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Seasonality of presentation and birth in catatonia

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ABSTRACT

Background: Catatonia is a neuropsychiatric syndrome associated with both psychiatric disorders and medical conditions. Understanding of the pathophysiology of catatonia remains limited, and the role of the environment is unclear. Although seasonal variations have been shown for many of the disorders underlying catatonia, the seasonality of this syndrome has not yet been adequately explored.

Methods: Clinical records were screened to identify a cohort of patients suffering from catatonia and a control group of psychiatric inpatients, from 2007 to 2016 in South London. In a cohort study, the seasonality of presentation was explored fitting regression models with harmonic terms, while the effect of season of birth on subsequent development of catatonia was analyzed using regression models for count data. In a case-control study, the association between month of birth and catatonia was studied fitting logistic regression models.

Results: In total, 955 patients suffering from catatonia and 23,409 controls were included. The number of catatonic episodes increased during winter, with a peak in February. Similarly, an increasing number of cases was observed during summer, with a second peak in August. However, no evidence for an association between month of birth and catatonia was found.

Conclusions: The presentation of catatonia showed seasonal variation in accordance with patterns described for many of the disorders underlying catatonia, such as mood disorders and infections. We found no evidence for an association between season of birth and risk of developing catatonia. This may imply that recent triggers may underpin catatonia, rather than distal events.

1. Introduction

Catatonia is a severe neuropsychiatric syndrome that includes motor, behavioral and neurovegetative symptoms and signs. Described by Kraepelin as a subtype of schizophrenia (Fink et al., 2010), it is today considered as a specifier of mental disorders, or associated with non-psychiatric conditions (American Psychiatric Association, 2013). Catatonia has been reported in 10 % of patients admitted to psychiatric wards (Fink et al., 2010), and in 80 % of cases is thought to be caused by a primary psychiatric disorder (Oldham, 2018). The main psychiatric illnesses associated with catatonia are mood disorders (unipolar depression, bipolar depression and mania), schizophrenia, postpartum psychosis, and autism (Solmi et al., 2018). In 20 % of cases, a catatonic syndrome has been observed in patients suffering from non-psychiatric conditions (Oldham, 2018; Solmi et al., 2018), such as metabolic alterations, infections, inflammatory conditions, structural abnormalities or trauma to the central nervous system (CNS), and intoxication with various drugs or substances of abuse (Oldham, 2018). However, inflammation of the CNS seems to be one of the main causes of catatonia in patients without a history of psychiatric disorders, either of an infective or auto-immune etiology (Rogers et al., 2019). As for autoimmune causes, a large spectrum of autoimmune disorders has been

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described, including anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis (Rogers et al., 2019). Similarly, catatonia has been recently defined as a "red flag" for the suspicion of autoimmune encephalitis in patients presenting with (almost) isolated psychotic symptoms (Pollak et al., 2020). Therefore, catatonia can be considered as a transdiagnostic syndrome across various neuropsychiatric etiologies, and seems to represent an intersection between psychiatry, neurology, immunology and infectious diseases medicine.

Regarding the epidemiology of catatonia, findings are still controversial. According to some authors (Mahendra, 1981; Tanskanen et al., 2021), a decline in the prevalence of catatonia over several decades has been evident, this being attributed to various hypotheses, including earlier and better treatment of underlying disorders, better hospital conditions, and less exposure to "catatoniogenic infections", such as poliomyelitis. However, according to a recent meta-analysis (Solmi et al., 2018), catatonia is not a rare syndrome, and its prevalence has been estimated around 9.2 % among inpatient populations, this being stable across several years (1935–2017). Finally, a recent large study by Rogers et al., 2021 (Rogers et al., 2021) found an incidence of 10.6 catatonic episodes per 100,000 person-years, with cases increasing between 2007 and 2016, possibly as a result of improved diagnosis and use of novel psychoactive drugs. Overall, catatonia is still underdiagnosed by clinicians and often confused with other conditions (Walther et al., 2019).

The relationship between catatonia and potential environmental external triggers e.g., infectious diseases or antipsychotic-induced catatonia, is gaining research interest (Hirjak et al., 2021; Rogers et al., 2019), but still little is known about the environmental factors playing a role in its pathophysiology and clinical course. Interestingly, regardless of the underlying disorder, catatonia usually responds well to specific treatments, including benzodiazepines (lorazepam in particular) and electro-convulsive therapy (ECT). In 80 % of cases, lorazepam is an effective treatment (Solmi et al., 2018). When catatonia persists in spite of high doses of benzodiazepines, electro-convulsive therapy (ECT) should be considered (Pelzer et al., 2018). Catatonia treatment does not depend on the underlying disorder, which clearly suggests some common pathophysiological mechanisms for the syndrome.

Environmental factors have a major role in psychiatry, as they are potentially modifiable events, thus a target for prevention. One of the first environmental features to be studied in medicine and thus psychiatry is the effect of seasons on diseases. Physicians identified that the incidence of some disorders was not equally distributed over the year (Fisman, 2007). For example, seasonal variations have been studied for infectious, cardiovascular and rheumatologic diseases (Fisman, 2007; Iikuni et al., 2007; Stewart et al., 2017). Two main categories of studies published in the literature exist on the relationship between seasons and psychiatric disorders.

