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THÈSE POUR LE DIPLÔME D'ÉTAT
DE DOCTEUR EN MÉDECINE

Saisonnalité du syndrome catatonique

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Liste des abréviations

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

GABA – Gamma-Aminobutyric Acid

ADN – Acide Désoxyribonucléique

PM – Particulate Matter

CNS – Central Nervous System

NMDAR – N-Methyl-D-Aspartate Receptor

ECT – Electro-Convulsive Therapy

CRIS – Clinical Records Interactive Search

NHS – National Health Service

UK – United Kingdom

BFCSI – Bush-Francis Catatonia Screening Instrument

ICD-10 – International Classification of Diseases, Tenth Revision

ONS – Office for National Statistics

AIC – Akaike's Information Criterion

STROBE – Strengthening the Reporting of Observational Studies in Epidemiology

OR – Odds Ratio

CI – Confidence Interval

SD – Standard Deviation

IQR – Interquartile Range

n – number

IRR – Incidence Rate Ratio

d.f. – degrees of freedom

HSP – Heat Shock Proteins

DNA – Deoxyribonucleic Acid

TRP – Transient Receptor Potentials

BRC – Biomedical Research Centre

NIHR – National Institute for Health Research

SPAQ – Seasonal Pattern Assessment Questionnaire

PMSI – Programme de Médicalisation des Systèmes d'Information

Préambule

Liens d’intérêts

L’auteur de cette thèse et le Directeur de thèse déclarent n’avoir aucun lien d’intérêt.

Résumé

Contexte : La catatonie est un syndrome neuropsychiatrique sévère, notamment associé en psychiatrie aux troubles de l'humeur et à la schizophrénie. La compréhension des mécanismes physiopathologiques de la catatonie est encore limitée, et le rôle de l'environnement peu étudié. Si des fluctuations saisonnières ont été montrées pour les maladies psychiatriques associées à la catatonie, la saisonnalité de ce syndrome n'as pas encore été explorée.

Méthode : Dans cette thèse, nous avons étudié la saisonnalité de la catatonie à travers deux études originales de recherche. La première inclut une cohorte de patients catatoniques dans le sud de Londres, entre 2007 et 2016. La deuxième correspond à une étude concernant la population de l'ensemble des patients catatoniques en France métropolitaine, entre 2015 et 2022. Un modèle cosinor a été utilisé pour les analyses de saisonnalité.

Résultats : Nous avons inclus 955 patients dans le sud de Londres, et 42,893 patients en France métropolitaine. Nous avons retrouvé un effet de saisonnalité dans la présentation du syndrome catatonique, avec un premier pic d'épisodes en hiver et un deuxième pic en été. Ce pattern de saisonnalité semble particulièrement présent chez les patients catatoniques souffrant de troubles de l'humeur. Chez les patients catatoniques et schizophrènes, deux pics ont été retrouvés au printemps et en automne. Nos résultats ne mettent pas en évidence un effet du mois de naissance sur le développement d'un syndrome catatonique au cours de la vie.

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1. Introduction générale

1.1. Catatonie

La catatonie est un syndrome psychomoteur sévère, qui se présente par des signes et symptômes moteurs, comportementaux et neurovégétatifs. Initialement décrite par Kreapelin en 1899 comme un sous-type clinique de schizophrénie, on considère actuellement la catatonie comme une entité clinique et nosographique qui peut s'associer et compliquer différentes pathologies, à la fois psychiatriques et non-psychiatriques (1,2). En effet, jusqu'à 10% des patients hospitalisés en psychiatrie pourraient développer un syndrome catatonique, et dans 80% des cas une maladie psychiatrique est retrouvée comme étiologie principale (2,3). Les pathologies psychiatriques les plus fréquemment associées à la catatonie sont les troubles de l'humeur (dépression unipolaire, bipolaire et épisodes maniaques), la schizophrénie, la psychose post-partum et l'autisme (4). Des conditions non-psychiatriques sont retrouvées comme cause sous-jacente de la catatonie dans 20% des cas, parmi lesquelles on peut citer les pathologies métaboliques, les infections, les pathologies inflammatoires, les traumatismes ou affections qui touchent le système nerveux central, mais également les intoxications ou les sevrages à différentes substances (3). L'inflammation au niveau du système nerveux central, d'origine infectieuse ou immunitaire, semble être une des causes principales de catatonie chez des patients sans antécédents psychiatriques, comme décrit par exemple dans les cas d'encéphalites virales ou auto-immunitaires (5).

Le diagnostic du syndrome catatonique est clinique. Selon le Manuel Diagnostique et Statistique des Maladies Mentales (DSM-5) (1), au moins trois signes parmi les suivants sont nécessaires pour poser le diagnostic : stupeur, catalepsie, flexibilité

cireuse, mutisme, négativisme, prises de posture, maniérismes, stéréotypies, agitation, expressions faciales grimaçantes, écho-phénomènes (écholalie et/ou échopraxie).

La prise en charge de ce syndrome nécessite un examen clinique complet et un interrogatoire détaillé, ainsi qu'un bilan sanguin et une imagerie cérébrale pour exclure les principales causes non-psychiatriques. Des explorations complémentaires, e.g., ponction lombaire et électroencéphalogramme peuvent être également réalisés selon les différentes situations cliniques (6,7).

Indépendamment de l'étiologie retrouvée, le traitement de la catatonie consiste en l'administration de benzodiazépines, plus spécifiquement Lorazepam, qui serait efficace dans 80% des cas, et d'électroconvulsivothérapie en cas de non réponse (4,8). Ceci suggère que des mécanismes physiopathologiques communs seraient à la base de tout syndrome catatonique. Actuellement, on considère qu'une altération de la neurotransmission glutamatergique et GABAergique au niveau cortical provoquerait un dysfonctionnement au niveau des noyaux gris centraux, d'où les anomalies motrices du syndrome catatonique (9,10).

Concernant les données épidémiologiques, les études montrent des résultats controversés. Certains auteurs ont remarqué une diminution de la prévalence de la catatonie au cours de plusieurs décennies (11,12). Ceci pourrait être dû à une amélioration de la prise en charge et des conditions d'hospitalisations, mais également à une diminution des infections virales dans la population e.g., poliomyélite. Inversement, d'autres études ont rapporté une stabilité de la prévalence de catatonie au cours des années (9,2% chez des patients hospitalisés, entre 1935 et 2007) (4),

voire une augmentation (entre 2007 et 2016), ce qui serait lié à une meilleure détection de ce syndrome, ainsi qu'à l'utilisation de nouvelles substances psychoactives (13).

A ce jour, la compréhension des mécanismes à la base du syndrome catatonique et du rôle des facteurs environnementaux dans son développement reste très limitée, à la fois d'un point de vue physiopathologique et épidémiologique.

1.2. Saisonnalité en psychiatrie

L'impact des facteurs environnementaux dans l'étiopathogénie et physiopathologie des maladies psychiatriques a été étudié et répliqué largement au cours des dernières années (14–16). Un grand nombre de ces facteurs a été décrit, comprenant les variables socio-démographiques, familiales et les événements de vie stressants (e.g., niveau socio-économique, précarité sociale, histoire de migrations, antécédents de violences ou négligence), mais également les facteurs biologiques (e.g., infections, dénutrition, exposition à différentes substances ou toxiques au cours du neurodéveloppement) (14). Parmi les premiers facteurs de risque environnementaux explorés en médecine et en psychiatrie, on peut citer l'effet des saisons sur les fonctions physiologiques et sur les processus pathologiques (17). En effet, des variations saisonnières ont été montrées pour un grand nombre de maladies, comme par exemple des infections, des pathologies cardiovasculaires et des troubles rhumatologiques (17–19). Bien qu'il s'agisse d'un sujet de recherche de longue date en épidémiologie psychiatrique, l'impact des saisons sur la santé mentale reste un sujet d'intérêt, au vu de l'actuel débat public mondial autour des changements climatiques et du réchauffement global (20,21).

En littérature scientifique psychiatrique, il existe deux catégories principales d'études faisant le lien entre saisons et maladie mentale.

