



Research paper

Seasonal longitudinal effects of winter birth on psychopathology, cognition, and functioning in schizophrenia-spectrum and affective disorders: Findings from the PsyCourse Study

Anaid Pérez-Ramos^{a,b,c,d,1}, Monika Budde^{e,1}, Kristina Adorjan^{e,f}, Silvia Amoretti^{b,g,*}, Ion-George Anghelescu^h, Volker Aroltⁱ, Bernhard T. Baune^{j,k,l}, Udo Dannlowski^{m,ap}, Detlef E. Dietrich^{n,o,p}, Andreas J. Fallgatter^{q,r}, Christian Figge^s, Marina Garriga^{b,c,t,u}, Clemente Garcia-Rizo^{a,b,c,u,**}, Nora Guasch-Capella^{a,b,v}, Maria Heilbronner^e, Fabian U. Lang^w, Georg Juckel^x, Mojtaba Oraki Kohshour^{e,y}, Carsten Konrad^z, Anabel Martinez-Aran^{b,c,t,u}, Gisela Mezquida^{a,b,c,v}, Alba Navarro-Flores^{e,aa}, Daniela Reich-Erkelenz^{e,ab}, Jens Reimer^{ac,ad}, Eva Z. Reininghaus^{ae}, Fanny Senner^{e,ab,af}, Max Schmauß^{ag}, Andrea Schmitt^{ab,ah,ai}, Eva C. Schulte^{e,ab,aj,ak,aq}, Carsten Spitzer^{al}, Eduard Vieta^{b,c,t,u}, Jens Wiltfang^{am,an,ao}, Peter Falkai^{e,ab,ai,aq}, Thomas G. Schulze^{e,aq,ar,as}, Sergi Papiol^{e,ai}, Carla Torrent^{b,c,t,u,2}, Urs Heilbronner^{e,2}

^a Barcelona Clínic Schizophrenia Unit (BCSU), Neuroscience Institute, Hospital Clínic de Barcelona, Spain

^b Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain

^c Fundació Clínic per la Recerca Biomèdica-Institut d'Investigacions Biomèdiques August Pi i Sunyer (FCRB-IDIBAPS), Barcelona, Spain

^d Neuropsychopharmacology and Psychobiology Research Group, Department of Neuroscience, University of Cadiz, Cadiz, Spain

^e Institute of Psychiatric Phenomics and Genomics (IPPG), LMU University Hospital, LMU Munich, Munich, Germany

^f University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland

^g Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain

^h Department of Psychiatry and Psychotherapy, Mental Health Institute Berlin, Berlin, Germany

ⁱ Institute for Translational Psychiatry, University of Münster, Münster, Germany

^j Department of Psychiatry and Psychotherapy, University of Münster, Münster, Germany

^k Department of Psychiatry, Melbourne Medical School, University of Melbourne, Parkville, Victoria, Australia

^l Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria, Australia

^m Institute for Translational Psychiatry, University of Münster, Münster, Germany

ⁿ AMEOS Clinical Center Hildesheim, Hildesheim, Germany

^o Center for Systems Neuroscience (ZSN), Hannover, Germany

^p Department of Psychiatry, Medical School of Hannover, Hannover, Germany

^q Department of Psychiatry and Psychotherapy, Tübingen Center for Mental Health (TüCMH), University of Tübingen, Tübingen, Germany

^r German Center for Mental Health (DZPG), Partner Site Tübingen, Tübingen, Germany

^s Karl-Jaspers Clinic, European Medical School Oldenburg-Groningen, Oldenburg, Germany

^t Bipolar and Depressive Disorders Unit, Department of Psychiatry and Psychology, Hospital Clinic of Barcelona, Barcelona, Spain

^u Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Institut de Neurociències (UBNeuro), Universitat de Barcelona (UB), Barcelona, Spain

^v Department of Clinical Foundations, Pharmacology Unit, University of Barcelona, Barcelona, Spain

^w Department of Psychiatry II, Ulm University, Bezirkskrankenhaus Günzburg, Günzburg, Germany

^x Department of Psychiatry, Ruhr University Bochum, LWL University Hospital, Bochum, Germany

^y Department of Immunology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

^z Department of Psychiatry and Psychotherapy, Agaplesion Diakonieklinikum, Rotenburg, Germany

^{aa} International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany

^{ab} Department of Psychiatry and Psychotherapy, LMU University Hospital, LMU Munich, Germany

^{ac} Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

^{ad} Center for Psychosocial Medicine, Academic Teaching Hospital Itzehoe, Itzehoe, Germany

* Correspondence to: S. Amoretti, Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), VHIR Edifici Central, Pg Vall d'Hebron, 129, Horta-Guinardó, 08035, Barcelona, Spain.

** Correspondence to: C. Garcia-Rizo, Barcelona Clínic Schizophrenia Unit (BCSU), Neuroscience Institute, Hospital Clínic de Barcelona, Faculty of Medicine, University of Barcelona, CSM Esquerra Eixample c/Rosello 140 Bajos, 08036, Barcelona, Spain.

E-mail addresses: silvia.amoretti@vhir.org (S. Amoretti), cgarcia3@clinic.cat (C. Garcia-Rizo).

<https://doi.org/10.1016/j.jad.2026.121848>

Received 21 January 2026; Received in revised form 11 April 2026; Accepted 22 April 2026

Available online 23 April 2026

0165-0327/© 2026 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

^{ae} Department of Psychiatry and Psychotherapeutic Medicine, Research Unit for Bipolar Affective Disorder, Medical University of Graz, Graz, Austria

^{af} Centres for Psychiatry Suedwuerttemberg, Ravensburg, Germany

^{ag} Clinic for Psychiatry, Psychotherapy and Psychosomatics, Augsburg University, Medical Faculty, Augsburg, Germany

^{ah} Laboratory of Neuroscience, Institute of Psychiatry, University of Sao Paulo, São Paulo, Brazil

^{ai} Max Planck Institute of Psychiatry, Munich, Germany

^{aj} Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Bonn, Bonn, Germany

^{ak} Institute of Human Genetics, Faculty of Medicine and University Hospital Bonn, Bonn, Germany

^{al} Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Rostock, Rostock, Germany

^{am} Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany

^{an} German Center for Neurodegenerative Diseases, University of Göttingen, Göttingen, Germany

^{ao} Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal

^{ap} German Center for Mental Health (DZPG), Partner Site Munich/Augsburg, Munich/Augsburg, Germany

^{aq} Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

^{ar} Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA

^{as} Department of Psychiatry, Medical School and University Medical Center OWL, Protestant Hospital of the Bethel Foundation, Bielefeld University, Bielefeld, Germany

ARTICLE INFO

Keywords:

Winter birth
Psychopathology
Functioning
Cognitive impairment
Epiphenomena
Affective disorders
Schizophrenia-spectrum disorders

ABSTRACT

Aims: Winter birth (WB) is a replicated risk factor for mental health conditions, potentially due to third-trimester Vitamin D deficiency and maternal viral infections. Beyond diagnosis, WB is associated with psychopathology, cognition, and functionality as epiphenomena. We analysed these outcomes in psychosis and affective disorders, considering illness duration and sex-specific effects.

Methods: We included 535 individuals with schizophrenia-spectrum and 667 with affective disorders from the PsyCourse Study, evaluated at four time points over 18 months. Participants were stratified by the birth season: winter vs. other seasons and by duration of illness (</≥5 years). Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) for psychosis, Inventory of Depressive Symptomatology (IDS-C30) and Young Mania Rating Scale (YMRS) for affective disorders, functionality with the Global Assessment of Functioning Scale (GAF), and cognitive performance with Trail Making Tests A (TMT-A) and B (TMT-B), Verbal Digit Span, and Digit Symbol Test (DST). Linear mixed models adjusted for covariates were applied.

Results: No interaction effects between WB and diagnostic group or time remained significant after correction for multiple comparisons. In sex-stratified models, a significant WB × time interaction emerged for DST in females, with WB participants showing improvements over time in schizophrenia-spectrum disorders, and a crossover pattern in affective disorders.

Conclusions: WB has no robust effect on long-term outcomes on schizophrenia-spectrum or affective disorders. Subtle, sex-dependent effects on cognition were observed in females, with divergent longitudinal patterns between diagnostic groups, suggesting a possible early-life influence that attenuates over the course of illness.

1. Introduction

Winter birth (WB) is a well-replicated risk factor for the development of psychosis in adulthood (Cory et al., 2023; Davies et al., 2020) both in the Northern (Davies et al., 2003) and Southern hemispheres (McGrath and Welham, 1999). Nevertheless, WB has also shown its effect as a risk factor for other mental diagnoses such as affective disorders (Torrey et al., 1997) or attention deficit hyperactivity disorder (ADHD) (Hsu et al., 2021), despite some negative findings (Saleh et al., 2021). Although the pathophysiological mechanisms remain unclear, two main hypotheses have been proposed to explain this association, both related to abnormalities during the last trimester of pregnancy, low vitamin D levels, and increased prevalence of maternal respiratory viral infections.