The first includes studies focusing on the presentation of psychiatric symptoms. Here, we can cite the striking examples of studies on seasonal affective disorder, where depressive phases are more likely to occur in winter (Partonen and Lönnqvist, 1998), and bipolar disorder, where manic symptoms are more likely to be experienced during summer and depressive phases during winter (Geoffroy et al., 2014). More generally, the number of psychiatric admissions in hospitals has also been studied across seasons, showing consistent results in different countries. In particular, rates of admissions for psychiatric reasons seem to be significantly higher during summer, when temperatures are higher (Chan et al., 2018; Geoffroy and Amad, 2016; Hinterbuchinger et al., 2020; Nori-Sarma et al., 2022; Yoo et al., 2021).

The second category of studies around seasonality concerns the association between season of birth and the subsequent development of psychiatric disorders. One of the most replicated associations is the increased risk of developing schizophrenia among people born in (late) winter and (early) spring (Castrogiovanni et al., 1998; McCutcheon et al., 2020; Puthota et al., 2021; Radua et al., 2018). The earliest description of this effect seems to date back to 1929 (Hare et al., 1974; Tramer, 1929). Subsequently, several studies have been conducted and have replicated these results in different countries and across different years (Boyd et al., 1986; Castrogiovanni et al., 1998; Wang and Zhang, 2017). The effect of season of birth on mental illness has also been evaluated for other psychiatric disorders, such as eating disorders, bipolar disorders and suicidal behaviors (Boyd et al., 1986; Döme et al., 2010; Liang et al., 2018; Salib and Cortina-Borja, 2006). Neurobiologically, the association between season of birth and the subsequent development of psychiatric conditions should be interpreted in the light of the neurodevelopmental hypothesis of mental illness, as seasons may reflect differential exposure to environmental factors during the prenatal and perinatal stages of CNS development. Some of the exposures that are thought to be involved include infections, low levels of vitamin D, temperature, weather conditions, maternal diet and exposure to toxins (Puthota et al., 2021; Salib and Cortina-Borja, 2006; Watson et al., 1984).

As described above, previous literature provided numerous findings on the relationship between seasons and psychiatric disorders. However, to our knowledge there are no major studies evaluating the effect of seasons on catatonia. A previous study on 31 children in India evaluated the seasonal pattern of the presentation of catatonia, describing fewer cases from November to January and in April (Gupta et al., 2017). Another study on 59 patients with catatonia suffering from schizophrenia in Croatia explored the effect of season of birth, but did not find any significant seasonal patterns (Mimica et al., 1996). However, as previous studies on the relationship between season of birth and schizophrenia found associations with a modest effect size, studies including a large population are likely to be necessary to identify a significant association between season of birth and catatonia (McCutcheon et al., 2020).

Therefore, the objective of this study is to explore for the first time the seasonality of catatonia in a large sample. In particular, we hypothesize that 1) seasonal variations might exist for the presentation of catatonia during the year and 2) season of birth might represent a risk factor for subsequent development of catatonia. We hypothesised that seasonality in the presentation of catatonia might exist, considering its association not only with psychiatric disorders that have shown seasonal patterns, but also with infections. Similarly, we speculated that season of birth may predict the risk of catatonia, as the neurodevelopmental approach has already shown interesting results for psychiatric disorders that can cause catatonia. Finally, a seasonal pattern in the presentation of catatonia and/or an effect of season of birth would provide important insights into the mechanisms and risk factors of this still poorly understood psychomotor syndrome.

2. Methods

2.1. Setting, participants and study design

Data from the Clinical Records Interactive Search (CRIS) system, from the South London and Maudsley NHS Foundation Trust, UK, were used for this retrospective cohort and case-control study. CRIS allows researchers to access anonymized health-care records (Fernandes et al., 2013; Stewart et al., 2009), registered or imported since 1999, for patients being referred to specialist mental health services in four South London boroughs (Lambeth, Southwark, Lewisham and Croydon) and in national and specialist services also run by the Trust. The South London and Maudsley NHS Foundation Trust provides mental health services for a total local population of 1.3 million people, offering inpatient as well as community care (Fernandes et al., 2013; Rogers et al., 2021). CRIS currently contains data on electronic records for over 500,000 subjects (Rogers et al., 2021).

A cohort of patients suffering from catatonia was identified retrospectively through CRIS as described previously (Dawkins et al., 2022; Jeyaventhan et al., 2022; Rogers et al., 2021; Yeoh et al., 2022). In brief, a natural language processing service was used to identify catatonic

episodes. Then, records obtained with the natural language algorithm were analyzed manually, to ensure that identified episodes satisfied the inclusion criteria. The following inclusion criteria were established for this study: 1) a diagnosis of catatonia made by a clinician; 2) evidence of at least two features of catatonia according to the Bush-Francis Catatonia Screening Instrument (BFCSI) (Bush et al., 1996a, 1996b); 3) available date for the diagnosis of the catatonic episode; and 4) a time interval not longer than 30 days between date of onset of catatonia and the date of inclusion in the health-care records.

While the initial data extractions were performed between 2018 and 2021 (Rogers et al., 2021), two complementary data extractions were performed on 06/06/2022 and 09/06/2022, not modifying the number of patients included, but adding additional variables for seasonality analyses, such as number of total admissions by month, for all psychiatric disorders in the South London and Maudsley NHS Foundation Trust, from 2007 to 2016, and country of origin for patients included in the study.