La première comprend les études portant sur la présentation des symptômes psychiatriques selon les saisons. Les troubles de l'humeur à caractéristiques saisonnières en sont l'exemple principal. En effet, de nombreuses études ont montré une prévalence augmentée des épisodes dépressifs caractérisés en hiver, et une augmentation des cas de syndrome maniaque au cours de l'été (22,23). De manière plus générale, une saisonnalité a également été montrée en considérant le nombre d'admissions à l'hôpital pour motif psychiatrique – toute pathologie confondue, avec des taux plus élevés en été, lorsque les températures augmentent (21,24–27). D'un point de vue neurobiologique, les températures peuvent agir comme un facteur de stress exogène pouvant altérer la perméabilité de la barrière hémato-encéphalique et l'activité neuronale (28). L'hyperthermie a également un effet pro-inflammatoire et cytotoxique, liés à des dommages à l'ADN, à l'activation de l'apoptose et la peroxydation lipidique, qui pourraient jouer un rôle dans l'étiopathogénie des maladies psychiatriques (29–32). Les températures influencent l'état psychique également via le sommeil (21). En effet, les saisons reflètent non seulement un changement de températures mais aussi une modification des heures de lumière, d'ensoleillement et d'humidité, facteurs qui peuvent altérer les rythmes circadiens. L'altération du sommeil et le dérèglement des rythmes circadiens ont un rôle important dans l'évolution des troubles psychiatriques, notamment le trouble bipolaire, et sont responsables de fluctuations de l'humeur, de l'anxiété et de l'irritabilité (21,33,34). Les conditions météorologiques ont également un impact sur le niveau de pollution (35). Les polluants atmosphériques principaux e.g., les particules PM 2,5, peuvent altérer le fonctionnement cérébral via l'inflammation et le stress oxydatif (35,36). L'impact de la

neuro-inflammation causée par la mauvaise qualité de l'air a été étudié dans plusieurs modèles précliniques et cliniques, dans le cadre de pathologiques neurologiques et neuropsychiatriques (36–39). Les concentrations des principaux polluants ont été également associées à plusieurs troubles psychiatriques, notamment dépression, troubles anxieux, conduites suicidaires et troubles psychotiques (35,36,40,41). Par ailleurs, l'effet des saisons sur la santé mentale ne comprend pas seulement les changements météorologiques, mais aussi une série de facteurs sociaux et culturels, e.g., les facteurs de stress liés aux périodes scolaires ou de vacances, les facteurs professionnels, les comportements et relations interpersonnelles et les conduites sexuelles qui vont modifier l'incidence des infections virales ou des maladies sexuellement transmissibles (25,42,43).

La deuxième catégorie d'études autour de la saisonnalité en psychiatrie concerne les études ayant évalué l'association entre la saison de naissance et le développement de troubles psychiatriques. Une des associations les plus répliquées dans la littérature est celle entre la naissance en fin d'hiver ou début de printemps et le risque de développer une schizophrénie à l'âge adulte (44–47). Cet effet du mois de naissance sur le risque de présenter une schizophrénie semble avoir été décrit pour la première fois en 1929 (48,49). Successivement, cette association a été reproduite sur différentes années et au sein de différents pays dans le monde (44,50,51). L'effet de la saison de naissance sur la maladie mentale a également été évalué pour d'autres troubles psychiatriques, tels que les troubles du comportement alimentaire, le trouble bipolaire et les conduites suicidaires (50,52–54). D'un point de vue neurobiologique, l'association entre saison de naissance et développement d'un trouble psychiatrique plus tard au cours de la vie doit être explorée sous une perspective neurodéveloppementale. En effet, les différentes saisons peuvent refléter l'exposition

à différents facteurs environnementaux au cours de la vie prénatale et périnatale. Dans le cas de la schizophrénie, les principales hypothèses évoquées incluent l'exposition à des infections, le manque de vitamine D, la température, le régime alimentaire de la mère et l'exposition à des toxines (45,46,55).

Comme décrit jusque-là, les études de saisonnalité peuvent représenter un outil épidémiologique utile pour explorer les mécanismes physiopathologiques et le rôle des facteurs environnementaux dans le contexte des pathologies psychiatriques. Par ailleurs, un effet de saisonnalité a été montré et décrit pour des nombreuses pathologies pouvant causer une catatonie. Cependant, à notre connaissance, il n'existe pas d'étude majeure ayant évalué l'effet des saisons sur la catatonie. Une étude sur 31 enfants en Inde a évalué la saisonnalité de présentation de la catatonie, décrivant moins de cas entre Novembre et Janvier, et au mois d'Avril (56). Une 2ème étude sur 59 patients souffrant de catatonie et schizophrénie en Croatie a exploré l'effet de la saison de naissance, sans retrouver d'effet significatif (57).

1.3. Hypothèse

L'objectif de cette thèse est d'explorer la saisonnalité de la catatonie pour la première fois sur des larges échantillons de patients. Nous formulons les hypothèses que 1) la présentation de la catatonie au cours de l'année pourrait présenter une variation saisonnière, et celle-ci pourrait différer en fonction du sous-groupe diagnostic (notamment troubles de l'humeur et schizophrénie) et 2) la saison de naissance pourrait représenter un facteur de risque pour le développement d'une catatonie au cours de la vie.

2. Thèse – Article n°1

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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.

Key words: catatonia; seasonality; seasonality of presentation; season of birth; Cosinor model.

Seasonality of presentation and birth in catatonia

2.1. 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 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.

2.2. Methods

2.2.1. 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; 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 to 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).

2.2.2. 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.

2.2.2.1. 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.

2.2.2.2. 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.

2.3. 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% 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).

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

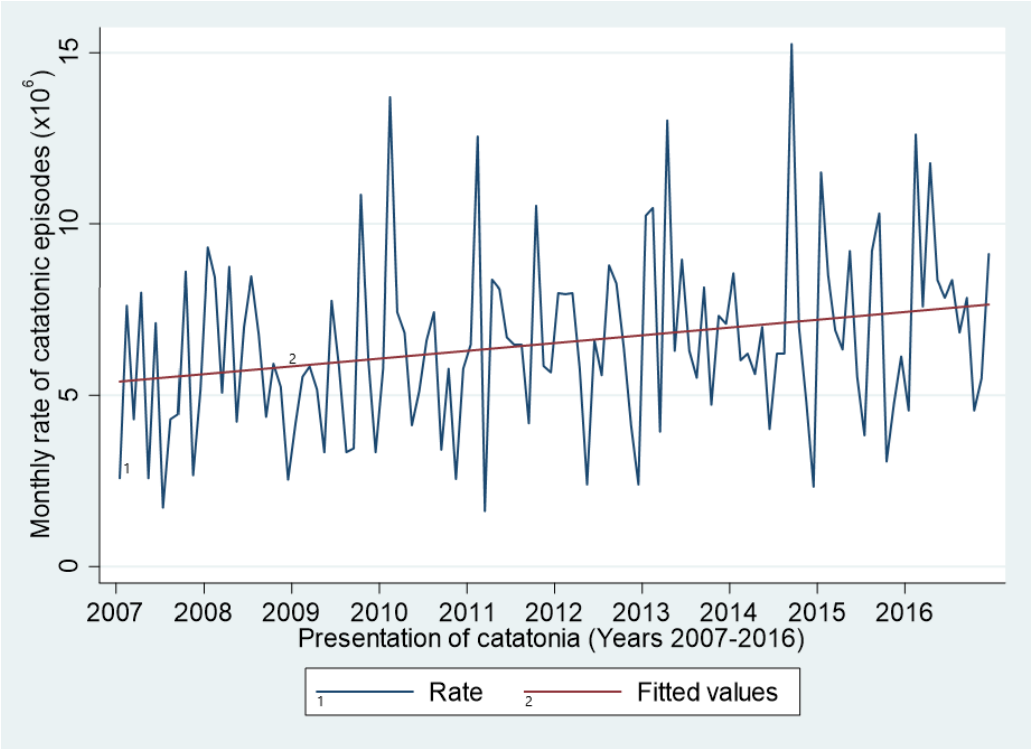
	Patients with catatonia n = 955	**Patients without catatonia n = 23,409**	**Odds Ratio (95% CI) Unadjusted analysis**	***p*-value**
Age, Mean (SD)	36.6 (16.5)	39.8 (17.1)	**0.89 (0.86-0.93) ***	**<0.001**
Median (Range, IQR)	33 (7-90, 23-47)	38 (5-100, 27-49)		
Not stated	n = 0	n = 3		
Sex, n (%)				
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)	5,762 (24.6)	**3.60 (3.11-4.17)**	**<0.001**
Asian / Asian British	74 (7.7)	1,206 (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)	1,125 (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)	1,553 (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)	8,391 (35.9)	-	-
BFCSI score, Mean (SD)	3.6 (1.7)	Not Applicable	-	-
Median (Range, IQR)	3 (2-14, 2-5)			
Diagnostic subgroup, n (%)				
Schizophrenia and related disorders (F20-F29)	481 (50.4)	5,464 (23.3)	1 (reference)	-
Mood disorders (F30-F39)	188 (19.7)	5,017 (21.4)	**0.43 (0.36-0.51)**	**<0.001**
Non-psychiatric mental disorder (F00-F09 & non-F codes)	42 (4.4)	1,255 (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)	2,242 (9.6)	**0.23 (0.17-0.31)**	**<0.001**
Personality and behavioral disorders (F50-F69 & F91-F94, F98)	22 (2.3)	1,494 (6.4)	**0.17 (0.11-0.26)**	**<0.001**
Substance use disorders (F10-F19)	27 (2.8)	4,254 (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.