Vitamin D reduction during winter due to less sunlight is associated with abnormal brain development (Cui et al., 2021). In a broad sense, vitamin D deficiency during pregnancy has been related to cognitive development and ADHD and autism-related traits in the offspring (García-Serna and Morales, 2020). Interestingly, levels of 25(OH) vitamin D in early-mid gestation might have a stronger beneficial effect on the offspring's neurodevelopment than in late gestation (García-Serna and Morales, 2020). Prenatal vitamin D deficiency has been associated with the later development of psychosis in the offspring (Eyles et al., 2018; McGrath et al., 2010) while low levels of vitamin D have also been described in patients with psychosis (Valipour et al., 2014). Animal models of vitamin D deficiency display similar characteristics to those with psychosis, like enlarged lateral ventricles (Costas-Carrera et al.,

2023; Eyles et al., 2003).

Maternal viral infections during the third trimester (winter with a higher prevalence of respiratory viruses) would promote immune reactions in the mother, affecting fetal development during the last trimester of pregnancy (Spann et al., 2018). Third-trimester influenza viral infection increases the risk of schizophrenia by 1.37, while third-trimester catastrophic events increase the risk by 1.02 (Davies et al., 2020). Animal models mimicking this situation are known as maternal immune activation (MIA), with several outcomes in different areas of the offspring related to psychosis and neurodevelopmental deviations (Guerrin et al., 2021; San Martín-González et al., 2023).

However, both models might also be interconnected, as vitamin D deficiency in animal models displays an intriguing sexual dimorphism. Although vitamin D deficiency does not alter baseline inflammatory cytokine levels in the placenta, a sex-specific response emerges under immune challenge. Specifically, upon exposure to polyinosinic:polycytidylic acid (a viral mimic), but not lipopolysaccharide (a bacterial mimic), placentas from male fetuses exhibit increased interleukin production, suggesting greater vulnerability of male fetuses to maternal viral exposures (Ali et al., 2018).

In addition to the proposed pathophysiological mechanisms linking season of birth to the risk of psychosis and affective disorders, other mental health outcomes beyond diagnosis have also been associated with season of birth. Regarding brain structural abnormalities, increased gyrification in the insula has been observed in summer-born patients, although this finding was not specific to any particular diagnosis, including schizophrenia, schizotypy, or healthy controls (Takahashi et al., 2023). In contrast, an older computed tomography study found that patients with schizophrenia born in winter displayed ventricular enlargement, particularly in those without a family history of psychosis

¹ Both to be considered co-first authors.

² Both to be considered co-senior authors.

(Sacchetti et al., 1992). In bipolar disorder (BD), white matter lesions have been reported more frequently among individuals born in winter (Moore et al., 2001), whereas a reduced hippocampal volume has been described in patients with depression born in summer (Schaub et al., 2022).

From a clinical perspective, individuals born in late winter and early spring have shown higher levels of psychometric schizotypy in the general population (Konrath et al., 2016). (Szöke et al., 2024) Notwithstanding, neither season of birth nor month of birth have been described as reliable predictors of anxiety and depression across the life course (Csajbók et al., 2022). Nevertheless, summer-born subjects displayed a significantly higher ratio of depressive symptoms (Zhou et al., 2023). In patients with schizophrenia, being born in winter was associated with a higher incidence of clozapine use. Additionally, for those whose illness onset was between 21 and 44 years old, being born in winter was associated with earlier clozapine initiation (Kim et al., 2017). In terms of functioning, lower income status was related to WB but only in females diagnosed with schizophrenia (Cheng et al., 2013), suggesting a sexual dimorphism. A similar sex difference was observed in a cohort of individuals with first-episode psychosis (FEP) (Garcia-Rizo et al., 2024). A recent longitudinal study in early psychosis patients described that WB was associated with poor functional outcomes (Restellini et al., 2024). WB patients had significantly lower global functionality, fewer positive symptoms, and non-significantly higher negative symptomatology during follow-up. In affective disorders, however, summer birth was partially associated with worse clinical course in a sample of major depressive disorder (MDD) (Park et al., 2016), while spring birth was associated with early-onset BD patients (Wang et al., 2020). (Soreca et al., 2013) As previously described, seasonal effects have been described in both early stages (Restellini et al., 2024) and chronic subjects (Cheng et al., 2013; Kim et al., 2017), although regarding metabolic outcomes, the impact of perinatal factors promoted differences between FEP and chronic subjects (Garriga et al., 2019), suggesting that early life stressful events might be detected only at initial stages (Garcia-Rizo and Bitanirwe, 2025).

We aim to investigate whether WB has a longitudinal effect on psychopathology, cognition, and functioning in schizophrenia-spectrum and affective disorders, considering illness duration and sex differences. To our knowledge, this is the first large-scale longitudinal study to evaluate the effects of WB across diagnostic categories within a single cohort. Specifically, we examine whether WB is associated with changes in clinical outcomes over time, whether these associations differ across diagnostic groups, and explore potential moderators by stratifying analyses according to biological sex and illness duration. This approach allows us to capture both overall associations and longitudinal trajectories while accounting for clinically meaningful subgroups.

2. Materials and methods

2.1. Properties of the PsyCourse study

PsyCourse is a multicentre study, conducted by a network of clinical sites in Germany and Austria (Budde et al., 2019; Heilbronner et al., 2023). The study protocol was approved by the respective ethics committee for each study centre and was carried out following the rules of the Declaration of Helsinki of 1975, revised in 2008. Study participants were assessed at four points in time, in intervals of 6 months, hereafter referred to as study visits 1 (T1; baseline), 2 (T2; 6 months), 3 (T3; 12 months), and 4 (T4; 18 months). At each study visit, a comprehensive set of phenotypic data was collected, such as anthropometric features, symptom dimensions, cognitive function, and self-report measures recorded. Study visits were carried out by trained interviewers.

2.2. Participants and broad diagnostic groups

Adult patients (over 18 years) with a lifetime DSM-IV diagnosis of

the affective-to-psychotic spectrum were eligible for study participation. Participants with a DSM-IV diagnosis of schizophrenia (SZ), constituted the group with schizophrenia-spectrum disorders in our analyses, whereas those with a lifetime DSM-IV diagnosis of bipolar disorder type I or II (BD-I or BD-II) or recurrent major depression (reMDD) constituted the affective disorder group. Clinical participants were excluded from the study if none of the above DSM-IV diagnoses could be confirmed using an adapted version of the Structured Clinical Interview for DSM-IV; Axis I Disorders (SCID-I) (Wittchen et al., 1997). Participants had to be proficient in the German language to enrol in the study. A total of 535 patients with schizophrenia-spectrum disorders (SZ:535) and 667 with an affective disorder diagnosis (BD-I:446, BD-II: 120 reMDD:101) were included. All participants gave written informed consent.

2.3. Psychopathology, educational status, and global functioning

Information on current psychopathology was obtained with clinician-rated assessment scales i.e., the Positive and Negative Syndrome Scale (PANSS), Inventory of Depressive Symptomatology–Clinician Rated (IDS-C30), and Young Mania Rating Scale (YMRS). The PANSS assesses the severity of typical symptoms of schizophrenia (Kay et al., 1987), the IDS-C30 measures the severity of depressive symptoms (Drieling et al., 2007); and the YMRS evaluates the severity of mania symptoms (Young et al., 1978). The severity of illness was measured with the Clinical Global Impression scale (CGI) (Busner and Targum, 2007) and global functioning was measured with the Global Assessment of Functioning (GAF) (Aas, 2011). To ensure comparability with English-speaking educational systems information on specialized schools, high schools and professional education in Germany were combined to form an ordinal educational scale (1–6) with “6” being the highest level of education obtained. Detailed information on the educational scale can be found in the PsyCourse Codebook (Heilbronner et al., 2023).

2.4. Neuropsychological outcome

The neuropsychological battery included measures that assess cognitive domains, including attention, processing speed, working memory, and executive functions. Trail-Making Test (TMT) (Reitan, 1958) part A and the Digit-Symbol Test (DST) (Wechsler, 1997) assessed processing speed. The forward verbal digit span assessed short-term memory, and the backward verbal digit span was used to measure working memory (Wechsler, 1997). TMT-B addressed executive functions. In both TMT-A and TMT-B, longer completion times indicated poorer performance.

2.5. Statistical analysis

Continuous and categorical variables were summarized using means and standard deviations or frequencies and percentages, respectively. Within each diagnostic group (schizophrenia-spectrum or affective disorders), differences between participants born in winter (WB) and those born during the rest of the year were assessed using independent *t*-tests for continuous variables and chi-square (χ^2) tests for categorical variables.