A control group obtained from CRIS was used in this study including all patients admitted as psychiatric inpatients to the hospitals of the South London and Maudsley NHS Foundation Trust between 01/01/2007 and 31/12/2016. The control group included a large variety of psychiatric disorders, with patients' ages ranging from childhood to old age. To compare patients with catatonia and patients from the control group, and to minimize the percentage of missing data, the years' range from 2007 to 2016 was applied to all subjects included in this study (Rogers et al., 2021). The aim of the inclusion of this control group was to compare season of birth between patients with catatonia and patients suffering from a wide range of psychiatric disorders, without any catatonic symptoms.

Psychiatric diagnoses were classified according to the International Classification of Diseases, Tenth Revision (ICD-10) (World Health Organization, 2004). The total population living in the four boroughs of London included in CRIS, by month, from 2007 to 2016 was obtained from the Office for National Statistics (ONS). Data on mean temperatures by month in London, from 2007 to 2016, were obtained from London City Airport weather station.

The presentation of catatonia across seasons was explored using a cohort study design. The effect of month of birth on the subsequent development of catatonia was explored using both a cohort and a case-control study design.

All procedures used in this project comply with the ethical standards of National and Institutional Committees on Human Experimentation and follow the Declaration of Helsinki — Ethical principles for medical research involving humans. The use of CRIS system has been approved by the Oxfordshire C Research Ethics Committee (ref: 18/SC/0372) and this project was approved by the CRIS Oversight Committee (ref: 17-102) (Rogers et al., 2021).

2.2. Statistical analysis

First, descriptive analyses were conducted, summarizing socio-demographic factors and clinical characteristics such as age, gender, ethnicity, country of origin and psychiatric diagnoses. Patients with catatonia were compared to the control group by fitting logistic regression models, without adjustments. The odds ratio for age was calculated using age in decades. Missing data were handled using pairwise deletion and conducting available-case analyses.

2.2.1. Catatonia presentation — cohort study

Seasonal variation for the presentation of catatonia was analyzed using a Cosinor model, which expresses seasonal patterns as harmonic functions (Cox, 2006; Stolwijk et al., 1999). Regression models for count data (Poisson or negative binomial regression according to whether data exhibited overdispersion) were fitted to assess the potential effect of months on the frequency of catatonic episodes. Adjustment for year of presentation was included. The dispersion of count data was assessed using a likelihood-ratio test for equidispersion, testing the null hypothesis that mean equals variance ($p > 0.05$). Frequencies were standardized to 31-day months. For any episodes that occurred on 29th February, these were amended to 28th February, to standardize the length of February. When patients had more than one episode, only the first catatonic episode was included. The total population between 2007 and 2016, for the four London boroughs included in CRIS was used to calculate the rate of catatonic episodes by month. The logged total population was also included in the model as an offset term. Days of the months were transformed into angles from 0 to 2π, then trigonometric terms were created using *sine* and *cosine* functions. Seasonal patterns were modelled using yearly, semesterly and quarterly harmonics, to obtain sufficiently complex variations. A stepwise-type model selection procedure was used to build the final model, minimizing Akaike's information criterion (AIC). Both AIC and, for nested models, likelihood-ratio tests were used to choose the final model. Post-estimation analyses were performed for the models' diagnostics where appropriate, including analysis of residuals and exploration of influence. After the main model was fitted, sensitivity analyses were performed, including in the model the total number of admissions by month in psychiatric hospitals from the South London and Maudsley NHS Foundation Trust from 2007 and 2016, and the average monthly temperature in London. A likelihood-ratio test was then performed to compare this larger model, with a nested model not including the trigonometric terms.

2.2.2. Season of birth — cohort and case-control study

To explore the role of month of birth on the risk of developing catatonia, a Poisson or negative binomial regression was fitted, according to whether data exhibited overdispersion. The dispersion of count data was assessed using a likelihood-ratio test for equidispersion. The model was adjusted for year of birth, and an offset term was used to account for the different length of months. Post-estimation analyses were performed for the models' diagnostics where appropriate. After fitting this main model, the analyses were repeated in a subgroup of patients born in countries above and not crossing the Tropic of the Cancer.

Regarding the case-control study, a logistic regression was fitted to assess the effect of month of birth on subsequent development of catatonia. The model was adjusted for year of birth, gender, and ethnicity. After fitting the main regression, the analyses were repeated in the subgroup of patients born in countries above and not crossing the Tropic of the Cancer.

Statistical analyses were conducted on Stata MP 15.1. Statistical significance was set to $p < 0.05$. STROBE guidelines (von Elm et al., 2014) were applied to write this manuscript, and the checklist is showed in Supplementary Material (Table A1). Some of the graphical representations were finalized on Microsoft Excel LTSC MSO Version 2204.