2.3.1. Catatonia presentation – Cohort study

Figure 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.

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

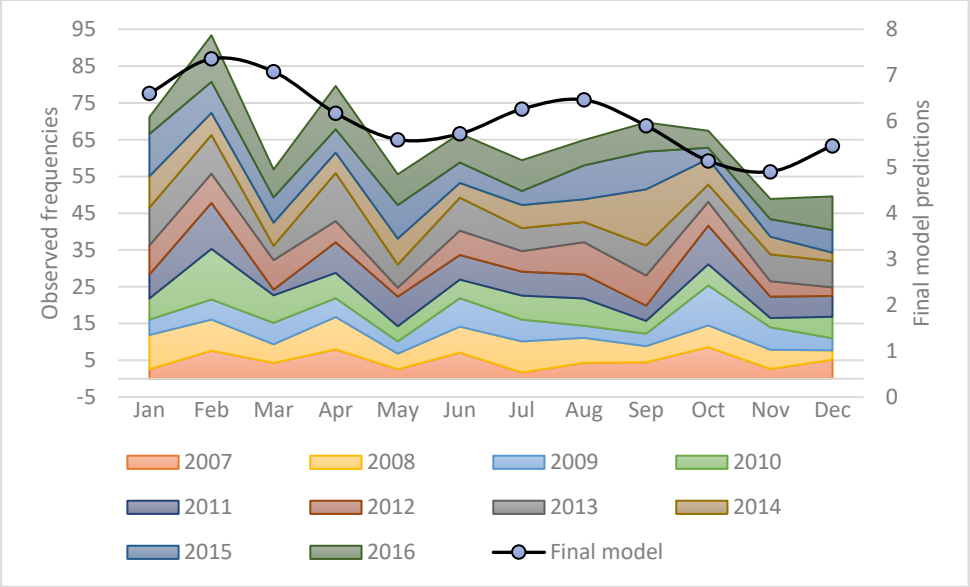


Regarding the Cosinor model, we obtained a final Poisson model, including a yearly harmonic component (sin1, Incidence Rate Ratio [IRR] = 1.097, p = 0.042, 95% CI 1.003-1.199) and a semesterly harmonic component (sin2, IRR = 1.15, p = 0.002, 95% CI 1.050-1.254). The model was adjusted for year of presentation, 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 (Figure 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 less than 0.5). However, when the most influential observations were excluded, the model did not show any significant changes.

Figure 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.

Figure 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.

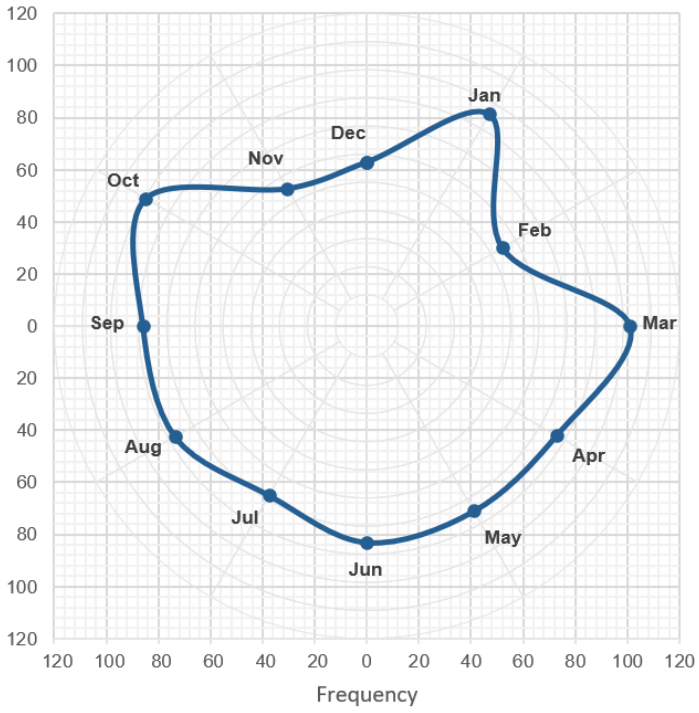


Sensitivity analyses were conducted adding to the main model the global number of admissions by month, in the psychiatric hospitals from the South London and Maudsley NHS Foundation Trust, from 2007 to 2016, and the average monthly temperature in London, for the same ten-year period. The likelihood-ratio 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).

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. Figure 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.

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



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). Residuals were found to be distributed following a clear pattern (Figure 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).

2.3.3. 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 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).

2.4. 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 socio-demographic 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 provided 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.

2.4.1. 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 to 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 (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.

2.5. Conclusions

Catatonia is still a poorly understood syndrome in terms of aetiology 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.

Data sharing statement

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.

Author contributions

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.

Declaration of interests

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

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.

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Supplementary Material

Figure A1. Pearson residuals plotted against the fitted values for the Poisson regression model

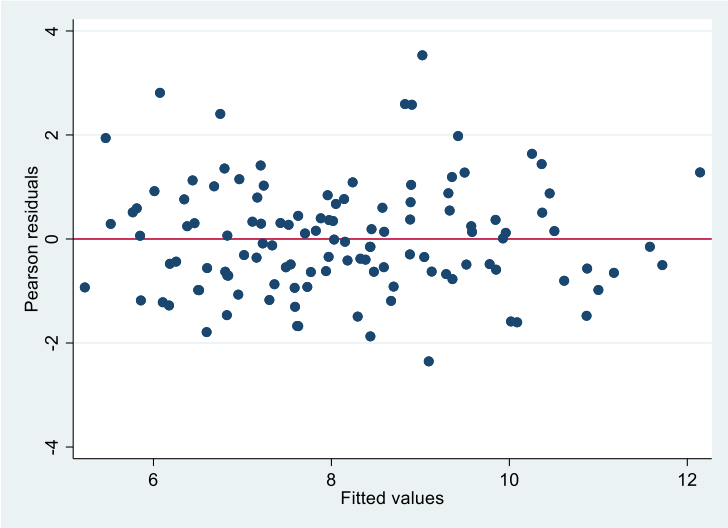

Figure A2. Pearson residuals plotted against the fitted values for the negative binomial regression model. Residuals showed a clear pattern in their distribution, as the outcome count contained a small number of unique variables. When compared to a Poisson model, residuals from the negative binomial regression model were found to be smaller, indicating a better fit.

