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Winter birth: A factor of poor functional outcome in a Swiss early psychosis cohort

Romeo Restellini [a,b,c], Philippe Golay [a,g], Raoul Jenni [b], Philipp S. Baumann [a], Luis Alameda [a,d,e], Larissa Allgäuer [b], Pascal Steullet [b], Lilith Abrahamyan Empson [a], Nadir Mebdouhi [a], Kim Quang Do [b], Philippe Conus [a], Daniella Dwir [b], Paul Klauser [b,f,*]

[a] Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[b] Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[c] Service of Emergency Medicine, Department of Acute Medicine, Geneva University Hospitals, Geneva, Switzerland
[d] Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College of London, London, UK
[e] Centro Investigacion Biomedica en Red de Salud Mental (CIBERSAM), Instituto de Biomedicina de Sevilla (IBIS), Hospital Universitario Virgen del Rocio, Departamento de Psiquiatria, Universidad de Sevilla, Sevilla, Spain
[f] Service of Child and Adolescent Psychiatry, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[g] La Source School of Nursing, HES-SO University of Applied Sciences and Arts Western Switzerland, Lausanne, Switzerland

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ABSTRACT

Objective: Winter birth has consistently been identified as a risk factor for schizophrenia. This study aimed to determine whether individuals born during this season are also at higher risk for early psychosis and whether this is associated with distinct functional and clinical outcomes.
Methods: We conducted a prospective study on 222 patients during their early phase of psychosis in Switzerland, nested in the Treatment and Early Intervention in Psychosis (TIPP) cohort. We compared the birth trimesters of these patients with those of the general Swiss population. Additionally, we evaluated the Global Assessment of Functioning scale (GAF) and the Positive and Negative Syndrome Scale (PANSS) scores among patients born in winter (January to March) versus those born during the rest of the year during a three-year follow-up period.
Results: A significantly higher proportion of patients experiencing early psychosis were born in winter compared to the general Swiss population. Patients born in winter had significantly lower GAF scores at 6 months, 24 months, and 36 months of follow-up, compared to patients born during the rest of the year. They also manifested fewer positive symptoms, as indicated by the PANSS positive subscale.
Conclusion: Birth in winter appears to be associated with a lower functional outcome and potentially distinct symptomatology in the early phase of psychosis.

1. Introduction

With a lifetime risk of 1 % (McGrath et al., 2008; van der Werf et al., 2014), schizophrenia represents the third cause of disability in adolescents and young adults, after unipolar depressive disorders and road traffic accidents (Gore et al., 2011). Schizophrenia classically unfolds through a prodromal phase followed by a first psychotic episode (Agius et al., 2010). Because psychotic symptoms can be seen in other psychiatric disorders, diagnosis is often difficult early in the disorder, leading to great diagnosis instability during the first years after a first psychotic episode. Schizophrenia represents however the most frequent diagnosis ten years after a first admission for psychosis (Bromet et al., 2011).

Season of birth has been repeatedly identified as a risk factor for schizophrenia (Coury et al., 2023; Davies et al., 2020, 2003; Hsu et al., 2021), with many studies reporting a higher rate of schizophrenia in patients born in winter, particularly in the non-tropical northern hemisphere (Coury et al., 2023; Davies et al., 2020, 2003). The first trimester of the year has been identified as the period with the higher risk for schizophrenia (Mortensen et al., 1999), but also for schizotypy (Konrath et al., 2016). Interestingly, the seasonality of birth in

* Corresponding author at: Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.
E-mail address: Paul.Klauser@unil.ch (P. Klauser).

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schizophrenia exists in both hemispheres (Coury et al., 2023), but with a stronger effect in the northern hemisphere and a magnitude related to latitude (Davies et al., 2003).