3. Results

A sample of 955 patients with catatonia was obtained for this study, from 1st January 2007 to 31st December 2016. Overall, 58.74 % of patients were diagnosed as having catatonia in hospital, 35.18 % were initially diagnosed in an outpatient setting and 6.07 % were missing this information. A sample of 23,409 inpatients suffering from psychiatric disorders, without any diagnosis of catatonia, was included as a control group. Table 1 describes and compares the demographic and clinical characteristics of patients with and without catatonia. Patients with catatonia were significantly younger (OR 0.89, $p < 0.001$, 95 % CI 0.86–0.93) and more likely to belong to an ethnic minority group (OR from 2.58 [95 % CI 1.95–3.40] to 3.60 [95 % CI 3.11–4.17]). Patients with catatonia were more likely to be born in Africa, Asia and North America, compared to psychiatric patients not suffering from catatonia (OR from 2.16 [95 % CI 1.59–2.95] to 3.03 [2.46–3.73]). In terms of the underlying disorder, patients with catatonia were less likely to suffer from mood disorders (ICD-10 codes F30–F39) (OR 0.43, $p < 0.001$, 95 %

Table 1
Socio-demographic and clinical characteristics of patients with and without catatonia.

	Patients with catatonia n = 955	Patients without catatonia n = 23,409	Odds ratio (95 % CI) unadjusted analysis	*p*-Value
Age, mean (SD)	36.6 (16.5)	39.8 (17.1)	**0.89 (0.86–0.93)***	**<0.001**
Median (range, IQR)	33 (7–90, 23–47)	38 (5–100, 27–49)		
Not stated	n = 0	n = 3		
Sex, n (%)				
Female	445 (46.6)	10,709 (45.8)	1 (reference)	–
Male	510 (53.4)	12,697 (54.2)	0.97 (0.85–1.10)	0.61
Not stated	0 (0.0)	3 (0.0)		
Ethnicity, n (%)				
White	315 (33)	14,488 (61.9)	1 (reference)	–
Black/African/ Caribbean/Black British	451 (47.2)	5762 (24.6)	**3.60 (3.11–4.17)**	**<0.001**
Asian/Asian British	74 (7.7)	1206 (5.2)	**2.82 (2.18–3.66)**	**<0.001**
Mixed/Multiple ethnic groups	35 (3.7)	567 (2.4)	**2.84 (1.98–4.07)**	**<0.001**
Other ethnic groups	63 (6.6)	1125 (4.8)	**2.58 (1.95–3.40)**	**<0.001**
Not stated	17 (1.8)	261 (1.1)	–	–
Continent of origin, n (%)				
Europe	334 (35)	11,825 (50.5)	1 (reference)	**–**
– United Kingdom	– 268 (80.2)	– 10,103 (85.4)		
Africa	133 (13.9)	1553 (6.6)	**3.03 (2.46–3.73)**	**<0.001**
Asia	48 (5.1)	785 (3.4)	**2.16 (1.59–2.95)**	**<0.001**
North America	43 (4.5)	607 (2.6)	**2.51 (1.81–3.48)**	**<0.001**
South America	9 (0.9)	189 (0.8)	1.69 (0.86–3.32)	0.131
Oceania	2 (0.2)	59 (0.2)	1.20 (0.29–4.93)	0.8
Not stated	386 (40.4)	8391 (35.9)	–	–
BFCSI score, mean (SD) **Median (range, IQR)**	3.6 (1.7) 3 (2–14, 2–5)	Not applicable	–	–
Diagnostic subgroup, n (%)				
Schizophrenia and related disorders (F20–F29)	481 (50.4)	5464 (23.3)	1 (reference)	–
Mood disorders (F30–F39)	188 (19.7)	5017 (21.4)	**0.43 (0.36–0.51)**	**<0.001**
Non-psychiatric mental disorder (F00–F09 & non-F codes)	42 (4.4)	1255 (5.4)	**0.38 (0.28–0.52)**	**<0.001**
Neurodevelopmental disorders (F70–F90 & F95)	34 (3.6)	496 (2.1)	0.78 (0.54–1.12)	0.173
Neurotic disorders (F40–F49)	45 (4.7)	2242 (9.6)	**0.23 (0.17–0.31)**	**<0.001**
Personality and behavioral disorders (F50–F69 & F91–F94, F98)	22 (2.3)	1494 (6.4)	**0.17 (0.11–0.26)**	**<0.001**
Substance use disorders (F10–F19)	27 (2.8)	4254 (18.2)	**0.07 (0.05–0.11)**	**<0.001**
Not stated (missing or F99)	116 (12.1)	3.187 (13.6)	**–**	–

* Odds ratio calculated using age in decades. Text in bold indicates statistical significance.

CI 0.36–0.51), non-psychiatric mental disorders (ICD-10 codes F00–F09 & non-F codes) (OR 0.38, $p < 0.001$, 95 % CI 0.28–0.52), neurotic disorders (F40–F49) (OR 0.23, $p < 0.001$, 95 % CI 0.17–0.31), personality and behavioral disorders (F50–F69 & F91–F94, F98) (OR 0.17, $p < 0.001$, 95 % CI 0.11–0.26) and substance use disorders (F10–F19) (OR 0.07, $p < 0.001$, 95 % CI 0.05–0.11).

3.1. Catatonia presentation — cohort study

Fig. 1 shows the incidence of catatonic episodes per million person-years, in South London, from 2007 to 2016. The monthly rate of first catatonic episodes is showed as a line with several peaks across years, while the straight line running in the middle of the graph represents the fitted values for the monthly rate, and shows an increase of the incidence from 2007 to 2016.

