The Role of the Menstrual Cycle in Psychosis

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In memory of

Dr Valeria Frighi Pezzella (d. 2024)

and

James Treacy Martin Reilly (d. 2025)

Abstract

Female reproductive events are increasingly recognised as important risk factors for psychosis. In particular, the hormone fluctuations of the menstrual cycle have been associated with both worsening and development of psychotic disorders. This thesis aimed to characterise the phenomenon of psychotic episodes linked to the menstrual cycle ('menstrual psychosis') and more broadly to examine the menstrual cycle in psychotic disorders.

The first chapter summarises the evidence linking the menstrual cycle with psychosis, within the framework of the oestrogen hypothesis. Chapter 2 comprises a systematic review and phenotypic analysis of menstrual psychosis case-reports in which 417 cases of menstrual psychosis are described according to their clinical features. Notably, the disorder mainly presents in adolescence, with a modal age of onset of 14 years. Affective symptoms are present in 70% of cases, with the most common symptom being depressed mood.

Chapter 3 identified unpublished cases of menstrual psychosis by searching electronic health records of a large mental health service. I identified 38 menstrual psychosis cases, none of which had previously been published as case-reports. Compared to matched controls experiencing psychosis not linked to menstruation, cases were more likely to show symptoms of incoherence/derailment (Odds Ratio 5.48, 95% Confidence Interval:1.83 – 17.6), clouded consciousness (Odds Ratio 4.23, 95% Confidence Interval: 1.88 – 9.65) and labile affect (Odds Ratio 3.09, 95% Confidence Interval: 1.45 – 6.76). Compared to case-reports, these electronic health record cases had a greater number of symptoms described but were otherwise similar in symptomatology and age of onset.

Chapter 4 used the UK Biobank to investigate menstrual dysfunction in patients with schizophrenia (n=614). While rates of irregular menstruation were similar between schizophrenia and healthy controls, patients with schizophrenia had a later age of menarche (β=0.11, 95% Confidence Interval: 0.04 – 0.18) and earlier age of menopause (β=-0.84, 95% Confidence Interval: -1.21 – -0.47). Oestradiol levels were lower in schizophrenia, though this was not statistically significant when adjusting for potential confounding lifestyle factors.

Chapter 5 used data from the PSYSCAN study to examine hormones in female patients with first episode psychosis (n=72), those at clinical high risk for psychosis (n=74) and healthy controls (n=50). Prolactin was significantly increased in first episode psychosis (β=22.1, 95% Confidence Interval: 1.95 – 42.2), though this was driven by participants who were prescribed prolactin-raising antipsychotic medication. There were no differences in oestradiol between groups.

Collectively, these findings indicate that the menstrual cycle can be associated with discrete psychotic episodes and these cases often present in adolescence with a strong affective component. In patients with established psychotic disorders like schizophrenia, there is evidence of lower circulating oestradiol compared with healthy controls; however, this is not the case in younger patients at an early stage of illness. Future research should attempt to identify a 'hormone-sensitive' subgroup of patients with psychosis. To this end, I discussed the development of a smartphone questionnaire to prospectively examine the relationship of psychosis symptoms across the menstrual cycle.

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Personal contribution to the work:

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Wrote the full chapter text and created Figures 1, 2, and 5.

Chapter 2

Designed the study, wrote the pre-registration, conducted the literature search, extracted all data, developed and performed the analyses, interpreted the findings, wrote the chapter text, and created all figures.

Chapter 3

Designed the study, wrote the study proposal, specified the electronic health record search strategy, extracted the data, developed and performed the analyses, interpreted the results, wrote the chapter text, and created all figures.