Schizophrenia etiopathology likely results from a combination of genetic, epigenetic and environmental risk factors (Alameda et al., 2022; Karl and Arnold, 2014) affecting the brain years before the onset of psychotic symptoms (Rapoport et al., 2012). Studies on animal models have shown that environmental stressors such as hypoxia, nutritional deficiency, maternal stress and maternal immune challenge impact normal brain development and alter the behavioral phenotype of the offspring (Ali et al., 2019; Gundacker et al., 2023; Takada et al., 2016). Malnutrition and infection during gestation affect neuronal proliferation and differentiation as well as synaptic maturation (Schmitt et al., 2014; Vasistha and Khodosevich, 2021). For instance, increased ventricular CSF and decreased grey matter in specific brain regions of patients were associated with high level of maternal IL-8 during pregnancy (Ellman et al., 2010). These brain development alterations seem to be partly mediated by the neuroimmune system and by oxidative stress (Dowell et al., 2019), affecting in particular parvalbumin interneurons (Allgäuer et al., 2023; Callahan et al., 2013; Komitova et al., 2013; Steullet et al., 2017), which are notably sensitive to oxidative stress and whose impairment are a hallmark of schizophrenia (Hardingham and Do, 2016; Lewis et al., 2012). Interestingly, delivery complications, nutritional deficits, maternal stress and infectious agents during pregnancy have all also been described as early environmental risk factors for schizophrenia (Davies et al., 2020). These environmental risk factors seem at least to partly explain the seasonality of birth in schizophrenia (Robinson et al., 2023).

Birth in winter is associated with a higher risk of schizophrenia, but little is known about the clinical evolution of patients born in this period of the year (Coury et al., 2023; Davies et al., 2020, 2003). Poor clinical evolution in schizophrenia is associated with several parameters including male sex, early disease onset (Meltzer et al., 1997), long duration of untreated psychosis (Golay et al., 2023) and poor premorbid adaptation (Caspi et al., 2007). Previous studies have reported an association between winter birth and possible indicators of poor prognosis, such as increased risk of treatment resistance (Kim et al., 2017), lower anthropometric measures (Garcia-Rizo et al., 2024), and lower income status (Cheng et al., 2013). An association between winter birth and a measure of global functional outcome has not yet been explored in a prospective study. Identifying different trajectories in early psychosis could help targeting treatment and early intervention for this frequent and often life-changing mental illness (Ramain et al., 2022).

In this study we first assessed the association between psychosis onset and birth in winter. We then assessed the clinical evolution of early psychosis patients and compared those born in winter with those born during the rest of the year. We hypothesized that within an early psychosis cohort, birth in winter would be more frequent than during the rest of the year, and that those born in winter have a poorer outcome, both functionally and clinically, in comparison to patients born during the rest of the year.

2. Material and methods

2.1. Participants

Treatment and Early Intervention In Psychosis Program (TIPP) is a specialized early psychosis program in Lausanne (Switzerland), implemented since 2004 at the Department of Psychiatry of Lausanne University Hospital (Baumann et al., 2013). Patients presenting with a psychotic episode reaching the psychosis threshold as defined by the Comprehensive Assessment for At Risk Mental States (CAARMS) (Yung et al., 2005), aged between 18 and 35 years old, and living in Lausanne catchment area are invited to take part in the TIPP. Patients who have received antipsychotic medication for more than 6 months, who have an intoxication or organic-brain disease induced psychosis or who have an intellectual quotient of less than 70 are referred to other psychiatric follow-ups.

This study is nested in the TIPP three years prospective follow-up cohort. To assess the effect of seasonality of birth on prognosis over the 36-month period, patients who were not born in Switzerland or who had a final diagnosis of short-lasting psychosis (schizophreniform disorder or brief psychotic episode) were excluded from these analyses.

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Canton of Vaud (CER-VD; protocol #2020–00272). The data of all patients were used in the study if the latter did not explicitly object to the use of their data for research purposes. Only four patients refused the use of their clinical data for research.

2.2. Control population

For the part of this study exploring the association between early psychosis and winter birth, birth dates of patients were compared to the Swiss population as listed by the Swiss national statistical office (Office fédéral de la statistique, 2023). The control population was limited to years of birth corresponding to the TIPP cohort.