Regarding the Cosinor model, we obtained a final Poisson model, including a yearly harmonic component (sin*1*, incidence rate ratio [IRR] = 1.097, $p = 0.042$, 95 % CI 1.003–1.199) and a semesterly harmonic component (sin*2*, IRR = 1.15, $p = 0.002$, 95 % CI 1.050–1.254). The model was adjusted for year of presentation, showing a significant increase of 3.9 % in the annual risk of catatonia, from 2007 to 2016 (IRR = 1.039, $p = 0.001$, 95 % CI 1.016–1.062). The likelihood-ratio test for equidispersion found Poisson to be the best model to fit (Chi-squared value = 0.56, $p = 0.227$, d.f. = 1). Similarly, residuals were found to be normally distributed with a constant variance (Fig. A1, in Supplementary Material), confirming the appropriateness of the systematic part of the Poisson model. To look for potentially influential observations, Cook's distances were calculated. No influential observations were found (all distances <0.5). However, when the most influential observations were excluded, the model did not show any significant changes.

Fig. 2 shows the final Cosinor model, with its predictions, compared to the observed frequencies of catatonic episodes, by month and by year, standardized to 31-day months. Observed frequencies are represented using a stacked area chart. The model predicted a first peak of episodes around February, and a secondary peak of cases around August. A trough of catatonic episodes appeared around November. According to the predictions made by this model, the month of February showed a 50 % increased risk of catatonic cases, compared to November, while the month of August showed a 32 % increased risk of catatonic cases, compared November. The month of February showed a 14 % increased risk of catatonic cases, compared to August.

Sensitivity analyses were conducted adding to the main model the global number of admissions by month, in the psychiatric hospitals from the South London and Maudsley NHS Foundation Trust, from 2007 to 2016, and the average monthly temperature in London, for the same ten-year period. The likelihood-ratio test compared this larger model, with a nested model not including the trigonometric terms. The model including the trigonometric terms provided statistical evidence for an improvement in the fit (Chi-squared value = 11.12, $p = 0.004$, d.f. = 2).

3.2. Season of birth — cohort study

The same cohort of patients with catatonia (n = 955) was used to explore the effect of season of birth on subsequent development of catatonia. Fig. 3 shows the frequency of births aggregated by month and year (1921–2007), for patients developing catatonia later in life. All frequencies were standardized to 31-day months.

To explore the effect of season of birth on subsequent development of catatonia, a negative binomial regression model was fitted. The model was standardized for year of birth and an offset term was used to account for the different length of every month. No evidence was found for an effect of month of birth on subsequent development of catatonia (IRR 0.98, $p = 0.147$, 95 % CI 0.961–1.006). The likelihood-ratio test for equidispersion found the negative binomial regression to be the best model to be fitted (Chi-squared value = 73.14, $p < 0.001$, d.f. = 1).

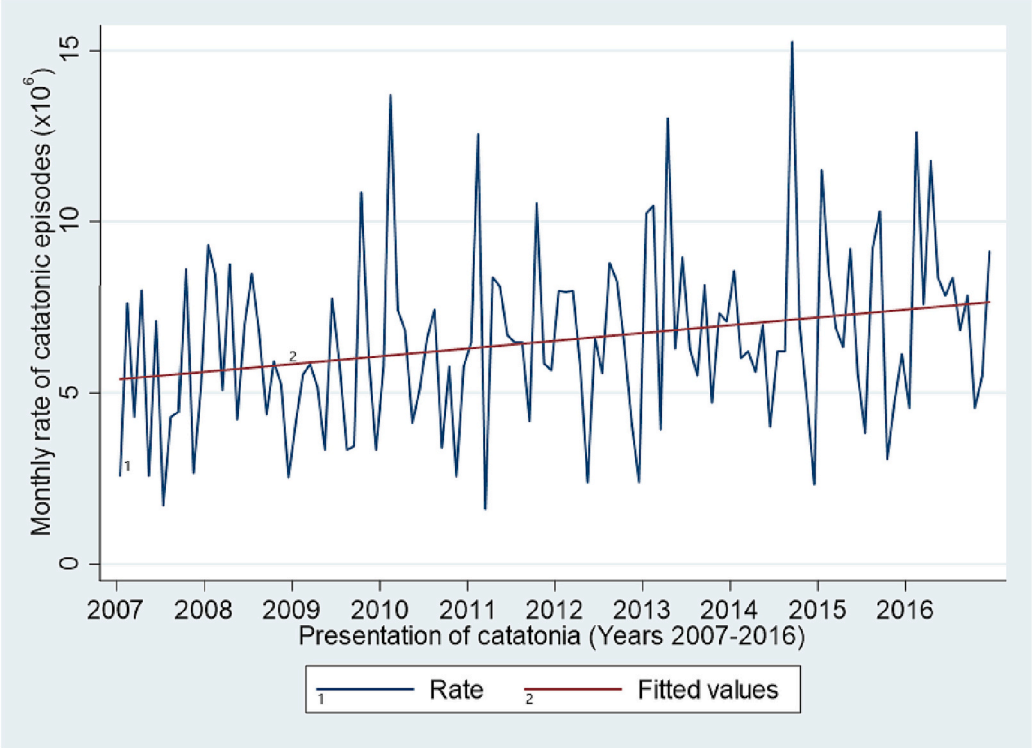

Fig. 1. Monthly rate of first catatonic episodes per million people, from 2007 to 2016.