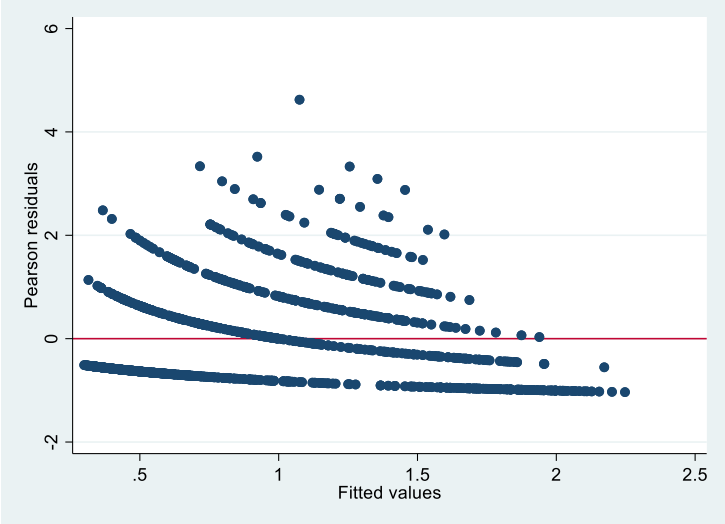

Table A1. STROBE checklist

	Item No	Recommendation	Location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction/Hypothesis
Methods			
Study design	4	Present key elements of study design early in the paper	Methods/Setting, participants and study design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods/Setting, participants and study design
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Methods/Setting, participants and study design
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not Applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods

Bias	9	Describe any efforts to address potential sources of bias	Methods
Study size	10	Explain how the study size was arrived at	Methods
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Quantitative variables left as continuous, not dichotomized.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods/Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	Not Applicable
		(*c*) Explain how missing data were addressed	Methods
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Methods
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, Table 1
		(b) Give reasons for non-participation at each stage	Methods
		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results
		(b) Indicate number of participants with missing data for each variable of interest	Results/Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time	Results/Figures
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Results/Table 1

		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results/Table 1
		(*b*) Report category boundaries when continuous variables were categorized	Not Applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion/Strengths, limitations, perspectives
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion/Strengths, limitations, perspectives
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Methods

3. Thèse – Article n°2

Exploring Seasonality in Catatonia: Evidence from a Large-Scale Population Study

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Abstract

Catatonia is a severe psychomotor syndrome, mainly associated with psychiatric disorders, such as mood disorders and schizophrenia. Seasonal patterns have been described for these psychiatric disorders, and a previous study conducted in South London showed for the first time a seasonal pattern in the onset of catatonia. In this study, we aim to extend those findings to a larger national sample of patients admitted to French metropolitan hospitals, between 2015 and 2022, and to perform subgroup analyses by the main associated psychiatric disorders. A total of 42,893 patients diagnosed with catatonia were included. A seasonal pattern for catatonia was described, using cosinor models. Four peaks of catatonic cases were described in March, June, September and December. Depending on the associated psychiatric disorder, the seasonality of catatonia differed. In patients suffering from mood disorders, peaks of catatonia were found in January and July. For patients suffering from schizophrenia, peaks of catatonia were described in March and September.

Keywords: Catatonia, catatonic syndrome, seasonality, seasons, onset of catatonia

Highlights

- Hospitalisations for catatonia in metropolitan France, from 2015 to 2022 show a seasonal pattern, with four peaks of admissions in March, June, September and December
- In patients suffering from mood disorders, admissions for catatonia were more frequent in winter and summer
- In patients suffering from schizophrenia, admissions for catatonia were more frequent in spring and autumn

Exploring Seasonality in Catatonia: Evidence from a Large-Scale Population Study

3.1. Introduction

Catatonia is a severe neuropsychiatric syndrome that includes motor, behavioral, affective and neurovegetative symptoms and signs. According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), catatonia can be diagnosed as a specifier of a mental disorder, or as associated with non-psychiatric conditions (American Psychiatric Association, 2013). In 80% of cases, catatonia is thought to be associated with psychiatric disorders, such as mood disorders or schizophrenia (Oldham, 2018). In 20% of cases, non-psychiatric conditions are found as the principal cause of catatonia, including inflammatory, autoimmune, infectious and neurodegenerative disorders, as well as traumatic or drug-related conditions (Oldham, 2018; Rogers et al., 2019; Solmi et al., 2018). In spite of the diverse etiologies of catatonia, this syndrome usually responds well to treatment. Lorazepam is used as first-line medication, and in cases of treatment-resistance, electroconvulsive therapy (ECT) is recommended (Bush et al., 1996; Solmi et al., 2018). If not recognized or rapidly treated, catatonia can lead to death via numerous complications, including infections, rhabdomyolysis, and thromboembolic phenomena (Funayama et al., 2018). The pathophysiology of catatonia is still unknown, and brain mechanisms underlying this syndrome are being studied using various neuroimaging techniques (Cattarinussi et al., 2022; Magnat et al., 2022; Walther et al., 2019). Similarly, epidemiological and clinical approaches have proven useful in elucidating the links between environmental factors and the development of catatonia (Mastellari et al., 2023; Rogers et al., 2021; Yeoh et al., 2022).

One epidemiological approach that has been used for the study of the different risk factors involved in psychiatric disorders is the analysis of seasonality (Zhang et al., 2021). Seasonality studies have largely been conducted in mood disorders and schizophrenia, allowing interesting insights into pathophysiological mechanisms and etiopathogenesis (Castrogiovanni et al., 1998; Geoffroy et al., 2014; Hinterbuchinger et al., 2020; Maruani et al., 2018; McCutcheon et al., 2020). Regarding mood disorders, for example, studies of seasonality have resulted in pathophysiological theories involving the role of circadian rhythms, core clock genes, temperature and daylight hours (Ambar Akkaoui et al., 2022; Geoffroy et al., 2015, 2014). As for schizophrenia, the role of infections during the perinatal period was suggested in the light of studies of seasonality (Watson et al., 1984). Interestingly, the role of seasonality in psychiatric disorders can also be assessed clinically, at the individual level, using psychometric instruments, such as the Seasonal Pattern Assessment Questionnaire (SPAQ) (Reynaud et al., 2021).

Although still scarce, research on seasonality of catatonia might be helpful to identify the underlying mechanisms and causes of this clinical syndrome. Moreover, for many of the disorders that can cause catatonia, a seasonal pattern has been described. In terms of psychiatric causes, studies on the seasonality of mood disorders and psychosis have been replicated several times worldwide, and have shown that seasonal patterns are associated with more severe manifestations (Bauer et al., 2021; Geoffroy et al., 2013). If we consider mood disorders, depressive phases have been described as more common during early winter, while manic phases have been found to be more frequent in early summer (Geoffroy et al., 2014, 2013; Partonen and Lönnqvist, 1998). Similarly, studies of schizophrenia have shown a seasonal presentation of psychotic symptoms during the year (Hinterbuchinger et al., 2020;

Owens and McGorry, 2003; Zhang and Volkow, 2023). Seasonality studies of other psychiatric disorders exist, but results have been far less replicated (Ambar Akkaoui et al., 2022; Geoffroy and Amad, 2016; Liang et al., 2018; Pires et al., 2022). Regarding non-psychiatric conditions, seasonal patterns are known for certain infections, as well as for the activity of the human immune system (Dopico et al., 2015; Fisman, 2007; Wyse et al., 2021), which both seem to play a role in some forms of non-psychiatric catatonia (Rogers et al., 2019).

Regarding the seasonality of catatonia, a seasonal pattern was recently described for the first time in a cohort of 955 patients, throughout ten years in South London (Mastellari et al., 2023). An initial peak of cases was found at the end of winter, and a second peak at the end of summer. It was suggested that this seasonal pattern of catatonia reflected the impact of the underlying psychiatric disorders, e.g., mood disorders, which show a similar seasonal pattern. However, no stratified analyses by the underlying disorder could be performed to confirm that hypothesis, due to insufficient statistical power and limited sample size. Moreover, the external validity was limited, as cases were limited to one geographic area.

The aim of the present study is 1) to examine for a seasonal pattern in the onset of catatonia, extending previous findings in a larger independent sample and 2) to perform subgroup analyses, stratifying by main associated psychiatric disorder (focusing on mood disorders and psychosis).

3.2. Methods

3.2.1. Database and study population

Catatonic cases were included using the French national hospitals database, *Programme de Médicalisation des Systèmes d'Information* (PMSI). This database includes all hospital admissions in the French territory. Details on the date of admission, length of stay, hospital code number and main and secondary diagnoses are registered. Principal diagnosis is usually the main reason for admission, while secondary or associated diagnoses are often related to comorbidities and more than one associated diagnosis is possible. Diagnoses are classified using the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Each patient receives a national identification number, that remains constant and unique across hospitalisations.