Chapter 4

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List of abbreviations

AMDP	Association for Methodology and Documentation in Psychiatry
ANOVA	Analysis of Variance
BMI	Body Mass Index
BPRS	Brief Psychiatric Rating Scale
CAARMS	Comprehensive Assessment of At-Risk Mental States
CHR-P	Clinical High Risk for Psychosis
CI	Confidence Interval
CRIS	Clinical Record Interactive Search
DRSP	Daily Record of Severity of Problems
CPZ	Chlorpromazine equivalents
DSM	Diagnostic and Statistical Manual of Mental Disorders
EHR	Electronic Heath Record
FEP	First Episode Psychosis
FSH	Follicle Stimulating Hormone
HDRS	Hamilton Depression Rating Scale
HRT	Hormone Replacement Therapy
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
IQ	Intelligence Quotient
IQR	Inter-Quartile Range
LH	Luteinising Hormone
NHS	National Health Service
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PANSS	Positive and Negative Syndrome Scale
PMDD	Premenstrual Dysphoric Disorder
PMS	Premenstrual Syndrome
PRS	Polygenic Risk Score
SD	Standard Deviation
UHPLC-QqQ	Ultra-High Performance Liquid Chromatography coupled with Triple Quadrupole

1 Introduction

1.1 Overview

The menstrual cycle has been postulated as a contributing factor in psychotic disorders for hundreds of years, with the first reports of psychotic episodes linked to the menstrual cycle dating back to the 19th century. Despite this, reproductive events like the menstrual cycle have received comparatively little research attention. In clinical practice, psychiatrists rarely incorporate the menstrual cycle into their assessment of patients with psychotic illnesses.

The interest in the menstrual cycle and other female reproductive life events has increased since the popularisation of the 'oestrogen protection hypothesis' in the 1990s. This hypothesised that falling oestrogen levels occurring in relation to the menstrual cycle, postpartum and menopause can exacerbate psychosis. It further proposed that endogenous oestrogen is generally protective against psychosis and that exogenous oestrogen could be a potential treatment.

In this thesis, the menstrual cycle was investigated in two broad ways. Firstly, I identified descriptions of psychotic episodes linked to the menstrual cycle (menstrual psychosis) from published case reports or extracted through the anonymous search of electronic health records. Secondly, I examined menstrual cycle characteristics and hormone measures in patients who have been diagnosed with psychotic disorders. The purpose of this was to identify menstrual cycle dysfunction in patients diagnosed with psychosis. The full spectrum of psychotic disorders was examined, from those at clinical high risk of psychosis (CHR-P), to those experiencing first episode psychosis (FEP), to those with established disorders, like schizophrenia.

Through these approaches, I advanced the understanding of the menstrual cycle as a potentially modifiable risk factor for psychosis, which can ultimately be leveraged to improve clinical care of female patients suffering from this disorder.

1.2 Psychotic disorders

Psychosis is a form of severe mental disorder, characterised by delusions, hallucinations and disorganised speech. While acute psychotic episodes can be effectively treated with antipsychotic medication, these come with various short and long-term adverse effects.[1] More insidious negative symptoms, such as lack of motivation, anhedonia and social isolation, do not respond to available treatments.[2] Psychotic disorders have enormous costs for the individual affected, their family and wider society.[3] People diagnosed with psychosis have a 15 –

20-year reduced life expectancy.[4] Mortality due to suicide or natural causes is increased compared to the general population.[4] Despite psychosis being recognised as a major contributor to global morbidity, there have been no major therapeutic advances since the serendipitous discovery of dopamine receptor-blocking antipsychotics in the 1950s.

A strategy to mitigate the long-term negative outcomes of chronic psychotic disorders, such as schizophrenia, is to intervene at the earliest stages of psychosis.[5] This seeks to engage individuals at their first psychotic episode or even before onset of frank psychosis in an effort to alleviate the course of illness. The clinical high-risk state of psychosis (CHR-P), aims to identify young people within the putatively prodromal stage of illness, characterised by subthreshold psychotic symptoms and anomalous experiences.[6] Approximately 25% of those meeting criteria for this high-risk state will develop frank psychosis over a three-year period.[7] From the perspective of psychosis research, identifying individuals early in their illness mitigates against confounding factors associated with psychosis, such as long-term medication use, institutionalisation and social decline.