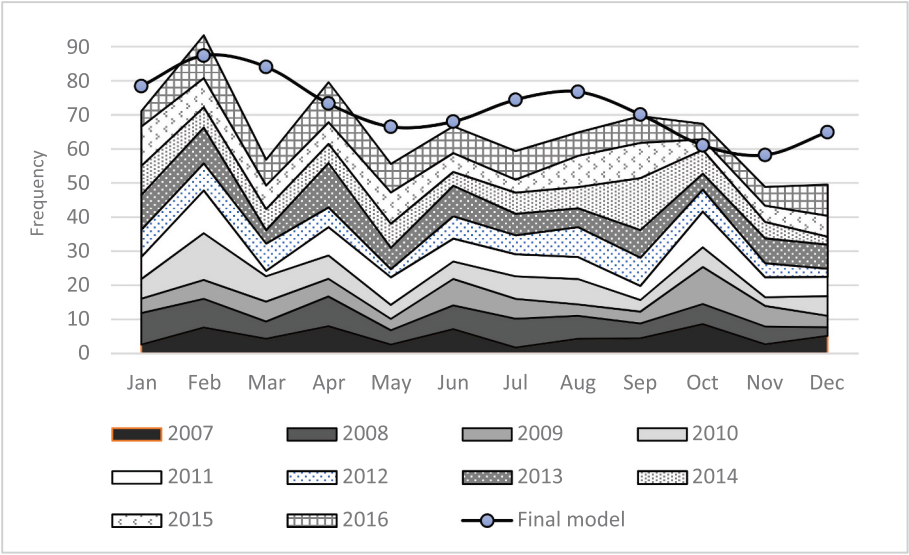

Fig. 2. Graphical representation of the predictions obtained with the Cosinor model, compared to the observed frequencies of catatonic episodes, by month and year, standardized to 31-day months. Observed frequencies are represented using a stacked area chart.

Residuals were found to be distributed following a clear pattern (Fig. A2, in Supplementary material), as the outcome count contained a small number of unique variables. However, the negative binomial regression model had smaller residuals compared to the Poisson model, indicating a better fit. To look for potentially influential observations, Cook's distances were calculated. No influential observations were found (all distances were lying under 0.5). However, when the most influential observations were excluded, the model did not show any significant changes.

After fitting this main model, the analyses were repeated in a subgroup of patients being born in countries above and not crossing the Tropic of the Cancer, to obtain a more homogeneous sample in terms of characteristics of the seasons. This subgroup sample of patients with catatonia consisted of 359 patients (37.6 % of the initial sample). Similarly to the main analyses, a negative binomial regression was fitted and showed no evidence for an effect of month of birth on later development of catatonia (IRR 0.97, $p = 0.10$, 95 % CI 0.94–1.01).

3.3. Season of birth — case-control study

For the case-control section of this study, a logistic regression model was fitted to evaluate the association between month of birth and later

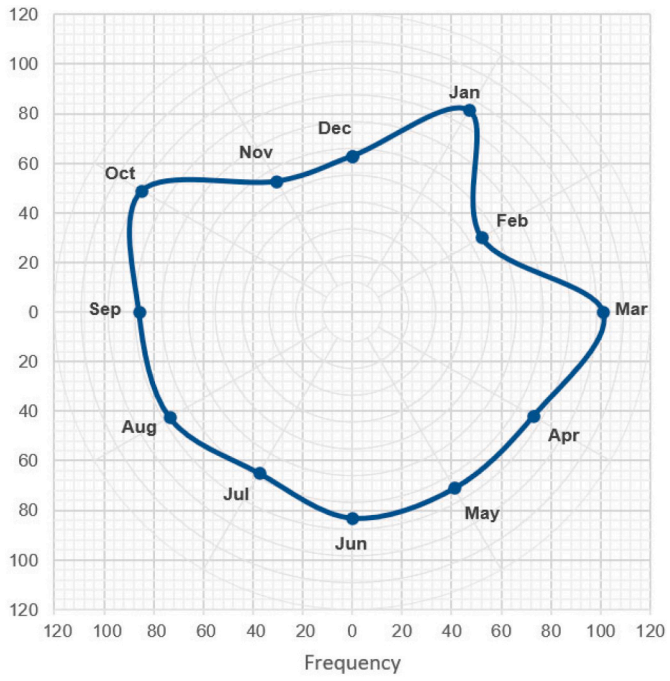

Fig. 3. Polar plot showing the frequency of births aggregated by month and year (1921–2007)

development of catatonia, adjusting for gender, ethnicity, and year of birth. No evidence for an effect of month of birth was found in developing catatonia (OR 0.99, $p = 0.463$, 95 % CI 0.974–1.011). When focusing the analyses on patients with catatonia (n = 359) and controls (n = 12,243, 52.3 % of the initial control group) born in countries above and not crossing the Tropic of the Cancer, a similar logistic regression found no evidence for an effect of month of birth on later development of catatonia (OR 0.99, $p = 0.396$, 95 % CI 0.957–1.018).

4. Discussion

To our knowledge, this study was the first one to explore the seasonality of catatonia in a large sample of patients. Both season of onset of the catatonic syndrome and the effect of season of birth for patients with catatonia were studied.