2.3. Clinical assessments and outcomes

All patients included in the TIPP are fully assessed at baseline and a specifically designed questionnaire – the TIPP Initial Assessment Tool (Service of General Psychiatry, 2021) – is completed for every patient. Data are collected on demographic characteristics (including date of birth), past medical history, symptoms, and level of functioning, as well as premorbid level of functioning. A psychiatrist and a case manager are assigned to each patient and offer a 3-year follow-up with regular interactions. During this period, patients have more than a hundred instances of contact with a multidisciplinary team, including their case managers but also with their psychiatrist and psychologist. Formal follow-up assessments are carried out at 2, 6, 12, 18, 24, 30 and 36 months, exploring various aspects of treatment, evolution of psychopathology and functional level. This consists of functional and clinical scales, including the Global Assessment of Functioning scale (GAF) (Jones et al., 1995) and Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987). Diagnosis results from an expert consensus discussed at 18 and 36 months, based on the DSM-IV criteria using the information from medical reports from treating psychiatrists, as well as from the TIPP-assigned psychiatrist and case manager.

2.4. Statistical analysis

Patients were classified in one of the four trimesters of the year, according to their month of birth: January to March, April to June, July to September and October to December. Birth rate by trimester was then compared between patients and the Swiss population, and tested using a goodness of fit test.

Patients were then categorized in two groups: those born in the winter (January to March) and those born during the rest of the year (April to December). Mixed effects models repeated measures analysis of variance (MMRM) was used to determine group differences over time (0, 2, 6, 12, 18, 24, 30 and 36 months) on the GAF. Time was introduced as a within-group factor and birth period as a between-groups factor. MMRM is advantageous because it includes all existing data in the model, without imputation or substitution of missing data. All existing data comprise the model.

Multiple linear regression was performed to assess effect of birth in winter on GAF at program discharge (36 months) while adjusting for variables known to be clinically relevant: sex, age at psychosis onset, duration of untreated psychosis and premorbid adaptation (Caspi et al., 2007; Meltzer et al., 1997). Premorbid adaptation was assessed with the Cannon-Spoor's Premorbid Adjustment Scale (Shapiro et al., 2009).

A mean value of all available PANSS was calculated over the 36 months of follow-up and compared between patients born in winter and patients born during the rest of the year. Because average PANSS scores deviated from normality, we used a non-parametric approach and a Mann-Whitney test was used to assess significance.

Finally, patients were categorized again into four groups according to their birth trimester (January to March, April to June, July to September and October to December). GAF at program discharge (36 months) was compared between these four groups. Group differences were assessed with an ANOVA.

All available data was used for each patient. All tests were done using Stata software, version 14.2 (Statacorp). Statistical significance was set at $\alpha = 0.05$.

3. Results

3.1. Participants

Among the 474 patients with a first episode psychosis followed at the TIPP program, 222 met inclusion criteria: 216 were not born in Switzerland, 8 had an unrecorded place of birth, and 30 had a final diagnosis of short-lasting psychosis (schizophreniform disorder or brief psychotic disorder). Baseline clinical and sociodemographic data are outlined in Table 1. A total of 2,465,903 birth dates were included from the Swiss general population with years of birth corresponding to the patients group included in this study (1971 to 2001).

3.2. Seasonality of a first episode psychosis

Birth rate in the early psychosis cohort was the highest in the winter (first trimester of the year, i.e. January to March) and the lowest in the third trimester (July to September), in contrast with the birth distribution of the Swiss population (Fig. 1). This difference was statistically significant ($p = 0.029$).

3.3. Seasonality and clinical outcome

Clinical evolution as measured with the GAF score was markedly different between patients born in the winter compared to the rest of the year (Fig. 2). The GAF score was lower at all time points for patients born in winter, with a significant difference over the 36 months follow up ($p = 0.026$). Difference for individual time-points was statistically significant at 6 months ($p = 0.012$), 24 months ($p = 0.043$) and 36 months ($p = 0.018$), but not at inclusion ($p = 0.056$). Post hoc analysis with schizophrenia only diagnosis revealed no group difference ($p = 0.051$).