PMSI allows access to anonymous data, under the regulation of the national French Public Health Agency. Therefore, ethical approvals are not required when accessing this specific database (Arrêté du 19 juillet 2013; Boudemaghe and Belhadj, 2017). All procedures used in this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and follow the Declaration of Helsinki, 1975 and revised in 2008.

Hospital admissions for a diagnosis of catatonia were identified searching ICD-10 codes F061 (Catatonic disorder due to a known physiological condition), F202 (Catatonic schizophrenia) and Y495 (Medical complication of antipsychotics) as a principal or associated diagnostic code. Cases of catatonia were included between 2015 and 2022. If catatonia was identified as the principal diagnosis, underlying mental disorders were looked for as associated diagnoses. If catatonia was identified as an

associated diagnosis, underlying mental disorders were looked for in the principal or in the associated diagnoses. Underlying mental conditions were searched using the following codes: F20-F29 (Schizophrenia and related disorders), F30-F39 (Mood disorders), F00-F09 & non-F codes (Non-psychiatric mental disorder), F70-F90 & F95 (Neurodevelopmental disorders), F40-F49 (Neurotic disorders), F50-F69 & F91-F94 & F98 (Personality and behavioral disorders), F10-F19 (Substance use disorders). For this study, hospitalisations in metropolitan France only were included. Hospitalisations in the overseas departments and territories were excluded, to avoid the inclusion of hospitals where seasons are extremely different over the course of the year.

3.2.2. Statistical analyses

Descriptive analyses were performed using absolute numbers and percentages for qualitative variables and median and interquartile range (IQR) for quantitative variables.

Analyses were performed using *R* Studio version 4.4.2., and the *season* package version 0.3.15,, which examines seasonal trends using a cosinor model (Hughes, 2022). An adjusted significance level of 0.025 was used, as conducted in previous studies performing analyses of seasonality (Ambar Akkaoui et al., 2022). After identifying a seasonal pattern, a linear regression model was performed to detect peaks (with β as the coefficient). Analyses of seasonal patterns were repeated in two main diagnostic subgroups: schizophrenia or related disorders, and mood disorders, as these are considered to be disorders that are more frequently associated with catatonia (Solmi et al., 2018). For these subgroup analyses, patients suffering from both schizophrenia and mood disorders were excluded. Sensitivity analyses were

conducted, excluding the period of the COVID-19 pandemic (2020 to 2022) from the seasonality analyses. Analyses of seasonality were also performed considering hospital admissions for any psychiatric reason in metropolitan France, to look for a global seasonal pattern that might explain a seasonal pattern found for catatonia. Data extraction was performed using SAS Enterprise Guide.

3.3. Results

A total of 58,586 hospitalisations for catatonia were found between 2015 and 2022, in metropolitan France, corresponding to 42,893 unique patients. Socio-demographic and clinical characteristics of the included patients are shown in Table 1.

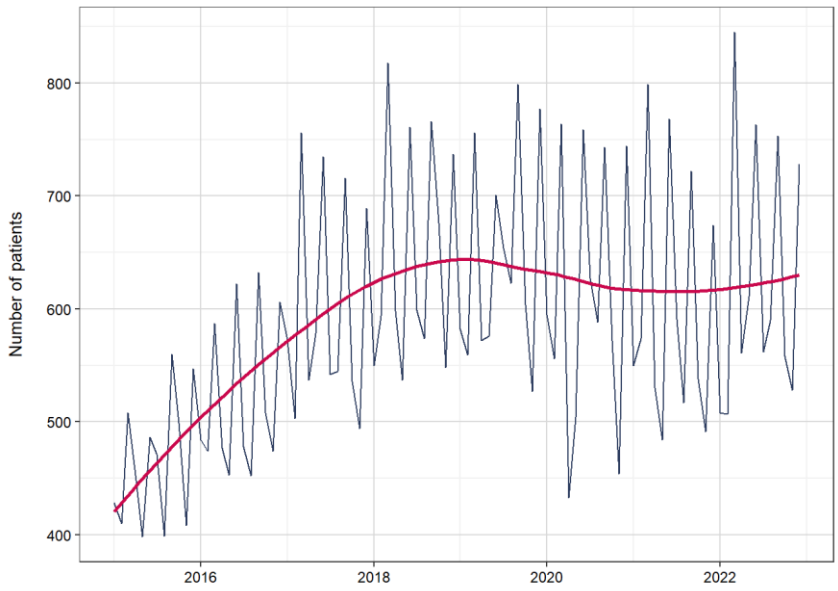
Table 1. Socio-demographic and clinical characteristics of patients with catatonia

	Number (%)*	**Age, Median (IQR)**	**Sex (Female), *n* (%)**
Catatonia	42,893 (100)	71 (55-83)	23,210 (54.1)
Diagnosis associated to Catatonia			
Mood disorders (F30-F39)	10,740 (25.0)	69 (58-79)	6,807 (63.38)
Schizophrenia and related disorders (F20-F29)	7,894 (18.4)	61 (46-72)	3,877 (49.11)
Neurotic disorders (F40-F49)	7181 (16.7)	74 (58-84)	4,625 (64.41)
Substance use disorders (F10-F19)	5066 (11.8)	56 (41-68)	1,730 (34.15)
Personality and behavioral disorders (F50-F69 & F91-F94, F98)	3838 (9.0)	65 (40-81)	1,919 (50)
Neurodevelopmental disorders (F70-F90 & F95)	1624 (3.8)	49 (27-60)	669 (41.19)
Non-psychiatric mental disorder (F00-F09 & non-F codes)	42,441 (99.0)	72 (55-83)	23,021 (54.24)

*As more than one associated diagnosis is possible, the total percentage for this column is > 100%.

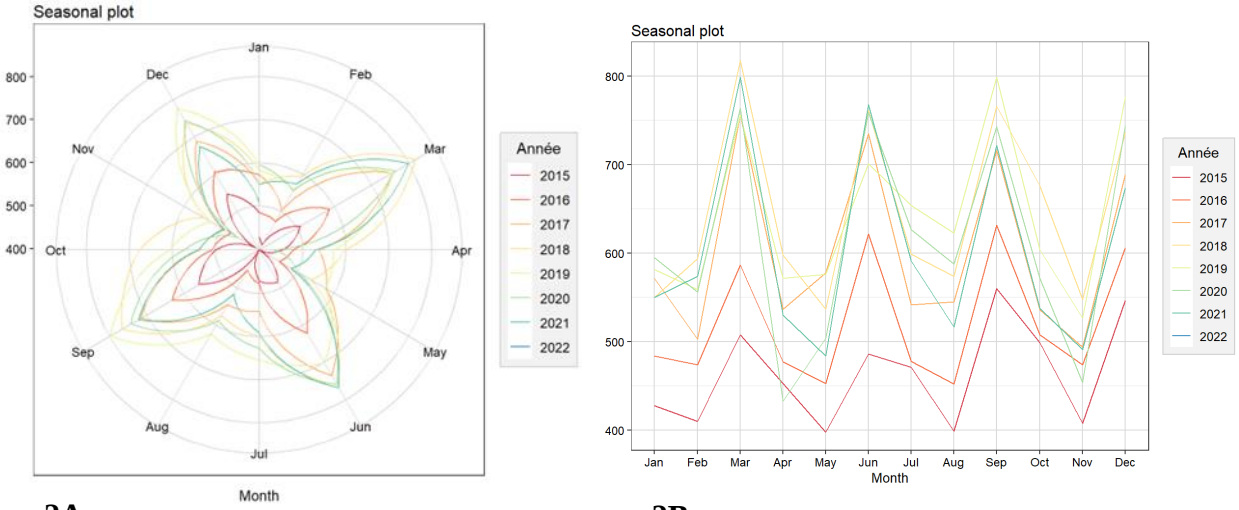
The number of cases of catatonia in metropolitan France increased from 2015 to 2018 (*n* = 5567 in 2015, *n* = 6247 in 2016, *n* = 7203 in 2017, *n* = 7758 in 2018, corresponding to an increase of 10.9% in 2016 compared to 2015, 13.3% in 2017 compared to 2016, 7.2% in 2017 compared to 2016, and 7.2% in 2018 compared to 2017). Then, a slight decrease of diagnoses appeared from 2019 to 2021 (*n* = 7730 in 2019, *n* = 7339 in 2020, *n* = 7238 in 2021, corresponding to a decrease of 0.4% in 2019 compared to 2018, 5.3% in 2020 compared to 2019, and 1.4% in 2021 compared to 2020), followed by an increase of cases in 2022 (*n* = 7514 in 2022, corresponding to an increase of 3.7% in 2022, compared to 2021) (see Figure 1).

