcelona, Spain.

[10] The University of Manchester Humanitarian and Conflict Response Institute, UK.

[11] Department of Psychiatry, RCSI University of Medicine and Health Science, Dublin, Ireland.

[12] Servicio de Psiquiatría, Hospital Universitario Doctor Peset, Universitat de València, CIBERSAM, Valencia, Spain.

[13] Psychiatry Department, Bellvitge University Hospital-IDIBELL; University of Barcelona, Barcelona, CIBERSAM, Barcelona, Spain.

[14] Department of Psychiatry, School of Medicine, CIBERSAM, University of Oviedo, Spain.

[15] Department of Neurosciences, University of the Basque Country, UPV/EHU; Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM; Department of Psychiatry, Cruces University Hospital, BioCruces Health Research Institute, Spain.

[16] Instituto de Investigación Hospital 12 de Octubre (i + 12), Madrid, Spain; CIBERSAM, Spain.

[17] Parc Sanitari Sant Joan de Déu, Teaching, Research & Innovation Unit, Sant Boi de Llobregat, Barcelona; CIBERSAM, Sant Joan de Déu Research Foundation, Esplugues de Llobregat, Barcelona; Department of Personality, Evaluation and Psychological Treatment, Faculty of Psychology, University of Barcelona, Spain.

[18] FIDMAG Hermanas Hospitalarias Research Foundation. Network Centre for Biomedical Research in Mental Health (CIBERSAM), Spain.

[19] Servicio de Psiquiatría, Hospital Ramón y Cajal, Universidad de Alcalá, CIBERSAM, IRYCIS, Madrid, Spain.

[20] Clinic Hospital (INCLIVA), Valencia, Spain.

[21] Group of Psychiatry, Mental Health and Addictions, Psychiatric Genetics Unit, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain; Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Spain.

[22] Department of Basic Clinical Practice, Pharmacology Unit, University of Barcelona, Barcelona, Spain.