A time-response pattern related to the season of birth was observed. GAF at program discharge (36 month) was the lowest for patients born in the first trimester, and increased progressively in the second trimester to reach the highest functioning for patients born in third trimester and then declined again in the fourth trimester (Fig. 3). Difference between groups (trimesters) was statistically significant ($p = 0.042$).

Simple linear regression showed a strong association between birth in winter and lower GAF at program discharge (36 months, $p = 0.018$, $r^2 = 0.035$). When adjusted for other variables classically associated with a poorer outcome (sex, age at psychosis onset, duration of untreated psychosis and premorbid adaptation) this association remained significant ($p = 0.018$).

On average and over the 36 months of follow up and despite a lower level of global functioning, patients born in winter had less positive symptoms as measured with the PANSS ($p = 0.016$) while there was no association with negative symptoms for these patients.

Table 1
Patients' characteristics by season of birth (winter vs rest of the year).

	Birth in winter ($N = 65$)	Birth rest of the year ($N = 157$)	p value
Sex, male, % (n)	72 (47)	70 (110)	0.74
Age at psychosis onset, year, m (SD)	23 (4.67)	22 (4.77)	0.28
Age at inclusion, year, m (SD)	24 (4.10)	24 (4.60)	0.94
Days of untreated psychosis, m (SD)	332 (593)	524 (959)	0.13
Premorbid adjustment scale, m (SD)	0.33 (0.15)	0.32 (0.17)	0.82
Socio-economical level, % (n)			0.10
Low	52 (34)	37 (58)	
Intermediate	35 (23)	49 (77)	
High	12 (8)	14 (22)	
Regular cannabis use, % (n)	48 (31)	40 (63)	0.30
Diagnosis at program discharge, % (n)			
Schizophrenia	64.62 (42)	64.33 (101)	0.76
Schizoaffective disorder	12.31 (8)	8.92 (14)	
Mood disorder with psychotic features	13.85 (9)	14.65 (23)	
Psychosis NOS	9.23 (6)	12.10 (19)	

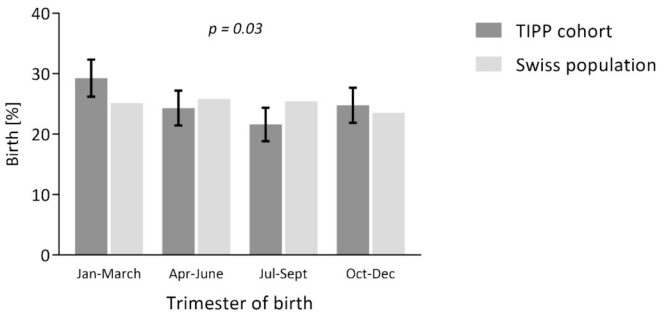

Fig. 1. Distribution of birth by trimester in the TIPP cohort compared with Swiss population.
Bars depicts proportion of birth of the TIPP cohort (dark grey) and Swiss population (light grey), with standard error of the mean. Comparison using Goodness of fit test.

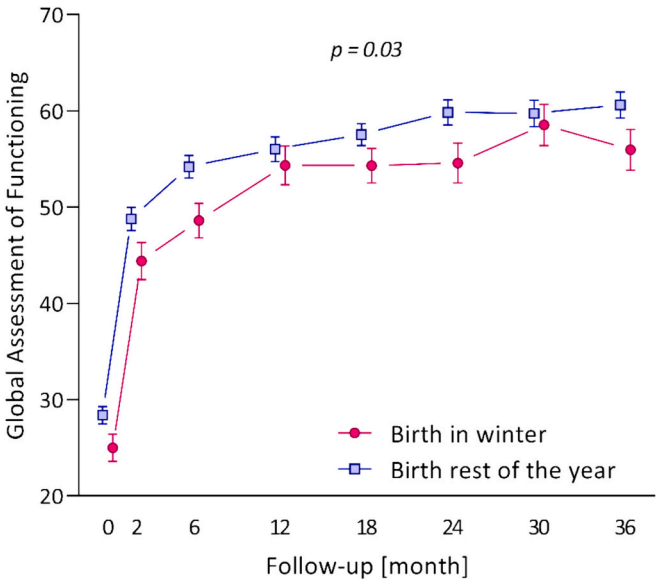

Fig. 2. GAF over the 36 months follow-up in patients born in winter (January to March, pink round dots) compared with patients born during the rest of the year (April to December, blue square dots). Means are shown with standard error. Comparison using a mixed model for repeated measures. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