Patients were categorized by birth season based on the meteorological season dates: summer (June, July, August), autumn (September, October, November), winter (December, January, February), and spring (March, April, and May). Patients were then categorized into two groups: those born in the winter and those born during the rest of the year (1st March to 30th November). For simplicity, this variable is referred to as WB throughout the statistical analyses. Patients were also categorized in terms of diagnosis, schizophrenia-spectrum disorders, and affective disorders for independent analysis. (Nordentoft et al., 2014; Norman et al., 2018).

2.5.1. Longitudinal effects of WB

Longitudinal changes in psychopathological, functional, and cognitive outcomes were analysed using linear mixed-effects models (LMMs) with random intercepts to account for within-subject correlations. Time was included as a continuous variable. Models were estimated using Full Information Maximum Likelihood, which allows the inclusion of all available data under the assumption that missing data are missing at random. Inspection of missing data patterns did not suggest violations of this assumption (Wendel et al., 2021).

Two main analytical strategies were conducted. First, to assess whether the effect of WB differed between diagnostic groups, models including an interaction term between WB and diagnostic group (WB × group) were fitted in the full sample. Second, to evaluate longitudinal trajectories, separate LMMs were conducted within each diagnostic group including an interaction between WB and time (WB × time), allowing assessment of whether WB influenced the evolution of outcomes over follow-up.

Dependent variables included psychopathological measures (PANSS positive, negative, general, and total scores, IDS-C30, and YMRS), functional outcome (GAF), and neurocognitive performance (Trail Making Test A and B, Digit Span forward and backward, and Digit Symbol Test). LMMs included random intercepts for study centre and subject (random = ~1 | study centre/subject) to account for clustering due to multi-site recruitment and repeated measures. Fixed-effect covariates included age, sex, study centre, duration of illness (modelled as a continuous variable), and time. Clinical Global Impression (CGI) scores were additionally included as a covariate in all models except those examining GAF, given conceptual overlap between CGI and global functioning measures. Neurocognitive variables were log-transformed for modelling to improve normality and reduce the influence of outliers. However, descriptive statistics are reported in their original scale for clinical interpretability.

2.5.2. Analyses stratified by illness duration and sex

Secondary analyses were conducted to explore potential modifiers of the association between WB and outcomes. Specifically, analyses were stratified by duration of illness and biological sex. Duration of illness was additionally examined as a categorical variable using a cut-off of 5 years (<5 vs ≥5 years). This threshold was selected based on evidence indicating that the first 2–5 years represent a critical period for recovery and long-term prognosis, underscoring the importance of early intervention (Nordentoft et al., 2014; Norman et al., 2018). Analyses were stratified by biological sex to account for known sex-specific developmental trajectories. This stratification allows us to explore potential sex-dependent effects of WB on psychopathology, cognitive performance, and functional outcomes. These analyses are considered exploratory.

Results from all linear mixed-effects models are reported as fixed-effect estimates (β), degrees of freedom, and corresponding p-values. To account for multiple comparisons, false discovery rate (FDR) correction was applied separately within each domain (psychopathology, cognitive performance, and functional outcomes) using the Benjamini-Hochberg procedure. Descriptive statistics are presented as 95% confidence intervals (CI) values. For any results that survive FDR correction, predicted values from the models were plotted to visualize the longitudinal trajectories and facilitate interpretation of the interaction effects. Statistical analyses were performed with R version 4.5.3.

3. Results

3.1. Clinical and demographic characteristics

Descriptive statistics of schizophrenia-spectrum and affective patients at baseline and 18-month follow-up are presented in Table S1. No significant differences were observed between individuals born in winter and those born during the rest of the year with regard to socio-demographic variables, psychopathology, global functioning, or

cognitive performance, either at baseline or at follow-up, in either diagnostic group.

3.2. Longitudinal effects of WB

Analyses included 1202 patients (Schizophrenia-spectrum disorders, N = 535; Affective disorders, N = 667).

3.2.1. Diagnostic differences

No significant WB × Group interactions were observed across psychopathology, functioning, or cognitive domains (see Table 1). A nominal effect was seen for the DST, but this did not survive FDR correction.

3.2.2. Longitudinal changes

When examining longitudinal trajectories over the 18-month follow-up, no significant WB × Time interactions were observed across psychopathology, functioning, or cognitive domains after FDR correction (Table 2). A nominal effect was seen for IDS-C30 in schizophrenia-spectrum disorders, but these did not survive FDR correction.

3.3. Analyses stratified by illness duration and sex

When stratifying by illness duration (<5 years vs. ≥5 years; Table S2), no WB × Time interactions reached significance after FDR correction across psychopathology, functioning, or cognitive domains in

Table 1
Linear mixed-effects model results for WB × Group interactions across psychopathology, functioning, and cognitive domains.

	Estimate	SE	95% CI	df	p value	pFDR
Psychopathology						
PANSS positive	0.067	0.466	−0.848, 0.981	1019.11	0.887	0.887
PANSS negative	0.703	0.590	−0.455, 1.862	1034.03	0.234	0.702
PANSS general	0.815	0.841	−0.836, 2.465	1033.68	0.333	0.887
PANSS total	1.341	1.621	−1.840, 4.522	1032.33	0.410	0.820
IDS-C30	−0.792	1.334	−3.410, 1.826	1035.70	0.553	0.830
YMRS	0.586	0.487	−0.369, 1.542	836.21	0.229	0.702
Functioning						
GAF	−0.807	1.596	−3.938, 2.325	1087.37	0.613	–
Cognitive function						
TMTA	0.079	0.045	−0.009, 0.167	1080.46	0.159	0.241
TMTB	0.067	0.052	−0.034, 0.169	1031.37	0.193	0.241
Verbal digit span (forward digit span)	−0.001	0.028	−0.055, 0.054	1059.42	0.976	0.976
Verbal digit span (backward digit span)	−0.051	0.039	−0.127, 0.026	1059.09	0.193	0.241
Digit symbol test	−0.081	0.037	−0.153, −0.009	1061.31	0.028*	0.140

SE, standard error; 95% CI, 95% confidence interval; df, degrees of freedom; p value, unadjusted p-value; pFDR, false discovery rate-adjusted p-value; GAF, Global Assessment of Functioning; IDS-C30, Inventory of Depressive Symptomatology; PANSS, Positive and Negative Syndrome Scale for Schizophrenia; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; YMRS, Young Mania Rating Scale.

Table 2

Linear mixed-effects model results for WB × Time interactions across psychopathology, functioning, and cognitive domains in schizophrenia-spectrum disorders and affective disorders.

	Schizophrenia-spectrum disorders						Affective disorders					
	Estimate	SE	95% CI	df	p value	pFDR	Estimate	SE	95% CI	df	p value	pFDR
Psychopathology												
PANSS positive	-0.037	0.032	-0.100, 0.027	963.73	0.260	0.664	-0.023	0.020	-0.062, 0.017	1152.12	0.261	0.609
PANSS negative	0.040	0.041	-0.041, 0.12	968.92	0.332	0.664	0.047	0.031	-0.014, 0.107	1110.48	0.130	0.609
PANSS general	0.047	0.056	-0.064, 0.157	1018.63	0.408	0.664	-0.029	0.047	-0.12, 0.063	1113.59	0.540	0.756
PANSS total	0.026	0.106	-0.181, 0.233	969.18	0.805	0.805	0.001	0.079	-0.154, 0.156	1102.61	0.991	0.999
IDS-C30	0.139	0.069	0.004, 0.274	892.44	0.043*	0.258	-8.8e ⁻⁰⁵	0.085	-0.168, 0.167	1023.88	0.999	0.999
YMRS	0.016	0.031	-0.047, 0.078	942.39	0.627	0.805	-0.023	0.036	-0.094, 0.049	1096.47	0.533	0.756
Functioning												
GAF	-0.001	0.104	-0.205, 0.202	989.78	0.990	-	0.056	0.082	-0.106, 0.217	1085.54	0.500	-
Cognitive function												
TMTA	0.002	0.002	-0.003, 0.006	848.75	0.433	0.947	-1.9e ⁻⁰⁴	0.002	-0.004, 0.004	1001.02	0.924	0.938
TMTB	-0.001	0.002	-0.005, 0.004	770.62	0.821	0.947	-0.003	0.002	-0.007, 0.001	935.65	0.193	0.415
Verbal digit span (forward digit span)	0.002	0.001	-0.001, 0.005	829.23	0.150	0.750	0.001	0.001	-0.001, 0.004	983.02	0.249	0.415
Verbal digit span (backward digit span)	-1.6e ⁻⁰⁴	0.002	-0.004, 0.004	841.44	0.940	0.947	0.001	0.002	-0.003, 0.004	980.45	0.750	0.938
Digit symbol test	-0.001	0.002	-0.005, 0.003	827.77	0.568	0.947	0.002	0.001	-0.001, 0.005	934.28	0.114	0.415

SE, standard error; 95% CI, 95% confidence interval; df, degrees of freedom; p value, unadjusted p-value; pFDR, false discovery rate-adjusted p-value; GAF, Global Assessment of Functioning; IDS-C30, Inventory of Depressive Symptomatology; PANSS, Positive and Negative Syndrome Scale for Schizophrenia; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; YMRS, Young Mania Rating Scale.

either schizophrenia-spectrum ($N = 138$ [<5 years], 186 [≥ 5 years]) or affective disorders ($N = 381$ [<5 years], 418 [≥ 5 years]). At the nominal level, a WB × Time interaction was observed for PANSS Positive symptoms in schizophrenia-spectrum patients with illness duration <5 years, indicating that WB individuals showed a decrease in positive symptoms over time compared with Rest of the year individuals, but this effect did not survive FDR correction.