Regarding the seasonality of presentation in catatonia, a first peak of cases was described around February. Based on frequencies of catatonia by month from 2007 to 2016, our model predicted increasing cases from early winter to late winter. Then, a smaller peak was observed around August, with cases increasing throughout the summer.

The interpretation of seasonal disease patterns is complex and multifactorial. Approximately 20 % of our catatonic sample had a diagnosis of mood disorders, thus the increased number of catatonic episodes at the end of winter and during summer could be related to exacerbations of depression or mania — with catatonia as a common end-point. Similarly, the summer peak of catatonia could be related to more psychiatric consultations, as described in the literature during periods of high temperatures (Nori-Sarma et al., 2022). However, our analyses included the total number of admissions for psychiatric reasons in South London, and suggested this was not explaining our findings.

Low and high temperatures can affect brain functioning through various mechanisms. High temperature can act as an exogenous stressor, altering the permeability of the blood-brain barrier and modify neuronal activity (Wang et al., 2014). Through the activation of heat shock proteins (HSP), hyperthermia also has a pronounced pro-inflammatory effect, which might play a role in psychiatric disorders (Miller and Fort, 2018; Sonna et al., 2002). Heat can then be considered as an external stressor with a cytotoxic effect, derived by DNA damage, apoptosis, protein oxidation and lipid peroxidation (Belhadj Slimen et al., 2014). Moreover, psychiatric disorders have been associated with the activity of Transient Receptor Potentials (TRP) channels, which can be activated by different stimuli, including temperature (Nazıroğlu and Demirdaş, 2015). Cold can also trigger cellular stress responses, modifying the gene expression of some specific HSP, and activating cold-induced apoptosis (Sonna et al., 2002). However, the effect of cold temperatures on mental health is less studied, and findings are still controversial, including both protective and harmful outcomes (He et al., 2022; Li et al., 2022; Mullins and White, 2019). Interestingly, autonomic and thermoregulatory alterations can occur in severe forms of catatonia, suggesting that these patients may be particularly susceptible to extreme temperatures, that usually happen in winter and summer. Another reason that could link altered thermoregulation and catatonia may be related to patients treated with antipsychotics to target the underlying condition. Antipsychotic drugs can alter thermoregulatory processes and metabolism, and represent a risk factor for the neuroleptic malignant syndrome, which can be considered as a cause of malignant catatonia. In our study, mean monthly temperature was included in the analyses, which suggested it was not explaining our findings. However, mean temperature did not capture the impact of extremely high and low temperatures.

Infections are another environmental factor that could explain the seasonal pattern of catatonia. In fact, various pathogens have been described as a cause of catatonia (Rogers et al., 2019). A recent study analyzing seasonal patterns of infections in England and Wales, found a seasonality for most of the pathogens included, with higher rates in winter and end of summer (Cherrie et al., 2018).

Furthermore, catatonia has been associated with autoimmune disorders and immune dysregulation (Rogers et al., 2019). Interestingly, human immunity showed seasonal patterns in terms of gene regulation and inflammatory response. Recent studies have suggested that the immune activity may be more pro-inflammatory during winter in Europe, with levels of C-Reactive Protein, Interleukin-6, and different peripheral blood mononuclear cells, such as neutrophils and lymphocytes, being significantly higher during the winter months (Dopico et al., 2015; Wyse et al., 2021). Finally, one of the most common autoimmune etiologies of catatonia is anti-NMDAR encephalitis. A few studies have evaluated a potential seasonal pattern in this condition and have shown evidence for peaks in the warm season (Adang et al., 2014; Lai et al., 2021).

A previous study conducted in India on 31 children has also described a seasonal pattern in the presentation of catatonia, with fewer cases in November–January and in April (Gupta et al., 2017). However, a direct comparison with our findings might be difficult, considering the different climatic seasons as well as the different cultural and sociodemographic characteristics of the populations included.

Regarding the effect of month of birth on subsequent development of catatonia, we did not find any evidence for an association. Month of birth did not predict the development of catatonia, both in the whole population included and in patients being born exclusively in countries above and not crossing the Tropic of the Cancer. Similarly, patients with catatonia and controls did not show significant differences in terms of month of births. The effect of season of birth on the development of illnesses later in life is to be interpreted using a neurodevelopmental perspective, where prenatal, perinatal and early postnatal factors might play a role in generating disease vulnerability. If an effect of month of birth has been shown for schizophrenia, such an effect could not be replicated for movement disorders that share with catatonia some common pathophysiological pathways, such as Parkinson's disease (Gardener et al., 2010; Palladino et al., 2015; Postuma et al., 2007).

Similarly to our findings, a previous study conducted in Croatia on 59 patients suffering from catatonic schizophrenia did not provide any evidence for an effect of season of birth (Mimica et al., 1996). However, it is important to note that catatonia is not a frequent condition and that even our sample was probably not powerful enough to identify an effect

of month of birth on the development of the condition.