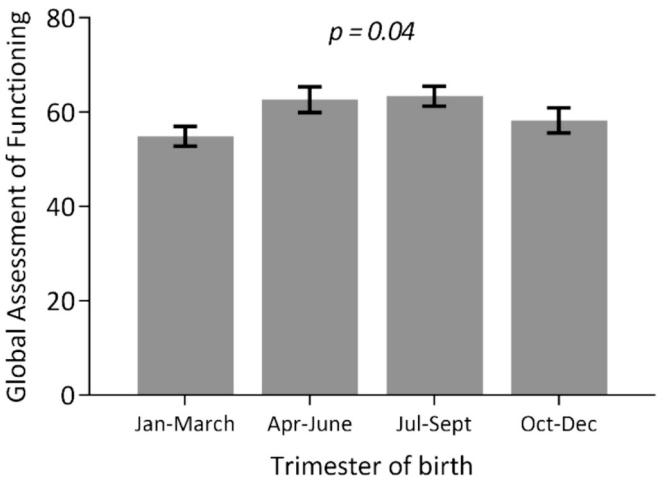

Fig. 3. GAF at the end of TIPP (36 months) by trimester of birth.
Bars depicts GAF at 36 months with standard error of the mean. Comparison using ANOVA.

4. Discussion

Season of birth is a highly replicated risk factor for schizophrenia (Davies et al., 2020, 2003; Hsu et al., 2021), but little evidence exists on long-term effects of this risk factor on patients' outcome (Kim et al., 2017). In this study, we first observed that birth in winter was more frequent in our cohort than in the general population. This supports the hypothesis that birth in winter is associated with a higher risk of early psychosis. Second, we showed for the first time that birth in winter is associated with a poorer functional outcome in the early phase of psychosis. The magnitude of this poorer outcome over the course of the year was stronger as births approached winter and was independent of other known factors of poor prognosis such as age of onset, male sex, duration of untreated psychosis and premorbid adaptation. Moreover, patients born in winter seemed to exhibit a different pattern of symptoms with less positive symptoms despite a lower level of functioning.

Schizophrenia is a clinical syndrome that may result from different etiologies (Arnedo et al., 2015). Excess of birth in winter might be related to a discrete disease subtype with its specific etiology, with different mechanisms and their related risk factors specific to a time of the year. Our study adds to this hypothesis, identifying a specific group of patients with a poorer prognosis and a different pattern of symptoms, which may display specific brain alterations induced by environmental stressors occurring during or shortly after pregnancy.

Infections during pregnancy have been suspected to be responsible for the association between the season of birth and the risk for schizophrenia (Al-Haddad et al., 2020), notably maternal exposure to herpes simplex virus 2, *Toxoplasma gondii*, cytomegalovirus and influenza virus (Cheslack-Postava and Brown, 2022). In line with our study, maternal infection is also associated with affective psychosis (Rodriguez et al., 2021). Interestingly, one of the most robust association is severe maternal infection (that warrants hospital admission), including with a bacterial agent (Cheslack-Postava and Brown, 2022). Infectious agents might directly affect the fetus, but also trigger a pro-inflammatory cytokine response with subsequent neuroinflammation (Brown and Meyer, 2018; Conway and Brown, 2019). To add to this hypothesis, elevated maternal C-reactive protein, a serum protein related to inflammation, has been shown to be associated with higher risk of schizophrenia in the offspring (Canetta et al., 2014). Infection related autoimmunity might also be involved in the schizophrenia pathophysiology, as for example with influenza infection during pregnancy affecting NMDA receptor via molecular mimicry (Kępińska et al., 2020). As most viral infections occur in winter, one would expect winter birth association with early psychosis to result from a third trimester insult. It remains however unclear what period of pregnancy is most at risk. Early studies pointed to second trimester infection for influenza (Wright et al., 1995) but more recent meta-analysis did not confirm this timing (Davies et al., 2020), most reporting infection or maternal immune activation without a clear gestational timing (Brown and Meyer, 2018). Interestingly, babies born in winter show indeed a different inflammatory profile than babies born in summer (Thysen et al., 2016).