When stratifying by biological sex, analyses included females with schizophrenia-spectrum disorders ($N = 184$), females with affective disorders ($N = 341$), males with schizophrenia-spectrum disorders ($N = 351$), and males with affective disorders ($N = 326$). No WB × Time interactions were significant after FDR correction across psychopathology or functioning domains in either schizophrenia-spectrum or affective disorders (Table S3). In the cognitive domain, significant interactions after FDR correction were observed for the DST in females in both schizophrenia-spectrum and affective disorders. As shown in Fig. 1, in females with schizophrenia-spectrum disorders (Panel A), WB individuals exhibited an increase in DST scores over time, whereas Rest of

the year individuals remained relatively stable. In females with affective disorders (Panel B), WB individuals initially had higher DST scores, but by later follow-up, Rest of the year individuals showed higher scores, indicating a crossover in processing speed performance. Additionally, a nominally significant effect ($p < 0.05$) was found for backward digit span in females with affective disorders, which did not survive FDR correction. No significant WB × Time interactions were observed in males across any cognitive outcomes.

4. Discussion

Our results suggest that being born in winter does not have a clear or consistent longitudinal impact on psychopathology, functioning, and cognition in both schizophrenia-spectrum and affective disorder patients. By contrast, analyses stratified by biological sex revealed a distinct longitudinal pattern in cognitive performance among females, with winter-born individuals showing different trajectories over time on the Digit Symbol Test (DST) across diagnostic groups.

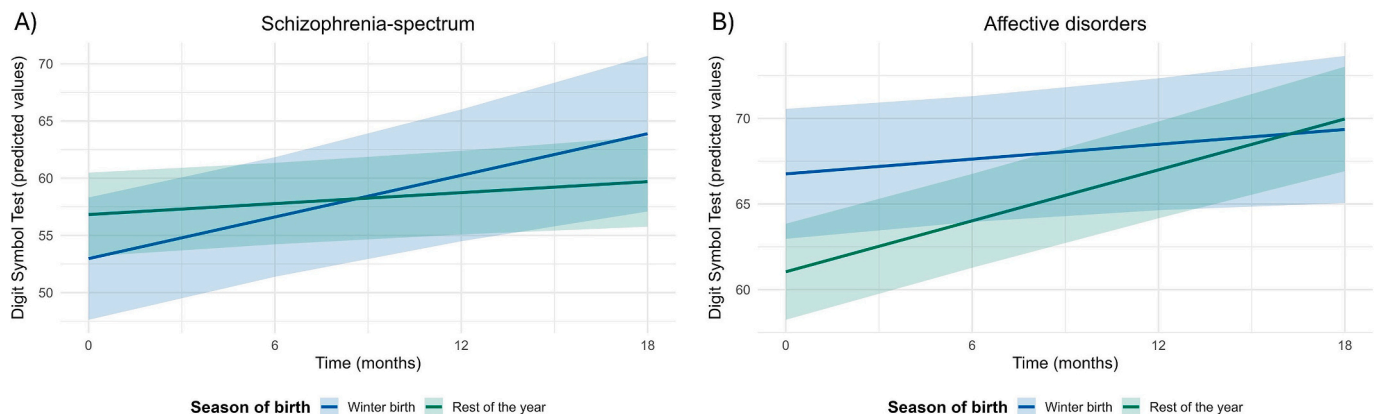


Fig. 1. Predicted trajectories of the digit symbol test in females by season of birth. A) Females with schizophrenia-spectrum disorders, and B) females with affective disorders.

Lines represent predicted values from linear mixed-effects models for winter birth (WB) and rest of the year groups, with shaded areas representing 95% confidence intervals.

Regarding psychopathology, our findings are broadly in line with previous reports suggesting subtle, but not robust, associations between WB and symptomatology. These results are partially supported by a previous study in early-onset patients (evolution less than 3 years) (Restellini et al., 2024) where higher mean scores for negative symptoms in WB were reported, although the differences did not reach statistical significance. Similarly, two studies evaluating stressful events in FEP during the perinatal period suggested worse negative symptomatology (Sagué-Vilavella et al., 2022; Verdolini et al., 2023), with one study describing specifically intrauterine events related to non-significant worse negative clinical outcomes (Verdolini et al., 2023). However, a recent meta-analysis investigating the perinatal origin of psychopathology in psychosis initially found no effect of perinatal stressful events on negative symptomatology (Forte et al., 2024). Only when random-effects meta-analysis along with leave-one-out sensitivity analyses were performed, a significant association with more prominent negative symptomatology emerged, suggesting that such effects may be method-dependent rather than robust. (Borkowska and Rybakowski, 2002; Stathopoulou et al., 2013; Wegelius et al., 2013).

Concerning functioning, our results are inconsistent with those of previous research. Studies in both FEP (Restellini et al., 2024) and schizophrenia individuals (Cheng et al., 2013) described worse functioning in WB subjects. Sexual dimorphisms was reported in other studies, as Cheng et al. described poorer functioning among winter-born females in a chronic schizophrenia cohort (Cheng et al., 2013). However, not all studies support this association. For example, Sagué-Vilavella found no differences in functioning when considering the presence of perinatal events (Sagué-Vilavella et al., 2022). Similarly, the previously mentioned meta-analysis evaluating the perinatal origin of psychopathology in psychosis found no effect of perinatal stressful events on functioning (Forte et al., 2024).

Our results in cognitive performance can be supported by a recent meta-analysis concerning obstetric complications and their cognitive outcomes in schizophrenia, describing abnormal verbal and working memory (Amoretti et al., 2022). Although the DST primarily measures processing speed, it is a multifaceted task that also engages working memory as it requires task rules in mind and continually updates required symbol-digit pairs. Similarly, other authors have reported similar findings; for instance, Borkowska et al. (Borkowska and Rybakowski, 2002) described worse functioning in the Stroop test, which, although it evaluated executive function, its performance is influenced by slower processing speed, especially in the incongruent condition. Brown et al. (Brown et al., 2009), evaluating intrauterine influenza infection, described worse letter-number sequencing. Animal studies confirm our findings as primates born to MIA-treated dams exhibited subtle changes in cognitive development (Vlasova et al., 2021). Specifically, maternal influenza infection during the early third-trimester has been shown to affect neural development in monkeys, leading to cognitive consequences (Short et al., 2010). (Willette et al., 2011) Aligning with previous findings, Costas-Carrera has described worse cognitive performance in FEP in relation to obstetric complications (Costas-Carrera et al., 2025, 2023).

By contrast, a specific pattern appeared in secondary analyses stratified by biological sex, in which WB females showed different trajectories over time on DST. Processing speed has been consistently associated with white-matter integrity and myelination, which are particularly dynamic during late gestation and early postnatal development (Gong et al., 2024). Population-based studies have suggested small season-of-birth-related differences in cognitive performance, although these effects are generally modest (Grootendorst-van Mil et al., 2017). Importantly, the effect observed in females on the DST suggests that early developmental influences may interact with sex-specific neurobiological trajectories, resulting in subtle and domain-specific longitudinal differences rather than broad cognitive effects.

(Gallagher et al., 2014)

When stratifying analyses by illness duration, WB did not show a

consistent pattern across early (<5 years) or later (≥ 5 years) stages of illness. This absence of effects is consistent with longitudinal evidence indicating relative stability of cognitive and clinical trajectories after illness onset, with limited modulation by illness duration (Watson et al., 2022).

Overall, our results minimally support previous independent findings in early psychosis and chronic schizophrenia that WB, beyond being a well-replicated risk factor for the development of psychosis, exerts some effect in other secondary outcomes. In our study, however, such effects were not robust across longitudinal clinical or cognitive trajectories, indicating that WB likely represents a weak proxy for early developmental influences whose downstream impact on illness course is modest. These observations are in line with previous findings in early psychosis and chronic schizophrenia describing small effects of WB on epiphenomenal outcomes, such as cognitive deficits, negative symptoms, or metabolic disturbances (García-Rizo and Bitanirwe, 2020, 2025, 2024). WB, through its theoretically possible underlying mechanisms related to Vitamin D and immune activation, may exert an imprinting in the fetal development during the third trimester, with long-lasting consequences in different areas and outcomes (García-Rizo and Bitanirwe, 2025).