While advances in genetics,[8] neuroscience[9] and neuroimaging[10] have improved our understanding of psychosis, these have not translated into better clinical care for people affected by these disorders. Examining the neuroendocrine system, specifically ovarian hormones, has been relatively overlooked in psychosis research. However, there is ample epidemiological and clinical evidence that endogenous fluctuations in these hormones can confer risk for psychotic disorders. Furthermore, stabilisation of hormone fluctuations is a viable treatment strategy that is already used for other mental disorders,[11] neurological conditions,[12] and gynaecological problems.[13]

1.3 Hormonal control of the menstrual cycle across the lifespan

The menstrual cycle is a physiological process orchestrated by hormonal feedback loops, known as the hypothalamic-pituitary-gonadal axis (Figure 1). Between the first menstrual period (menarche) and last (menopause), women experience this cycle marked by menstrual bleeding but also widespread effects throughout the body and brain. In many women, the cycles are interrupted at times by exogenous hormones (most commonly hormonal contraception) or pregnancy.

Menarche is triggered by a developmental cascade initiated by the hypothalamus.[14] Pulsatile gonadotrophin releasing hormone activity stimulates the anterior pituitary to release luteinising hormone (LH) and follicle stimulating hormone (FSH), which in turn stimulate ovarian follicle maturation and oestradiol production. Increased oestradiol levels contribute to the

development of secondary sexual characteristics and growth of the uterine endometrium. While the age of menarche is substantially heritable and highly polygenic,[15] it is also influenced by nutrition, weight and socio-economic status, with the average age in Western countries becoming younger with time.[16] The mean age in the UK is 13 years,[17] with a normal range between 10 – 16 years.[14] In the years following menarche, cycles are more likely to be anovulatory and irregular, due to immaturity of the hypothalamic-pituitary-gonadal axis.[18] Over time, cycles gradually become more regular and consistently ovulatory.

By convention, the cycle begins with the onset of menstrual bleeding.[19] The first half, the follicular phase, is variable in length and is characterised by a rise in FSH (responding to pulses of gonadotrophin releasing hormone from the hypothalamus). One follicle in the ovary becomes dominant and produces oestradiol. Rising oestradiol levels trigger a surge in LH which in turn causes the release of a mature oocyte from the follicle. The second half of the cycle, the luteal phase, has less variability, typically lasting 14 days. Here, the remnant of the follicle becomes the corpus luteum and secretes progesterone and oestradiol. If conception does not occur, progesterone levels fall, causing the uterine lining to be shed and the cycle to begin. The median cycle length in adults is 28 days, with 24 – 38 days being the normal range.[20] The cycle is associated with large shifts in hormones. Oestradiol levels rise by eight-fold and progesterone by 80-fold.[21] While these hormones are primarily responsible for control of the reproductive system, they have effects throughout the body, including in the brain. Oestrogen and progesterone receptors are widely expressed, particularly in the medial temporal lobe.[22,23] Oestradiol, the most bioactive form of oestrogen in humans, is a modulator of learning and memory.[24] It acts via two pathways. Classical signalling via regulation of gene transcription takes place over hours to days. While a more rapid non-classical signalling takes place via oestrogen receptors at the cell membrane. Across the menstrual cycle, oestradiol increases coherence in functional brain networks[25] and is associated with changes in medial temporal lobe structures.[26] Changes in progesterone across the menstrual cycle are also associated with changes in medial temporal lobe volumes.[26,27] Progesterone has neuroactive metabolites, one of which, allopregnanolone, is a positive allosteric modulator of the GABA-A receptor with anxiolytic and sedative properties.[28]