Figure 1. Number of patients diagnosed with catatonia in metropolitan France by month, from 2015 to 2022.



A significant seasonal pattern by month for catatonia was found ($p < 0.001$). Four peaks of cases are showed in March ($\beta = 792.12$, $p < 0.01$), June ($\beta = 699.37$, $p < 0.001$), September ($\beta = 711.37$, $p < 0.001$) and December ($\beta = 687.75$, $p < 0.001$) (see Figure 2).

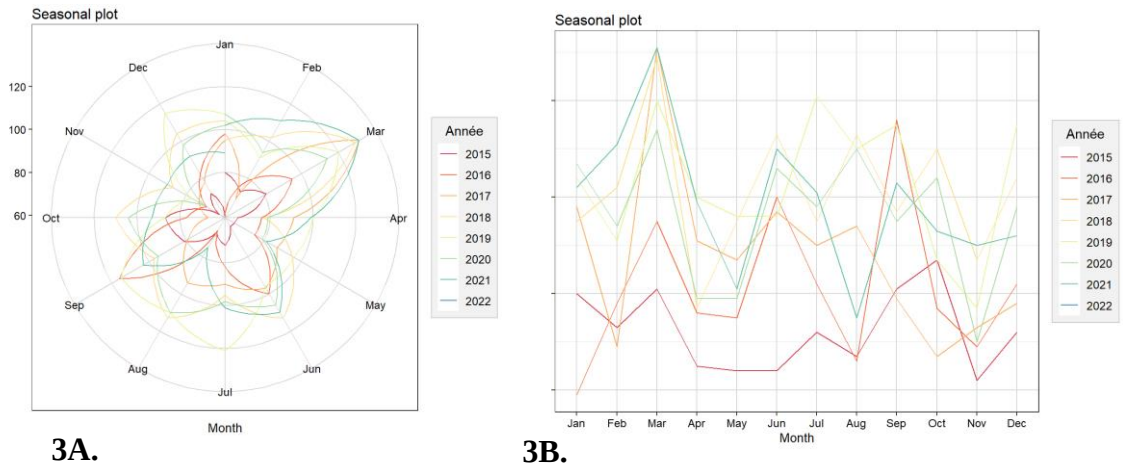
Figure 2. Number of hospitalisations for catatonia in metropolitan France by month, from 2015 to 2022, using a polar plot (2A) and a line chart (2B).



2A. **2B.**

A significant seasonal pattern by month was found, for patients with catatonia and suffering from schizophrenia and related disorders ($p < 0.001$). A first peak of cases is showed in March ($\beta = 117.62$, $p < 0.001$). Then, cases increase during summer with a second peak in September ($\beta = 99.62$, $p < 0.001$) (Figure 3).

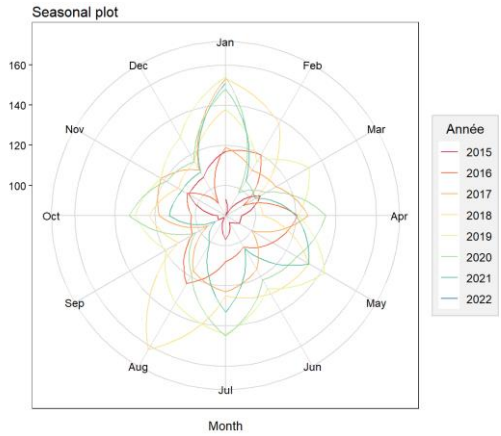
Figure 3. Number of hospitalisations for catatonia in metropolitan France by month, from 2015 to 2022, for patients suffering from schizophrenia and related disorders, using a polar plot (3A) and a line chart (3B).



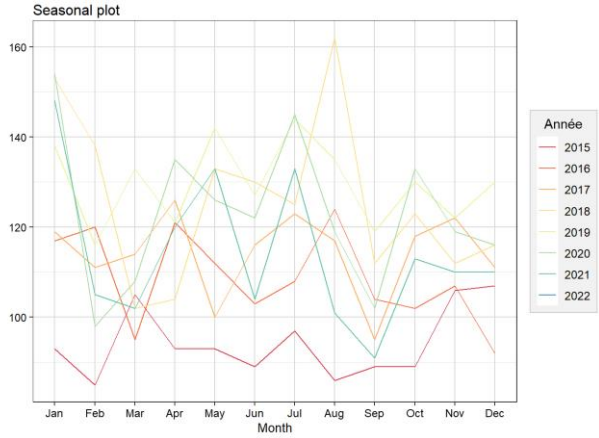
3A. **3B.**

A significant seasonal pattern by month was found, for patients with catatonia and suffering from mood disorders (p = 0.003). A first peak of cases is showed in January (β = 134.12, p < 0.001). Then, cases increase during summer with a second peak found in July (β = 124.75, p < 0.001) (see Figure 4).

Figure 4. Number of hospitalisations for catatonia in metropolitan France by month, from 2015 to 2022, for patients suffering from mood disorders, using a polar plot (3A) and a line chart (3B).



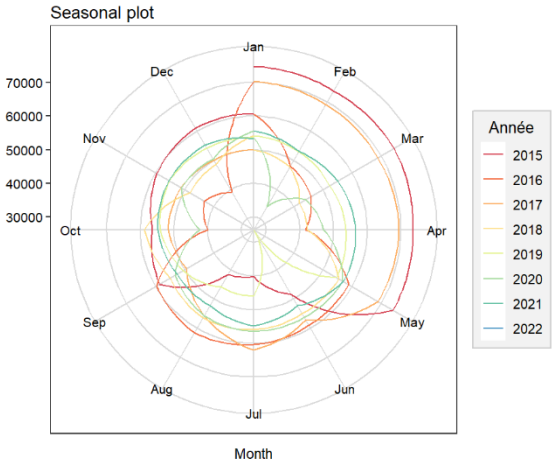
4A.



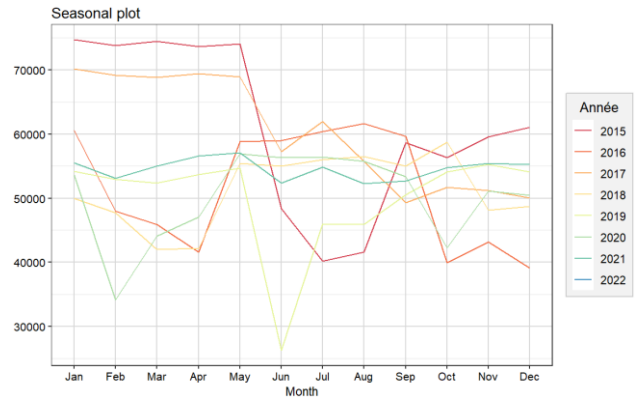
4B.

Analyses of seasonality were repeated for all psychiatric admissions to French hospitals, from 2015 to 2022 (Figure 5). No seasonal patterns were found (p = 0.30).

Figure 5. Number of hospitalisations for all psychiatric reasons in metropolitan France by month, from 2015 to 2022, using a polar plot (5A) and a line chart (5B).



5A.



5B.

Sensitivity analyses were performed, repeating the analyses of seasonality, but excluding years 2020 and 2021, when frequencies of hospitalisations might have been altered by the COVID-19 pandemic. No significant difference was found compared with the main analyses. A seasonal effect was still present, showing the same peaks across years ($p < 0.001$).

3.4. Discussion

To our knowledge, this study in metropolitan France between 2015 and 2022 (n = 42,893) is the first study of the seasonality of catatonia on a national scale and the first to stratify by the main associated psychiatric disorders.