Several limitations shall be acknowledged in our manuscript. First, patients involved were recruited from different settings in both Austria and Germany, with different patterns in terms of sunlight and climate, suggesting a different heterogeneous effect on the outcome. Second, potential residual confounding (e.g., socio-economic status, urbanicity, maternal factors) known to interact with season effects from which information was not available (Heinz et al., 2013). Third, the lack of direct measures of vitamin D or viral infections implies that WB can only be considered a proxy marker, not a direct environmental exposure (McGrath et al., 2010). Fourth, the dearth of research concerning WB in affective disorders complicates the interpretation of our results. Moreover, patients were medicated and the effects of drugs might have impacted our results (Ilzarbe and Vieta, 2023). Finally, cognitive deficits, negative symptoms and functional impairment are strongly interrelated in severe mental illness (Fujii and Muralidharan, 2017), and this interdependence may limit the interpretability of our domain-specific analyses. On the other hand, the comprehensive clinical characterization and longitudinal approach of the sample are strengths that enhance the possibility of detecting differences over time.

5. Conclusions

Our findings suggest that WB does not have a strong or consistent impact on clinical, cognitive, and functional outcomes in individuals with schizophrenia-spectrum or affective disorders over time. Subtle, duration- and sex-dependent variations suggest that late perinatal environmental factors may transiently shape early illness expression rather than long-term outcomes. Further research into the pathophysiology and biological mechanisms underlying the WB seasonal effect is required to better understand the heterogeneity of psychotic and affective disorders, and to implement strategies for improving outcomes in subjects diagnosed with schizophrenia-spectrum disorders.

CRedit authorship contribution statement

Anaid Pérez-Ramos: Writing – review & editing. **Monika Budde:** Writing – review & editing, Writing – original draft, Validation, Supervision. **Kristina Adorjan:** Writing – review & editing. **Silvia Amoretti:** Writing – review & editing, Writing – original draft. **Ion-George Angheliescu:** Writing – review & editing. **Volker Arolt:** Writing – review & editing. **Bernhard T. Baune:** Writing – review & editing. **Udo Dannlowski:** Writing – review & editing. **Detlef E. Dietrich:** Writing – review & editing. **Andreas J. Fallgatter:** Writing – review & editing. **Christian Figge:** Writing – review & editing. **Marina Garriga:** Writing – review & editing. **Clemente Garcia-Rizo:** Writing – original draft,

Visualization, Supervision. **Nora Guasch-Capella:** Writing – review & editing, Methodology. **Maria Heilbronner:** Writing – review & editing. **Fabian U. Lang:** Writing – review & editing. **Georg Juckel:** Writing – review & editing. **Mojtaba Oraki Kohshour:** Writing – review & editing. **Carsten Konrad:** Writing – review & editing. **Anabel Martinez-Aran:** Writing – review & editing. **Gisela Mezquida:** Writing – review & editing. **Alba Navarro-Flores:** Writing – review & editing. **Daniela Reich-Erkelenz:** Writing – review & editing. **Jens Reimer:** Writing – review & editing. **Eva Z. Reininghaus:** Writing – review & editing. **Fanny Senner:** Writing – review & editing. **Max Schmauß:** Writing – review & editing. **Andrea Schmitt:** Writing – review & editing. **Eva C. Schulte:** Writing – review & editing. **Carsten Spitzer:** Writing – review & editing. **Eduard Vieta:** Writing – review & editing. **Jens Wiltfang:** Writing – review & editing. **Peter Falkai:** Writing – review & editing, Project administration, Funding acquisition. **Thomas G. Schulze:** Writing – review & editing, Project administration, Funding acquisition. **Sergi Papiol:** Writing – review & editing. **Carla Torrent:** Writing – review & editing, Writing – original draft. **Urs Heilbronner:** Writing – original draft, Validation, Supervision.

Role of the funding source

The study was endorsed by the Ministry of Research, Technology and Space (BMFTR) (Bundesministerium für Forschung, Technologie und Raumfahrt) within the initial and the setup phase of the German Center for Mental Health (DZPG) (grant: 01EE2303A, 01EE2303F, 01EE2503F, 01EE2503A to Peter Falkai, MD, Thomas G Schulze, MD). TGS and PF were supported by the Deutsche Forschungsgemeinschaft (DFG) within the framework of the projects www.kfo241.de and www.PsyCourse.de (SCHU 1603/4-1, 5-1, 7-1; FA241/16-1). TGS was further supported by the Dr. Lisa Oehler Foundation (Kassel, Germany), the Bundesministerium für Bildung und Forschung (BMBF, Federal Ministry of Education and Research (projects: IntegraMent [01ZX1614K], BipoLife [01EE1404H], e:Med Program [01ZX1614K]), the European Union's Horizon 2020 Research and Innovation Programme (ERA-NET Neuron Projects GEPI-BIOPSY [BMBF No 01EW2005] and MulioBio [BMBF No 01EW2009]), and by the European Union Horizon 2020 Research and Innovation Program (PSY-PGx, grant agreement No 945151). UD was funded by the German Research Foundation (DFG, grant FOR2107 DA1151/5-1, DA1151/5-2, DA1151/9-1, DA1151/10-1, DA1151/11-1 to UD; SFB/TRR 393, project grant no 521379614) and the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster (grant Dan3/022/22 to UD). N. Guasch-Capella received the support from the predoctoral grant “Ajuts per a la contractació de personal investigador predoctoral en formació dins dels àmbits de les tecnologies STEP” (FI-STEP) (2025 STEP 00227). S.A. has been supported by the Sara Borrell Doctoral Programme (CD20/00177) and M-AES Mobility Fellowship (MV22/00002) from the Instituto de Salud Carlos III (ISCIII), and co-funded by the European Social Fund “Investing in your future” La Marató-TV3 Foundation grants 202234-30 (E.V.) and 202234-32 (S.A.). Dr. Amoretti (PI24/00671) and C.T. (PI20/00344; PI24/00407), E.V. and A.M.-A. (PI21/00787, PI24/00432) thank the support of The Ministry of Science, Innovation and Universities, funded by the Instituto de Salud Carlos III and cofinanced by the European Union (FEDER) “Una manera de hacer Europa” and Project 2021-SGR-1358, funded by the Department of Research and Universities of the Generalitat de Catalunya. Urs Heilbronner was supported by European Union's Horizon 2020 Research and Innovation Programme (PSY-PGx, grant agreement No 945151) and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, project number 514201724). CGR is supported by Maria i Núria Cunillera legacy (FCRB_CU1_2024) and projects “PI20/00661; PI24/00196”, funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union.

Declaration of competing interest

I-G. Anghelescu served as a consultant or speaker (unrelated to the present work) for Aristo, Idorsia, Johnson & JJohnson, Merck Recordati, and Schwabe. CGR has received grants from/or served as a consultant, advisor, or speaker for the following entities: Adamed, Angelini, Casen-Recordati, Janssen-Cilag, Lunbeck, and Newron. Volker Arolt lectures for Sanofi Germany. Peter Falkai received speaker fees by Abbott, GlaxoSmithKline, Boehringer-Ingelheim, Janssen, Essex, Otsuka, Lundbeck, Recordati, Gedeon Richter, Servier and Takeda and was member of advisory boards of these companies and Rovi. EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, AbbVie, Adamed, Adium, Alcediag, Angelini, Biogen, Beckley-Psytech, Biohaven, Boehringer-Ingelheim, Casen-Recordati, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Esteve, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, HMNC, Intra-Cellular therapies, Idorsia, Johnson & Johnson, Lundbeck, Luye Pharma, MedinCell, Merck, Mitsubishi Tanabe Pharma, Newron, Novartis, Organon, Orion Corporation, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva, and Viatrix, outside the submitted work. MG has received support from Ferrer, Janssen, Lundbeck and Viatrix.

The other authors declare no conflicts of interest.

Acknowledgements

The authors would like to thank the participants for their willingness.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jad.2026.121848>.