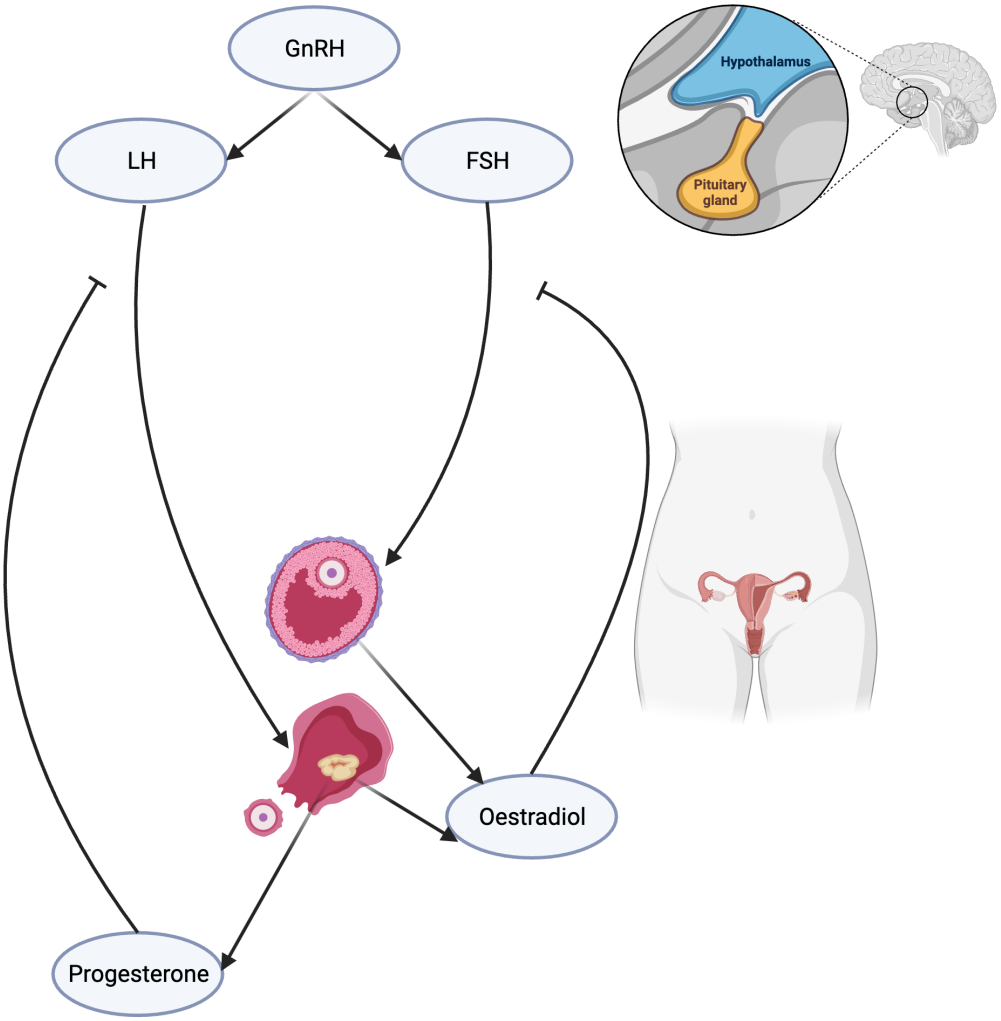


Figure 1. Illustration of the hypothalamic-pituitary-gonadal axis. GnRH - gonadotrophin releasing hormone, LH - luteinising hormone, FSH - follicle stimulating hormone. Created with BioRender.com.

If fertilisation does take place and the zygote implants into the uterine wall, the developing trophoblast produces human chorionic gonadotropin. This promotes the maintenance of the corpus luteum which continues to secrete progesterone and oestradiol, supporting the uterine endometrium. Around 8 – 10 weeks into pregnancy, the placenta becomes the main source of ovarian hormone production. Progesterone and oestrogen continue to rise throughout pregnancy. Prolactin levels also increase in preparation for lactation. Following childbirth and placental expulsion, levels of oestrogen and progesterone drop precipitously. Prolactin remains elevated if breastfeeding takes place.

The menopause is the cessation of menstruation, defined as 12 months after the final menstrual bleed. This may happen naturally, as ovarian follicles are depleted or it may be induced by surgery, medication or illness. The mean age of menopause in the UK is 51 years,

with a normal range of 45 – 55 years.[29] The time leading up to the menopause, sometimes referred to as the perimenopause or menopause transition, is one of hormonal flux.[30] The length of cycles may change and become irregular. Lower levels of oestrogen and progesterone are produced by the ovaries, due to depletion of the finite reserve of oocytes, while in response, levels of FSH and LH rise. Common symptoms include temperature dysregulation ('hot flushes'), night sweats, sleep disturbances, and low mood.[31]