The effect of season of birth on schizophrenia might as well be related to the seasonality of procreation in parents at risk for psychosis in their offspring. In a Swedish population, there was a higher rate of birth in winter in both patients with schizophrenia and their unaffected siblings (Karlsson et al., 2019). However, this effect does not account for the magnitude of the seasonality of birth in schizophrenia (Suvisaari et al., 2001).

This study has limitations. First, the goodness of fit Chi-squared test used to assess the difference of season of birth between the early psychosis cohort and the general population is not the most robust statistical test to explore seasonality. We only used raw data of the control population and classified birth by trimester. Further studies should confirm this association, and more generally the effect of seasonality with a dedicated statistical design, such as a Cosinor model. Second, the size of the sample limited the statistical power which was not sufficient to properly explore the association between the season of birth and PANSS scores: only a subgroup of patients was assessed and the difference in symptomatology was significant only for positive symptoms. Importantly, our cohort did not only include patients with schizophrenia, but also patients with early psychosis that may later evolve towards mood disorders. Our observation of an association between season of birth and outcome in different type of psychosis might also shed light on common etiological processes that encompass multiple psychiatric diagnoses. Further studies should investigate in greater detail and with a larger sample the role of diagnosis. Moreover, despite the care of our multidisciplinary teams to make a correct diagnosis, it is possible that the diagnosis may evolve after 3 years of follow-up in the TIPP program. Our sample might also not be perfectly representative as it does not include all early psychosis patients: our cohort is based on a public program in a catchment area and some early psychosis patients might get access to treatment elsewhere, such as in private practice. However, taking into consideration the local health system, this would likely represent only a very small proportion of early psychosis patients. Finally, socioeconomic level, or other demographic difference that were not reported in the control population, might also play as a confounding factor in the association of winter birth with risk of early psychosis.

In conclusion, this study supports the effect of seasonality on the development of early psychosis and points to a discrete and easily identifiable subgroup of patients with a poorer prognosis and a different pattern of symptoms. Hypotheses for this effect exist, but more work is needed to better understand its etiology and neurobiological mechanisms. Identifying discrete subgroups of psychotic patients with distinct pathophysiological processes will be critical for a better understanding of this highly debilitating mental illness (Arnedo et al., 2015). If these mechanisms are better understood, seasonality of birth could be implemented as a new variable for early identification of patients at risk of early psychosis or for multimodal prognosis models, and may also provide new opportunities for very early intervention, including during pregnancy.

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CRediT authorship contribution statement

Romeo Restellini: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Philippe Golay:** Writing - review & editing, Methodology, Validation. **Raoul Jenni:** Writing – review & editing, Investigation. **Philipp S. Baumann:** Writing - review & editing, Investigation. **Luis Alameda:** Writing – review & editing, Investigation. **Larissa Allgäuer:** Writing – review & editing, Conceptualization. **Pascal Steullet:** Writing – review & editing, Investigation. **Lilith Abrahamyan Empson:** Writing – review & editing, Investigation. **Nadir Mebdouhi:** Writing – review & editing, Investigation. **Kim Quang Do:** Writing – review & editing, Resources. **Philippe Conus:** Writing - review & editing, Supervision, Conceptualization, Resources. **Daniella Dwir:** Writing – review & editing, Supervision, Conceptualization. **Paul Klauser:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

None.

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