References

- Aas, I.M., 2011. Guidelines for rating global assessment of functioning (GAF). *Ann. Gen. Psychiatry*. <https://doi.org/10.1186/1744-859X-10-2>.
- Ali, A., Cui, X., Alexander, S., Eyles, D., 2018. The placental immune response is dysregulated developmentally vitamin D deficient rats: relevance to autism. *J. Steroid Biochem. Mol. Biol.* 180, 73–80. <https://doi.org/10.1016/j.jsbmb.2018.01.015>.
- Amoretti, S., Rabelo-da-Ponte, F.D., Garriga, M., Forte, M.F., Penadés, R., Vieta, E., Parellada, E., Ramos-Quiroga, J.A., Gama, C.S., Verdolini, N., Bitanihirwa, B., Garcia-Rizo, C., 2022. Obstetric complications and cognition in schizophrenia: a systematic review and meta-analysis. *Psychol. Med.* 1–11. <https://doi.org/10.1017/S0033291722002409>.
- Borkowska, A., Rybakowski, J.K., 2002. Does risperidone act better in schizophrenic patients who have a family or obstetric history? *Prog. Neuropsychopharmacol. Biol. Psychiatry* 26, 1349–1353.
- Brown, A.S., Vinogradov, S., Kremen, W.S., Poole, J.H., Deicken, R.F., Penner, J.D., McKeague, I.W., Kochetkova, A., Kern, D., Schaefer, C.A., 2009. Prenatal exposure to maternal infection and executive dysfunction in adult schizophrenia. *Am. J. Psychiatry* 166, 683–690. <https://doi.org/10.1176/appi.ajp.2008.08010089>.
- Budde, M., Anderson-Schmidt, H., Gade, K., Reich-Erkelenz, D., Adorjan, K., Kalman, J. L., Senner, F., Papiol, S., Andlauer, T.F.M., Comes, A.L., Schulte, E.C., Klöhn-Saghatolislam, F., Gryaznova, A., Hake, M., Bartholdi, K., Flatau, L., Reitt, M., Quast, S., Stegmaier, S., Meyers, M., Emons, B., Haußleiter, I.S., Juckel, G., Nieratschker, V., Dannlowski, U., Schaupp, S.K., Schmauß, M., Zimmermann, J., Reimer, J., Schulz, S., Wiltfang, J., Reininghaus, E., Anghelescu, I.G., Arolt, V., Baune, B.T., Konrad, C., Thiel, A., Fallgatter, A.J., Figge, C., von Hagen, M., Koller, M., Lang, F.U., Wigand, M.E., Becker, T., Jäger, M., Dietrich, D.E., Stierl, S., Scherk, H., Spitzer, C., Folkerts, H., Witt, S.H., Degenhardt, F., Forstner, A.J., Rietschel, M., Nöthen, M.M., Falkai, P., Schulze, T.G., Heilbronner, U., 2019. A longitudinal approach to biological psychiatric research: the PsyCourse study. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 180. <https://doi.org/10.1002/ajmg.b.32639>.
- Busner, J., Targum, S.D., 2007. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edmont)* 4, 28–37.
- Cheng, C., Loh, E.W., Lin, C.H., Chan, C.H., Lan, T.H., 2013. Birth seasonality in schizophrenia: effects of gender and income status. *Psychiatry Clin. Neurosci.* 67, 426–433. <https://doi.org/10.1111/PCN.12076>.
- Costas-Carrera, A., Verdolini, N., Garcia-Rizo, C., Mezquida, G., Janssen, J., Valli, I., Corripio, I., Sanchez-Torres, A.M., Bioque, M., Lobo, A., Gonzalez-Pinto, A., Rapado-Castro, M., Vieta, E., De La Serna, H., Mane, A., Roldan, A., Crossley, N., Penadés, R., Cuesta, M.J., Parellada, M., Bernardo, M., Forte, M.F., Gonzalez-Diaz, J.M.,