We showed a general increase in the number of cases of catatonia, from 2015 to 2022, as described by other recent studies performed on a population of patients with catatonia, in South London (Mastellari et al., 2023; Rogers et al., 2021). The slight decrease observed during the COVID-19 pandemic might be explained by the

underuse of healthcare systems and the diminished hospital admissions for all psychiatric and non-psychiatric reasons at that time (Tuppin et al., 2022). The main hypothesis regarding the increase of admissions for catatonia from 2015 to 2022 includes better recognition and increased research interest around this syndrome (Weleff et al., 2023).

We identified four main peaks of cases with catatonia in December, March, June and September. Interestingly, two similar peaks were found in a recent seasonality study, performed in South London, in which a first peak of cases was described at the end of winter, and a second peak at the end of the summer (Mastellari et al., 2023). Although various hypotheses might explain why catatonia presents a seasonal pattern (Mastellari et al., 2023), one of the main factors explaining this seasonality might include the role of the underlying psychiatric disorder, as catatonia is a common clinical end-point for several mental illnesses, explaining about 80% of the causes of this syndrome.

When stratifying for patients with catatonia suffering from mood disorders (unipolar depression or bipolar disorder), a first peak of cases is found in mid-winter (peak in January), and a second peak in mid-summer (peak in July). This is consistent with previous studies on mood disorders where depressive episodes were found to be more common in winter, and manic phases in summer (Geoffroy et al., 2014).

When analysing seasonal patterns for patients with catatonia suffering from schizophrenia and related disorders, a first peak of cases is found in March, then cases increase in the second part of year, with a peak around September. Previous studies on the seasonality of schizophrenia exist, but results are less homogeneous, compared to mood disorders. Kazuhiko Abe, 1963 (Abe, 1963) found that peaks of admissions

for affective disorders occurred about a month earlier than for schizophrenia, but this was not confirmed by further studies (Takei et al., 1992). Peaks in both winter and summer were described for schizophrenia, and various hypotheses developed, including the role of temperature and weather, photoperiod, neurobiological changes and social factors (Hinterbuchinger et al., 2020; Owens and McGorry, 2003; Zhang and Volkow, 2023). Moreover, peaks in spring and autumn might evoke the role of seasonal infections (Rogers et al., 2019). Finally, it is noteworthy that we could not identify any affective symptoms that might be associated with schizophrenia or related disorders, and that might influence the seasonal pattern.

One of the hypotheses to explain more cases of catatonia during summer is the increased number of admissions for all psychiatric reasons during the warmest months (Nori-Sarma et al., 2022). However, in our study we explored the seasonality of admissions to hospital for all psychiatric disorders, and no significant pattern was found.

In terms of limitations, it is a possible that a delay of several days or even weeks exists in some cases between the date of admission and the date of registration of the diagnosis, which would generate a measurement bias. However, in our study we did not consider dates of registration, and we included dates of admission only. The extremely precise pattern obtained for the number of hospitalisations for catatonia by month, in metropolitan France from 2015 and 2022 (Figure 2), might evoke the doubt of some artefacts in the data, explaining such regular peaks. However, artefacts would similarly impact the seasonal pattern for the number of hospitalisations for all psychiatric reasons (Figure 5), which is not the case. Underestimation of catatonic cases is also highly probable, due to under-reporting, under-coding or misdiagnosis during clinical practice (Jaimes-Albornoz and Serra-Mestres, 2013; Mustafa and

Nayar, 2020; van der Heijden et al., 2005). However, this underdiagnosis issue is not expected to differ between seasons and therefore impact our analyses. Similarly, outpatients with catatonia were not included in this study. However, catatonia usually requires rapid inpatient treatment, and cases of catatonia diagnosed in outpatient settings are likely to be transferred shortly to hospital. We did not include in our model meteorological variables such as temperature, hours of sunshine, percentage of humidity or pollution data, which could be interesting factors to adjust for in future studies. Further research should try to extend these findings to other countries and continents, to test the impact of different latitudes. Similarly, considering the seasonal pattern for catatonia in patients suffering from mood disorders, it would be interesting to explore if seasonal affective disorder is particularly linked to this syndrome. Finally, the seasonality of catatonia might also be assessed on the individual clinical level, allowing correlation with concomitant psychiatric symptoms and catatonic subtypes (e.g., periodic catatonia or catatonia resistant to benzodiazepine treatment).

3.5. Conclusion

In this study on the seasonality of catatonia, performed in metropolitan France, we showed that a seasonal pattern exists in the onset of this syndrome during the year. Four main peaks were described, in December, March, June and September for all causes of catatonia. However, seasonal patterns differ, according to the main associated psychiatric disorder. In patients with mood disorders, peaks of catatonia were identified in winter (January) and summer (July), as hypothesised based on previous literature. In patients suffering from schizophrenia, peaks of catatonia were described in spring (March) and autumn (September).

Declaration of interests

This study was not funded. We declare no competing interests.

CReDiT authorship contribution statement

Tomas Mastellari: Conceptualization, Methodology, Writing – original draft, Writing – review and editing. **Chloé Saint-Dizier:** Data curation, Formal analysis, Methodology, Writing – review and editing. **Thomas Fovet:** Methodology, Writing – review and editing. **Pierre-Alexis Geoffroy:** Writing – review and editing. **Jonathan Rogers:** Writing – review and editing. **Antoine Lamer:** Data curation, Formal analysis, Methodology, Writing – review and editing. **Ali Amad:** Conceptualization, Methodology, Writing – review and editing.

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4. Discussion générale

A travers les deux études présentées dans cette thèse, nous avons exploré pour la première fois, sur deux larges échantillons de patients, la saisonnalité du syndrome catatonique.

Nous avons montré une saisonnalité dans les hospitalisations pour syndrome catatonique, à la fois dans la première étude menée à Londres, et dans la deuxième étude, menée sur une base de données nationale, en France métropolitaine. La première étude, portant sur 955 patients catatoniques, a montré un premier pic des cas de catatonie en février, puis un deuxième pic en août. La deuxième étude, portant sur 42,893 patients catatoniques, a permis d'identifier quatre pics d'hospitalisations pour syndrome catatonique, en décembre, mars, juin et septembre. Au cours de la deuxième étude, grâce à une taille de l'échantillon plus importante, nous avons pu stratifier les analyses selon la principale pathologie psychiatrique associée au syndrome catatonique, et montrer un pattern de saisonnalité différent, selon le sous-groupe diagnostique.

Pour les patients catatoniques souffrant de trouble de l'humeur, nous avons décrit un pic de catatonies en janvier, puis en juillet. Ce résultat reprend le pattern de saisonnalité retrouvé dans le sud de Londres, où environ 20% des patients catatoniques souffraient d'un trouble de l'humeur. Si on considère qu'un pattern de saisonnalité a été décrit pour les troubles de l'humeur (plus de cas de dépression au début de l'hiver, et plus de cas d'(hypo-)manie au début de l'été) (22,23), on peut faire l'hypothèse d'un pic de catatonie qui suit les pics des troubles de l'humeur, en milieu et fin d'hiver (janvier, février), puis en milieu et fin d'été (juillet, août).

Pour les patients catatoniques souffrant de schizophrénie ou trouble psychotique, la deuxième étude de cette thèse a montré deux pics d'hospitalisations pour catatonie, en mars et en septembre. Une étude publiée en 1963 par Kazuhiko Abe avait montré que les pics d'hospitalisation pour les troubles de l'humeur se vérifiaient environ un mois avant les pics d'hospitalisation pour psychose (58). Toutefois, ces résultats n'ont pas été confirmés par les études successives (59). Des pics d'hospitalisation pour les patients schizophrènes ont été décrit à la fois en été et en hiver, et différentes hypothèses ont été faites concernant les mécanismes physiopathologiques pouvant expliquer cette saisonnalité. Parmi celles-ci, on peut retrouver le rôle des températures et des variables météorologiques, ainsi que des comportements sociaux et des altérations neurobiologiques (26,60,61). Le rôle des infections peut également être évoqué, en lien avec ces pics retrouvés au printemps et en automne (5,45).

Les pics de catatonie au cours de l'été pourraient également refléter l'augmentation des recours aux soins pour toute cause psychiatrique quand les températures sont élevées (21). Toutefois, les deux études présentées dans cette thèse ont montré que le pic de syndrome catatonique au cours de l'été n'était pas expliqué par les hospitalisations liées aux troubles psychiatriques, toutes causes confondues.