Exogenous ovarian hormones are commonly used in the general population either to control the menstrual cycle (for example, as contraception or to reduce menstrual-related symptoms) or to replace declining levels at the perimenopause using hormone replacement therapy (HRT). The most common hormonal method globally is the oral contraceptive with formulations of either combined (oestrogen and progestogen) or progestogen-only.[32] Non-oral forms can also use combined hormones (e.g., patches or vaginal rings) or progestin-only (e.g., injections, implants or the levonorgestrel-releasing intrauterine system). Combined contraceptives exert action primarily through the inhibition of ovulation, while progestin-only contraceptives act to thicken cervical mucus and thin the uterine endometrium.[33] HRT involves the administration of oestrogen, in combination with a progestogen for women with a uterus, or as monotherapy in those who have undergone hysterectomy.[29] Formulations for systemic replacement include oral, patch and nasal spray, while local treatment can be given in the form of vaginal oestrogen. Systemic HRT is highly effective for vasomotor symptoms of the perimenopause.[34]

Each of these physiological hormonal events and applications of exogenous hormones offers a window of how ovarian hormones affect mental disorders, akin to a natural experiment. Most notably, clinical observation of the interaction between hormones and psychosis led to the oestrogen hypothesis.

1.4 The oestrogen hypothesis

The notion that ovarian hormones may be important in psychosis can be traced back to the advent of psychiatry as a discipline. Sex-differences in the expression of psychotic illness have been evident since the time of Kraepelin.[35] Female reproductive life events such as childbirth have been recognised as inducing psychotic episodes in some women since antiquity,[36] while Manfred Bleuler recognised 'late-onset' schizophrenia beginning after the age of 40 was more common in women.[37] However, these clinical observations were not consolidated into a coherent hypothesis until the 1990s when two seminal works synthesised both clinical and epidemiological evidence for the protective effect of oestrogen in psychosis.

The first, 'The role of oestrogens in schizophrenia gender differences' from Seeman and Lang[38] was published in 1990, and three years later Riecher-Rössler and Häfner[39] published, 'Schizophrenia and oestrogens - is there an association?'. These two publications not only summarised the evidence for the protective role of oestrogen in psychosis, but provided a framework for hormonal research in psychosis and testable hypotheses.

There are two strands to the oestrogen hypothesis. Firstly, psychosis is characterised as a hypo-oestrogenic state, with patients having lower circulating levels of oestrogen. Secondly, oestrogen is characterised as having protective properties in psychosis with low or declining levels increasing the risk of development or worsening of psychosis.

1.4.1 Schizophrenia as a hypo-oestrogenic state

Prior to the advent of dopaminergic antipsychotics, small studies suggested that female patients with schizophrenia had low circulating levels of oestrogen.[39] Gynaecological examinations from this period reported 'small ovaries with few follicles' and small uteruses.[39] Determining whether lower oestrogen levels are a feature of psychotic illness or a consequence of treatment became more complicated after the widespread use of antipsychotics, whose principal mechanism of action is through dopamine receptor blockage.[40] This action, while effective for psychotic symptoms, increases prolactin levels in a dose-dependent manner by limiting the usual tonic inhibition of prolactin secretion by dopamine (see Figure 2).[41] Up to 90% of patients receiving D2 selective antipsychotic exhibit hyperprolactinaemia,[42] and a previous meta-analysis showed that more than two thirds of both female and male antipsychotic-treated patients with schizophrenia had elevated prolactin levels.[43] Raised prolactin levels inhibit the downstream secretion of ovarian hormones via a central hypothalamic mechanism involving the suppression of gonadotrophin releasing hormone.[44] Hence, a potential effect of hyperprolactinaemia in the clinical expression of psychosis may be mediated by a decrease in oestradiol in females.