- Cavone, V., Ordas, C., Zorrilla, I., Lopez-Zurbano, S., De La Camara, C., Puyuelo, D. V., Nacher, J., Fabra, M.J.E., Privat, A.T., Sadurni, L.M., Martín-Parra, S., Clougher, D., Baeza, I., Castro-Fornieles, J., Contreras, F., García-Portilla, M.P., González-Blanco, L., Rodríguez-Jimenez, R., Sánchez-Cabezudo, Á., Usall, J., Butjosa, A., Sarro, S., Pomarol-Clotet, E., Selma, J., Àvila-Parcet, A., Ribeiro, M., 2023. Difficulties during delivery, brain ventricle enlargement and cognitive impairment in first episode psychosis. *Psychol. Med.* 1–11. <https://doi.org/10.1017/S0033291723003185>.
- Costas-Carrera, A., Verdolini, N., Mezquida, G., Forte, M.F., Janssen, J., Garcia-Rizo, C., Martínez-Aran, A., Andres-Camazon, P., Sánchez-Torres, A.M., Berge, D., De La Serna, E., Penades, R., Valli, I., Amoretti, S., Guasch-Capella, N., Perez-Ramos, A., Merchán-Naranjo, J., Pina-Camacho, L., Roldán, A., Alonso-Solís, A., González-Pinto, A., Zorrilla, I., Lázaro, P.M.R., Vaquero-Puyuelo, D., Escarti, M.J., Rando, M. P., Man, A., Malagon, A., Serra-Navarro, M., Vieta, E., Castro-Fornieles, J., Baeza, I., Santo, F.D., García-Portilla, P., Echevarria, R.S., Rabadán, A.Z., Rodríguez-Jimenez, R., Martínez-Gras, I., Usall, J., Butjosa, A., Pomarol-Clotet, E., Salvador, R., Ibañez, A., Cuesta, M.J., Martínez, V.B., 2025. Obstetric complications, cortical gyrification, and cognition in first-episode psychosis. *Psychol. Med.* 55. <https://doi.org/10.1017/S0033291725100974>.
- Coury, S.M., Lombroso, A., Avila-Quintero, V.J., Taylor, J.H., Flores, J.M., Szejko, N., Bloch, M.H., 2023. Systematic review and meta-analysis: season of birth and schizophrenia risk. *Schizophr. Res.* 252, 244–252. <https://doi.org/10.1016/j.schres.2022.12.016>.
- Csajbók, Z., Kagstrom, A., Cermakova, P., 2022. Season of birth has no effect on symptoms of depression and anxiety in older adults. *Sci. Rep.* 12, 1–9. <https://doi.org/10.1038/s41598-022-10892-8>.
- Cui, X., McGrath, J.J., Burne, T.H.J., Eyles, D.W., 2021. Vitamin D and schizophrenia: 20 years on. *Mol. Psychiatry*. <https://doi.org/10.1038/s41380-021-01025-0>.
- Davies, G., Welham, J., Chant, D., Torrey, E.F., McGrath, J., 2003. A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. *Schizophr. Bull.* <https://doi.org/10.1093/oxfordjournals.schbul.a007030>. DHHS Public Health Service.
- 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, R. M., McGuire, P., Fusar-Poli, P., 2020. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. *Lancet Psychiatry* 7, 399–410. [https://doi.org/10.1016/S2215-0366\(20\)30057-2](https://doi.org/10.1016/S2215-0366(20)30057-2).
- Drieling, T., Schäfer, L.O., Langosch, J.M., 2007. The Inventory of Depressive Symptomatology: German translation and psychometric validation. *Int. J. Methods Psychiatr. Res.* 16. <https://doi.org/10.1002/mpr.226>.
- Eyles, D., Brown, J., Mackay-Sim, A., McGrath, J., Feron, F., 2003. Vitamin D3 and brain development. *Neuroscience* 118, 641–653. [https://doi.org/10.1016/S0306-4522\(03\)00040-X](https://doi.org/10.1016/S0306-4522(03)00040-X).
- Eyles, D.W., Trzaskowski, M., Vinkhuyzen, A.A.E.E., Mattheisen, M., Meier, S., Gooch, H., Anggono, V., Cui, X., Tan, M.C., Burne, T.H.J., Jang, S.E., Kvaskoff, D., Hougaard, D.M., Nørgaard-Pedersen, B., Cohen, A., Agerbo, E., Pedersen, C.B., Børglum, A.D., Mors, O., Sah, P., Wray, N.R., Mortensen, P.B., McGrath, J.J., 2018. The association between neonatal vitamin D status and risk of schizophrenia. *Sci. Rep.* 8, 17692.
- Forte, M.F., Oliva, V., De Prisco, M., Garriga, M., Bitanirhwe, B., Alameda, L., González-Segura, A., Vieta, E., Baeza, I., Parellada, E., Penadés, R., Ramos-Quiroga, J.A., Amoretti, S., Mezquida, G., Garcia-Rizo, C., 2024. Obstetric complications and psychopathology in schizophrenia: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 167, 105913. <https://doi.org/10.1016/J.NEUBIOREV.2024.105913>.
- Fujii, D., Muralidharan, A., 2017. Cognition in Serious Mental Illness.
- Gallagher, B.J., Jones, B.J., Eaton, K.E., 2014. A sex-specified effect of obstetrical complications in symptoms of schizophrenia. *Clin. Schizophr. Relat. Psychoses* 8, 143–148A. <https://doi.org/10.3371/CSRP.GAJO.030113>.
- García-Rizo, C., Bitanirhwe, B.K., 2020. Implications of early life stress on fetal metabolic programming of schizophrenia: a focus on epiphenomena underlying morbidity and early mortality. *Prog. Neuropsychopharmacol. Biol. Psychiatry*. <https://doi.org/10.1016/j.pnpbp.2020.109910>.
- García-Rizo, C., Bitanirhwe, B.K.Y., 2024. Deciphering the impact of metabolic anomalies in relation to severe mental illness. *Eur. Neuropsychopharmacol.* <https://doi.org/10.1016/j.euroneuro.2024.06.007>.
- García-Rizo, C., Bitanirhwe, B.K.Y., 2025. Epiphenomena in psychosis: how perinatal stressful events shape long-term outcomes. *Mol. Psychiatry* 30, 4992–5000. <https://doi.org/10.1038/s41380-025-03096-9>.
- García-Rizo, C., Crespo-Facorro, B., Oliveira, C., Gómez-Revueña, M., Kirkpatrick, B., Son, J.M., van de Hoz, L.C., Garriga, M., Garrido-Torres, N., Bernardo, M., Fernandez-Egea, E., Vázquez-Bourgon, J., Hoz, L.C. de la, Garriga, M., Garrido-Torres, N., Bernardo, M., Fernandez-Egea, E., Vázquez-Bourgon, J., 2024. Anthropometry in antipsychotic-naïve first-episode psychosis patients: an exploratory approach to the role of environmental early life events in two independent samples. *Schizophr. Res.* 266, 216–226. <https://doi.org/10.1016/j.schres.2024.02.020>.
- García-Serna, A.M., Morales, E., 2020. Neurodevelopmental effects of prenatal vitamin D in humans: systematic review and meta-analysis. *Mol. Psychiatry* 25, 2468–2481. <https://doi.org/10.1038/s41380-019-0357-9>.
- Garriga, M., Fernandez-Egea, E., Mallorqui, A., Serrano, L., Oliveira, C., Parellada, E., Kirkpatrick, B., Vieta, E., Bernardo, M., Garcia-Rizo, C., 2019. Antipsychotic-induced weight gain and birth weight in psychosis: a fetal programming model. *J. Psychiatr. Res.* 115, 29–35. <https://doi.org/10.1016/j.jpsychires.2019.05.004>.
- Gong, Z., Bilgel, M., An, Y., Bergeron, C.M., Bergeron, J., Zukley, L., Ferrucci, L., Resnick, S.M., Bouhrara, M., 2024. Cerebral white matter myelination is associated with longitudinal changes in processing speed across the adult lifespan. *Brain Commun.* 6 (6), fcae412. <https://doi.org/10.1093/braincomms/fcae412>. PMID: 39697833; PMCID: PMC11653079.
- Grootendorst-van Mil, N.H., Steegers-Theunissen, R.P., Hofman, A., Jaddoe, V.W., Verhulst, F.C., Tiemeier, H., 2017. Brighter children? The association between seasonality of birth and child IQ in a population-based birth cohort. *BMJ Open* 7 (2), e012406. <https://doi.org/10.1136/bmjopen-2016-012406>. PMID: 28213594; PMCID: PMC5318550.
- Guerrin, C.G.J., Doorduyn, J., Sommer, I.E., de Vries, E.F.J., 2021. The dual hit hypothesis of schizophrenia: evidence from animal models. *Neurosci. Biobehav. Rev.* <https://doi.org/10.1016/j.neubiorev.2021.10.025>.
- Heilbronner, U., Adorjan, K., Anderson-Schmidt, H., Budde, M., Comes, A.L., Gade, K., Heilbronner, M., Kalman, J., Kohshour, L., M.O., Papiol, S., Reich-Erkelenz, D., Schaupp, S.K., Schulte, E.C., Senner, F., Vogl, T., Falkai, P., Schulze, T.G., 2023. The PsyCourse Codebook, Version 6.0 [WWW Document]. Open Data LMU. <https://doi.org/10.5282/ubm/data.199>.
- Heinz, A., Deserno, L., Reininghaus, U., 2013. Urbanicity, social adversity and psychosis. *World Psychiatry* 12, 187–197. <https://doi.org/10.1002/wps.20056>.
- Hsu, C.W., Tseng, P.T., Tu, Y.K., Lin, P.Y., Hung, C.F., Liang, C.S., Hsieh, Y.Y., Yang, Y.H., Wang, L.J., Kao, H.Y., 2021. Month of birth and mental disorders: a population-based study and validation using global meta-analysis. *Acta Psychiatr. Scand.* 144, 153–167. <https://doi.org/10.1111/acps.13313>.
- Ilzarbe, L., Vieta, E., 2023. The elephant in the room: medication as confounder. *Eur. Neuropsychopharmacol.* <https://doi.org/10.1016/j.euroneuro.2023.03.001>.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276. <https://doi.org/10.1093/schbul/13.2.261>.
- Kim, J.S., Park, C.M., Choi, J.A., Park, E., Tchoe, H.J., Choi, M., Suh, J.K., Kim, Y.H., Won, S.H., Chung, Y.C., Bae, K.Y., Lee, S.H.K., Park, S.C., Lee, S.H.K., 2017. The association between season of birth, age at onset, and clozapine use in schizophrenia. *Acta Psychiatr. Scand.* 136, 445–454. <https://doi.org/10.1111/acps.12776>.
- Konrath, L., Beckius, D., Tran, U.S., 2016. Season of birth and population schizotypy: results from a large sample of the adult general population. *Psychiatry Res.* 242, 245–250. <https://doi.org/10.1016/j.psychres.2016.05.059>.
- McGrath, J.J., Welham, J.L., 1999. Season of birth and schizophrenia: a systematic review and meta-analysis of data from the Southern Hemisphere. *Schizophr. Res.* 35, 237–242. [https://doi.org/10.1016/S0920-9964\(98\)00139-X](https://doi.org/10.1016/S0920-9964(98)00139-X).
- McGrath, J.J., Eyles, D.W., Pedersen, C.B., Anderson, C., Ko, P., Burne, T.H., Nørgaard-Pedersen, B., Hougaard, D.M., Mortensen, P.B., 2010. Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. *Arch. Gen. Psychiatry* 67, 889–894. <https://doi.org/10.1001/archgenpsychiatry.2010.110>.
- Moore, P.B., El-Badri, S.M., Cousins, D., Shepherd, D.J., Young, A.H., McAllister, V.L., Ferrier, I.N., 2001. White matter lesions and season of birth of patients with bipolar affective disorder. *Am. J. Psychiatry* 158, 1521–1524. <https://doi.org/10.1176/appi.ajp.158.9.1521>.
- Nordentoft, M., Rasmussen, J.Ø., Melau, M., Hjorthøj, C.R., Thorup, A.A.E., 2014. How successful are first episode programs? A review of the evidence for specialized assertive early intervention. *Curr. Opin. Psychiatry* 27, 167–172. <https://doi.org/10.1097/YCO.0000000000000052>.
- Norman, R.M.G., Anderson, K.K., MacDougall, A., Manchanda, R., Harricharan, R., Subramanian, P., Richard, J., Northcott, S., 2018. Stability of outcomes after 5 years of treatment in an early intervention programme. *Early Interv. Psychiatry* 12, 720–725. <https://doi.org/10.1111/eip.12450>.
- Park, S.C., Sakong, J.K., Koo, B.H., Kim, J.M., Jun, T.Y., Lee, M.S., Kim, J.B., Yim, H.W., Park, Y.C., 2016. Potential relationship between season of birth and clinical characteristics in major depressive disorder in Koreans: results from the CRESCEND study. *Yonsei Med. J.* 57, 784–789. <https://doi.org/10.3349/ymj.2016.57.3.784>.
- Reitan, R.M., 1958. Validity of the trail making test as an indicator of organic brain damage. *Percept. Mot. Skills* 8, 271–276. <https://doi.org/10.2466/pms.1958.8.3.271>.
- Restellini, R., Golay, P., Jenni, R., Baumann, P.S., Alameda, L., Allgauer, L., Steullet, P., Abrahamyan Empson, L., Mebdouhi, N., Do, K.Q., Conus, P., Dvir, D., Klausner, P., 2024. Winter birth: a factor of poor functional outcome in a Swiss early psychosis cohort. *Schizophr. Res.* 274, 206–211. <https://doi.org/10.1016/j.schres.2024.09.022>.
- Sacchetti, E., Calzeroni, A., Vita, A., Terzi, A., Pollastro, F., Cazzullo, C.L., 1992. The brain damage hypothesis of the seasonality of births in schizophrenia and major affective disorders: evidence from computerised tomography. *Br. J. Psychiatry* 160, 390–397. <https://doi.org/10.1192/bjp.160.3.390>.
- Sagué-Vilavella, M., Amoretti, S., Garriga, M., Mezquida, G., Williams, E., Serra-Navarro, M., Forte, M.F., Varo, C., Montejo, L., Palacios-Garran, R., Madero, S., Sparacino, G., Anmella, G., Fico, G., Giménez-Palomo, A., Pons-Cabrera, M.T., Salgado-Pineda, P., Montoro Salvatierra, I., Sánchez Gistau, V., Pomarol-Clotet, E., Ramos-Quiroga, J.A., Undurraga, J., Reinares, M., Martínez-Arán, A., Pacchiarotti, I., Valli, I., Bernardo, M., Garcia-Rizo, C., Vieta, E., 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. *J. Psychiatr. Res.* 151, 461–468. <https://doi.org/10.1016/j.jpsychires.2022.05.005>.
- Saleh, A., King, M., Hamilton, J., Pigott, T., Elkhatib, R., Shah, A., Sele, S., 2021. Birth seasonality of schizophrenia and bipolar disorder? A review of inpatient records. *J. Affect. Disord.* 287, 15–18. <https://doi.org/10.1016/j.jad.2021.03.002>.
- San Martín-González, N., Castro-Quintas, Á., Marques-Feixa, L., Ayesa-Arriola, R., López, M., Fañanás, L., 2023. Maternal respiratory viral infections during pregnancy