4.1. Strengths, limitations, perspectives

To our knowledge, this study was the first to explore, in a large and ecological sample, the seasonality of catatonia, focusing on both season of presentation and effect of month of birth. In terms of sampling variation and chance, the large number of patients included in this study was likely to reduce the sampling error. Furthermore, we did not perform repeated tests, reducing the risk that our results were due to chance. In terms of selection bias, patients with catatonia were included using a standardized, rigorous and validated screening tool. The use of this tool depends on the physicians' clinical practice, potentially leading to underestimation of catatonic episodes in our study, but this is unlikely to differ across seasons. The inclusion of a large control group of inpatients allowed us to compare month of birth between patients with catatonia and patients suffering from psychiatric disorders without catatonia. Nevertheless, the inclusion of both inpatients and outpatients in the catatonic group is to be considered as a limitation, as it may represent a bias in terms of severity of catatonia, when compared to inpatient controls. However, it is likely that patients diagnosed with catatonia as outpatients are rapidly transferred to hospital to receive optimal treatment, which would mean still being classified as outpatients in CRIS. A measurement bias could result from a different latency between onset of catatonia and recognition of catatonia, but this is unlikely to be more than a few days, considering the severity of this syndrome. As for confounders, adjustments for gender, ethnicity and year of birth were conducted where appropriate. Data on prescribed medication were not available in our sample, which represents a limitation.

In terms of the methods, one of the main strengths of this study was the use of a Cosinor model, a specific statistical tool that allows the analysis of seasonal patterns using sinusoidal waves, as previously performed by other authors (Barnett and Dobson, 2010; Cox, 2006; Fisman, 2007; Stolwijk et al., 1999). In fact, although a large number of published studies have used Chi-squared tests to explore the seasonality of various phenomena, aggregating data by month or seasons (Hinterbuchinger et al., 2020; Liang et al., 2018; Suhail and Cochrane, 1998), these tests often do not detect efficiently the complexity of seasonal patterns (Salib and Cortina-Borja, 2006; Stolwijk et al., 1999). However, in our study, the use of a Cosinor model was not possible to explore the effect of month of birth on later development of catatonia, where a regression for count data without trigonometric terms was used instead. This was due to the unavailability of data on the total number of births by month, for the general population, between 1921 and 2007. As a matter of consistency with the previous section of the study, a first general exploratory analysis was performed to assess the effect of month of birth on the development of catatonia. Then, a subgroup was identified according to the country of birth. Although country of origin might perfectly reflect only the perinatal stages of CNS development, we consider it as a legitimate approximation for both prenatal, perinatal and postnatal life in most of the patients, and the Tropic of Cancer was chosen to identify more homogenous seasons in terms of weather conditions. However, the season of birth section of this study should be interpreted with caution in the light of these methodological limitations.

Future studies should try to replicate our findings focusing on births from a single country, where seasons might be more homogeneous in terms of weather conditions and social behaviors. This would also allow the use of a Cosinor model, where the total number of births by month could be included, to control for variations in the pattern of births for the general population (Borja and Haigh, 2007). For the presentation of catatonia, future studies might include in the analyses a more complete panel of variables, including maximum and minimal temperatures, percentages of humidity, hours of sunshine, and atmospheric pressure. The hypothesis of a peak of cases caused by infections might be tested analyzing the concentrations of inflammatory markers, acute viral serologies and alterations in the white cell count for patients included. Further studies might also focus on diagnostic subgroups for the underlying disorders, and on patients that show repeated episodes of catatonia. Stratifying for gender and age could also apport interesting insights. A study from Owens and McGorry (2003), found for example that first-episode schizophrenia was showing a peak in winter, in male patients only. Unfortunately, subgroup analyses and stratification were not possible in our study, as we were limited by statistical power and sample size. To repeat the study of seasonality in these subgroups of patients, a multicentered design might be necessary to increase the number of patients included, but would then require a higher complexity of adjustment. In terms of external validity, it is important to note that seasonal factors highly differ between countries, and that the prevalence of schizophrenia and related disorders was particularly high in our sample, which could be related to the high prevalence of cannabis consumption that has been described in South London.

5. Conclusions

Catatonia is still a poorly understood syndrome in terms of etiology and pathophysiology. Studies exploring seasonality are useful epidemiological tools that can help understand the mechanisms and risk factors of diseases. In our study, we found a seasonal pattern in the onset of catatonia, showing more cases in late winter and late summer. This is in accordance with the seasonality described for many of the disorders – both psychiatric and non-psychiatric – that are often associated with catatonia, and may suggest that proximal causes are of greater importance in the manifestation of catatonia. Moreover, psychiatric clinical services might anticipate seasonal peaks of catatonic episodes, that often require specific treatment, e.g., electroconvulsive therapy. No evidence was found for an effect of season of birth on the development of catatonia, but more robust studies are needed to better explore this neurodevelopmental factor.

CRediT authorship contribution statement

This study was designed and conceived by TM, JPR and GL. TM conducted the analyses, with support from JPR, MCB, AA and GL. TM drafted the manuscript with support from JPR, MCB, AA, GL, AD and MSZ.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. TM and JPR had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of competing interest

MSZ declares honoraria for a lecture from Eisai Co., Ltd. All other authors declare no competing interests.

Data availability

Data are owned by a third party, Maudsley Biomedical Research Centre (BRC) Clinical Records Interactive Search (CRIS) tool, which provides access to anonymised data derived from South London and Maudsley electronic medical records. These data can only be accessed by permitted individuals from within a secure firewall (i.e., the data cannot be sent elsewhere), in the same manner as the authors. For more information please contact: cris.administrator@slam.nhs.uk.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.03.015.

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