Concernant l'impact du mois de naissance sur le développement d'un syndrome catatonique au cours de la vie, nous n'avons retrouvé d'évidence statistiquement significative en faveur d'une telle association, au cours de la première étude, dans le sud de Londres. Cette association n'a pas été étudiée dans l'étude française, car l'accès aux dates de naissance n'était possible. L'effet du mois de naissance sur le développement de pathologies au cours de la vie devrait être interprété en utilisant une perspective neurodéveloppementale. Dans ce contexte, on considère que les facteurs prénataux, périnataux et postnataux précoces pourraient jouer un rôle dans

la genèse d'une vulnérabilité à la maladie. Un impact du mois de naissance sur le développement de la schizophrénie a été décrit largement dans la littérature scientifique (44–47). Ce même effet n'a pas été retrouvé dans le cadre de la maladie de Parkinson, par exemple, maladie neurologique qui partage avec la catatonie certains mécanismes physiopathologiques (62–64). Si on considère les études en neuroimagerie de la catatonie, seulement une étude a exploré les altérations de gyrification, montrant des anomalies qui pourraient suggérer une susceptibilité au syndrome catatonique, à partir de la période prénatale (65,66). Toutefois, ces altérations pourraient ne pas suivre un pattern de saisonnalité, ni être médiées par le mois de naissance. Comme dans l'étude croate sur 59 patients schizophrènes et catatoniques (57), où aucune association n'a été retrouvée entre le mois de naissance et la catatonie, notre étude incluant 955 patients catatoniques pourrait ne pas avoir assez de puissance statistique pour identifier un effet du mois de naissance sur le développement de la catatonie.

Pour finir, nous avons montré une augmentation des cas de catatonie entre 2007 et 2016 dans le sud de Londres, et également une augmentation globale des cas en France métropolitaine, entre 2015 et 2022. Ceci peut être lié à différents facteurs, parmi lesquels on peut citer l'utilisation de nouvelles drogues psychoactives, l'amélioration des diagnostics faits par les professionnels de santé, et une augmentation de la recherche scientifique autour de ce syndrome (13,67).

4.1. Forces et limites des deux études

A notre connaissance, les deux études citées dans cette thèse sont les premiers à montrer, dans des larges cohortes de patients, une saisonnalité dans la présentation du syndrome catatonique au cours de l'année. Dans les deux études, les analyses de saisonnalité ont été menées en utilisant le modèle cosinor, qui est un modèle spécifiquement validé pour toute analyse de saisonnalité (68,69). L'impact sur nos résultats d'éventuels pics d'hospitalisation pour toute cause psychiatrique a été écarté dans les deux études. Dans l'étude française des analyses stratifiées ont été réalisées sur deux sous-groupes de patients, souffrant de trouble de l'humeur ou de schizophrénie, montrant des pics de saisonnalité différents.

Concernant les limites de notre première étude, les patients catatoniques ont été inclus à l'aide d'un outil diagnostic standardisé, rigoureux et validé. L'utilisation de cet outil dépend des habitudes cliniques des médecins, ce qui pourrait entraîner une sous-estimation des catatonies dans notre étude, mais il est peu probable que cela diffère d'une saison à l'autre. Dans cette étude nous avons inclus des épisodes de catatonie à la fois chez des patients hospitalisés ou suivi en ambulatoire, ce qui pourrait générer un biais de sévérité. Cependant, il est probable que les patients diagnostiqués comme catatoniques en ambulatoire soient rapidement transférés à l'hôpital, pour la poursuite des soins et du traitement. Un biais de mesure pourrait également résulter d'un délai différent entre l'apparition de la catatonie et son diagnostic, mais il est peu probable qu'il soit supérieur à quelques jours, compte tenu de la gravité de ce syndrome, et qu'il diffère selon les saisons. Si le modèle cosinor a été utilisé pour les analyses concernant la présentation de la catatonie, ceci n'a pas pu être utilisé pour explorer l'effet du mois de naissance sur le développement de la catatonie, où une régression pour les données de comptage, sans termes trigonométriques, a été adoptée à la

place. Ceci était dû à l'indisponibilité des données sur le nombre total de naissances par mois, pour la population générale, entre 1921 et 2007 dans le sud de Londres.

En termes de limites pour la deuxième étude, il est possible qu'un délai de plusieurs jours, voire de plusieurs semaines, existe dans certains cas entre la date d'admission et la date de codage du diagnostic, ce qui pourrait générer un biais de mesure. Cependant, dans notre étude, nous n'avons pas pris en compte les dates de codage des diagnostics, et nous n'avons retenu que les dates d'admission. La sous-estimation des cas de catatonie est également possible, en raison d'un codage insuffisant ou d'un diagnostic erroné dans la pratique clinique. Cependant, ce problème de sous-diagnostic ne devrait pas différer d'une saison à l'autre et donc avoir finalement peu d’impact sur nos analyses. Dans cette étude, les patients examinés en ambulatoire n’ont pas été inclus. Cependant, comme expliqué précédemment, la prise en charge du syndrome catatonique nécessite généralement un traitement rapide en milieu hospitalier, et les cas de catatonie diagnostiqués en milieu ambulatoire sont susceptibles d'être transférés rapidement à l'hôpital. Concernant les analyses de saisonnalité, nous n'avons pas inclus dans notre modèle les variables météorologiques telles que la température, les heures de lumière, le pourcentage d'humidité ou les données relatives à la pollution, qui pourraient être des facteurs intéressants à prendre en compte par la suite.

5. Conclusion générale

Nous avons étudié pour la première fois la saisonnalité de la catatonie sur des larges échantillons de patients, en incluant au total 43,848 cas de catatonie, dont 955 patients inclus dans le sud de Londres, et 42,893 patients en France métropolitaine. Nous avons montré une saisonnalité dans la présentation du syndrome catatonique au cours des années, avec un premier pic en fin d'hiver et un deuxième pic en fin d'été. Ces pics en hiver et en été semblent particulièrement présents chez les patients souffrant de trouble de l'humeur. Chez les patients souffrant de schizophrénie ou autre type de psychose, le pattern de saisonnalité semble décalé au printemps et en automne. Des études supplémentaires sont nécessaires pour répliquer et confirmer nos résultats, notamment dans les principaux sous-groupes diagnostics.

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Mots-clés : catatonie ; syndrome catatonique ; saisonnalité ; saisons.

Résumé :

Contexte : La catatonie est un syndrome neuropsychiatrique sévère, notamment associé en psychiatrie aux troubles de l'humeur et à la schizophrénie. La compréhension des mécanismes physiopathologiques de la catatonie est encore limitée, et le rôle de l'environnement peu étudié. Si des fluctuations saisonnières ont été montrées pour les maladies psychiatriques associées à la catatonie, la saisonnalité de ce syndrome n'as pas encore été explorée.

Méthode : Dans cette thèse, nous avons étudié la saisonnalité de la catatonie à travers deux études originales de recherche. La première inclut une cohorte de patients catatoniques dans le sud de Londres, entre 2007 et 2016. La deuxième correspond à une étude concernant la population de l'ensemble des patients catatoniques en France métropolitaine, entre 2015 et 2022. Un modèle cosinor a été utilisé pour les analyses de saisonnalité.

Résultats : Nous avons inclus 955 patients dans le sud de Londres, et 42,893 patients en France métropolitaine. Nous avons retrouvé un effet de saisonnalité dans la présentation du syndrome catatonique, avec un premier pic d'épisodes en hiver et un deuxième pic en été. Ce pattern de saisonnalité semble particulièrement présent chez les patients catatoniques souffrant de troubles de l'humeur. Chez les patients catatoniques et schizophrènes, deux pics ont été retrouvés au printemps et en automne. Nos résultats ne mettent pas en évidence un effet du mois de naissance sur le développement d'un syndrome catatonique au cours de la vie.

Composition du Jury :

Président : Monsieur le Professeur Guillaume VAIVA

Assesseurs : Madame le Docteur Maeva MAGNAT

Directeur de thèse : Monsieur le Professeur Ali AMAD