- and offspring's neurodevelopmental outcomes: a systematic review. *Neurosci. Biobehav. Rev.* <https://doi.org/10.1016/j.neubiorev.2023.105178>.
- Schaub, N., Ammann, N., Conring, F., Müller, T., Federspiel, A., Wiest, R., Hoepner, R., Stegmayer, K., Walther, S., 2022. Effect of season of birth on hippocampus volume in a transdiagnostic sample of patients with depression and schizophrenia. *Front. Hum. Neurosci.*, 354 <https://doi.org/10.3389/FNHUM.2022.877461>.
- Short, S.J., Lubach, G.R., Karasin, A.I., Olsen, C.W., Styner, M., Knickmeyer, R.C., Gilmore, J.H., Coe, C.L., 2010. Maternal influenza infection during pregnancy impacts postnatal brain development in the Rhesus Monkey. *Biol. Psychiatry* 67, 965–973. <https://doi.org/10.1016/j.biopsych.2009.11.026>.
- Soreca, I., Cheng, Y., Frank, E., Fagioli, A., Kupfer, D.J., 2013. Season of birth is associated with adult body mass index in patients with bipolar disorder. *Chronobiol. Int.* 30, 577–582. <https://doi.org/10.3109/07420528.2012.754452>.
- Spann, M.N., Monk, C., Scheinost, D., Peterson, B.S., 2018. Maternal immune activation during the third trimester is associated with neonatal functional connectivity of the salience network and fetal to toddler behavior. *J. Neurosci.* 38, 2877–2886. <https://doi.org/10.1523/JNEUROSCI.2272-17.2018>.
- Stathopoulou, A., Beratis, I.N., Beratis, S., 2013. Prenatal tobacco smoke exposure, risk of schizophrenia, and severity of positive/negative symptoms. *Schizophr. Res.* 148, 105–110. <https://doi.org/10.1016/j.schres.2013.04.031>.
- Szöke, A., Richard, J.R., Ladea, M., Ferchiou, A., Ouaknine, E., Briciu, V.A., Pirlog, M.C., Bran, M., Pignon, B., Schürhoff, F., 2024. Season of birth and schizotypy in a sample of undergraduate students. *Soc. Psychiatry Psychiatr. Epidemiol.* <https://doi.org/10.1007/S00127-024-02719-W>.
- Takahashi, T., Sasabayashi, D., Takayanagi, Y., Kobayashi, H., Torigoe, M., Sakamoto, K., Yuasa, Y., Tsujii, N., Noguchi, K., Suzuki, M., 2023. Birth season and gross brain morphology associated with early neurodevelopment in schizophrenia spectrum patients and healthy subjects. *Psychiatry Res. - Neuroimaging* 335. <https://doi.org/10.1016/j.psychres.2023.111714>.
- Torrey, E.F., Miller, J., Rawlings, R., Yolken, R.H., 1997. Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. *Schizophr. Res.* [https://doi.org/10.1016/S0920-9964\(97\)00092-3](https://doi.org/10.1016/S0920-9964(97)00092-3).
- Valipour, G., Saneei, P., Esmailzadeh, A., 2014. Serum vitamin D levels in relation to schizophrenia: a systematic review and meta-analysis of observational studies. *J. Clin. Endocrinol. Metab.* 99, 3863–3872. <https://doi.org/10.1210/JC.2014-1887>.
- Verdolini, N., Mezquida, G., Valli, I., Garcia-Rizo, C., Cuesta, M., Vieta, E., Bioque, M., Lobo, A., Gonzalez-Pinto, A., Pina-Camacho, L., Corripio, I., Garriga, M., Baeza, I., Martinez-Sadurni, L., Bitanirwre, B., Cannon, M., Bernardo, M., Amoretti, S., Forte, F., Merchán-Naranjo, J., Urbiola, E., Alonso-Solís, A., Grasa, E., Zorrilla, I., Corres, E.G., De la Camara, C., Ruiz-Lazaro, P.M., Escarti, M.J., Rivero, O., Trabsa, A., Legido, T., Serra, M., Sague-Vilella, M., de la Serna, E., Castro-Fornielles, J., Contreras, F., García-Portilla, M.P., Saiz, P., Segarra, R., Zabala, A., Sanchez-Pastor, L., Rodriguez-Jimenez, R., Usall, J., Butjosa, A., Sarró, S., Pomarol-Clotet, E., Ibañez, A., Sanchez-Torres, A.M., Balanzá-Martínez, V., 2023. Obstetric complications and clinical presentation in first episode of psychosis. *Acta Neuropsychiatr.* <https://doi.org/10.1017/neu.2023.9>.
- Vlasova, R.M., Iosif, A.M., Ryan, A.M., Funk, L.H., Murai, T., Chen, S., Lesh, T.A., Rowland, D.J., Bennett, J., Hogrefe, C.E., Maddock, R.J., Gandal, M.J., Geschwind, D.H., Schumann, C.M., Van de Water, J., Kimberley McAllister, A., Carter, C.S., Styner, M.A., Amaral, D.G., Bauman, M.D., 2021. Maternal immune activation during pregnancy alters postnatal brain growth and cognitive development in nonhuman primate offspring. *J. Neurosci.* 41, 9971–9987. <https://doi.org/10.1523/JNEUROSCI.0378-21.2021>.
- Wang, M.Q., Hao, Y., Wang, R.R., Guo, H., He, J., Wang, Z.R., 2020. Is being born in spring significantly associated with early-onset bipolar affective disorder? A case-control study. *Chronobiol. Int.* 37, 1644–1649. <https://doi.org/10.1080/07420528.2020.1764013>.
- Watson, A.J., Harrison, L., Preti, A., Wykes, T., Cella, M., 2022. Cognitive trajectories following onset of psychosis: a meta-analysis. *Br. J. Psychiatry.* 221 (6), 714–721. <https://doi.org/10.1192/bjp.2022.131>. PMID: 36149012.
- Wechsler, D., 1997. Wechsler Adult Intelligence Scale-Third Edition and Wechsler Memory Scale—Third Edition Technical Manual. San Antonio, TX. <https://doi.org/10.1037/149755-000>.
- Wegelius, A., Pankakoski, M., Lehto, U., Suokas, J., Häkkinen, L., Tuulio-Henriksson, A., Lönnqvist, J., Paunio, T., 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 Res.* 205, 18–24. <https://doi.org/10.1016/j.psychres.2012.08.026>.
- Wendel, B., Papiol, S., Andlauer, T.F.M., Zimmermann, J., Wiltfang, J., Spitzer, C., Senner, F., Schulte, E.C., Schmauß, M., Schaupp, S.K., Reppe, J., Reininghaus, E., Reimer, J., Reich-erkelenz, D., Opel, N., Nenadić, I., Meinert, S., Konrad, C., Klöhn-Saghatolislam, F., Kircher, T., Kalman, J.L., Juckel, G., Jansen, A., Jäger, M., Heilbronner, M., von Hagen, M., Gade, K., Figge, C., Fallgatter, A.J., Dietrich, D.E., Dannowski, U., Comes, A.L., Budde, M., Baune, B.T., Arolt, V., Angheluescu, I.G., Anderson-Schmidt, H., Adorjan, K., Falkai, P., Schulze, T.G., Bickelböller, H., Heilbronner, U., 2021. A genome-wide association study of the longitudinal course of executive functions. *Transl. Psychiatry* 11, 1–8. <https://doi.org/10.1038/s41398-021-01510-8>.
- Willette, A.A., Lubach, G.R., Knickmeyer, R.C., Short, S.J., Styner, M., Gilmore, J.H., Coe, C.L., 2011. Brain enlargement and increased behavioral and cytokine reactivity in infant monkeys following acute prenatal endotoxemia. *Behav. Brain Res.* 219. <https://doi.org/10.1016/j.bbr.2010.12.023>.
- Wittchen, H.-U., Zaudig, M., Fydrich, T., 1997. *Strukturiertes Klinisches Interview für DSM-IV (SKID-I und SKID-II)*. Göttingen, Germany.
- Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. *Br. J. Psychiatry* 133, 429–435. <https://doi.org/10.1192/bjp.133.5.429>.
- Zhou, H., Peng-Li, D., Chen, J., Sun, D., Wan, B., 2023. Early life climate and adulthood mental health: how birth seasonality influences depressive symptoms in adults. *BMC Public Health* 23. <https://doi.org/10.1186/s12889-023-15145-5>.