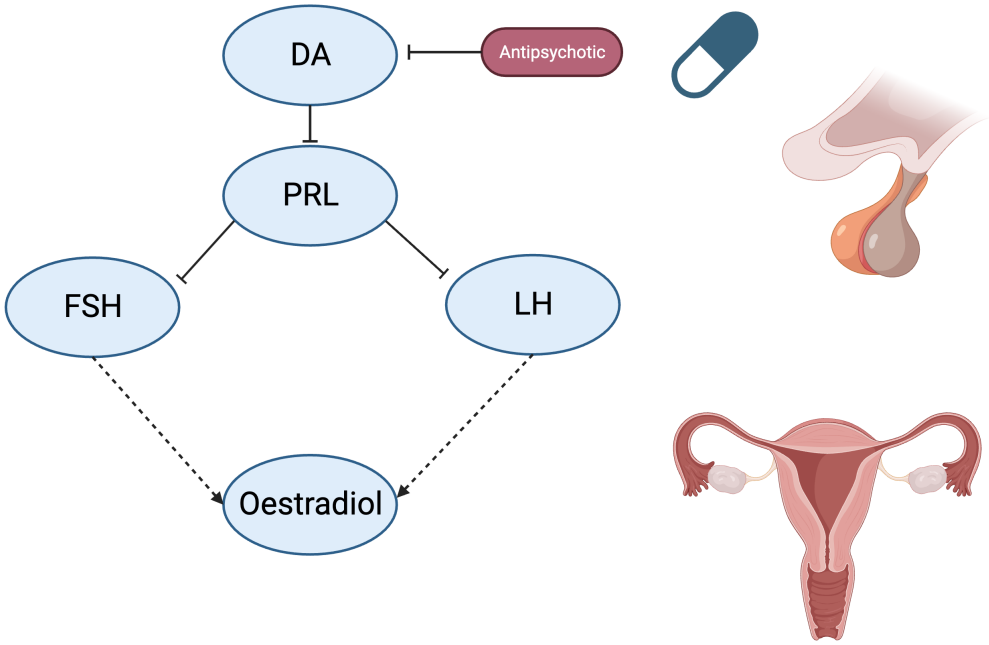


Figure 2. Antipsychotic medication blocks the usual dopaminergic inhibition of prolactin. Hyperprolactinaemia then inhibits FSH and LH, resulting in hypo-oestrogenism. DA - dopamine, PRL - prolactin, FSH - follicle stimulating hormone, LH - luteinising hormone. Created with BioRender.

More recently, small studies have shown decreased oestradiol in schizophrenia. Riecher-Rössler et al. found decreased oestradiol levels and reduced variation across the menstrual cycle in 32 female patients, the majority of whom were prescribed antipsychotic medication.[45] Huber et al. observed lower levels of oestradiol in 43 female inpatients with psychosis compared with healthy controls, though only a minority were free from antipsychotic medication.[46] The largest study, comprising 75 women with schizophrenia, was published by Bergemann et al. in 2005.[47] They reported that 60% of patients had hypo-oestrogenism, compared with reference values. Hypo-oestrogenism is thought to explain menstrual cycle irregularities found in psychosis, with the largest study to date (n=139) reporting a prevalence of 41%.[48]

While hypo-oestrogenism in psychosis has been suggested for decades, it is yet to be definitively demonstrated. Studies to date have suffered from small sample sizes and lack of adequate controls. Another complicating factor is the confounding effect of antipsychotic medication. To overcome these limitations, I examined menstrual cycle characteristics and oestradiol levels in a large sample obtained from the UK Biobank with well-characterised demographic, lifestyle and medication variables (Chapter 4).

There is more evidence for the protective effects of oestrogen in psychosis and conversely for times of declining oestrogen to be periods of increased risk. These associations of oestrogen and increased psychosis risk will be examined next.

1.4.2 Hormonal fluctuations as periods of vulnerability

Associations of oestrogen with vulnerability to psychosis can be examined both through the natural fluctuation of hormones during the reproductive life-cycle (menarche, the menstrual cycle, pregnancy/postpartum and menopause transition), through the administration of exogenous ovarian hormones as part of commonly used contraceptives and HRT, and through the examination of exogenous hormones as part of randomised clinical trials. Increased vulnerability to psychosis may manifest in the development of new psychotic episodes, relapse in psychotic disorders, or the exacerbation of psychotic symptoms. Whether fluctuations in ovarian hormones result in increased vulnerability for psychosis can thus be examined through a variety of observations and study designs.

1.4.3 Menarche

As menarche is a discrete event, it can act as a marker of pubertal development, more easily recalled than any marker of male puberty. In both sexes, the incidence of schizophrenia-spectrum disorders rises throughout adolescence, peaking at the age of 20 years.[49] However, from the age of 12 years, the rise in cumulative incidence is steeper in girls than boys, increasing from 0.1 per 100 persons to almost 0.5 per 100 persons by the age of 16 years.[50]

Earlier age at menarche was associated with more severe psychotic-like experiences in a large US sample of adolescents (n=4,422).[51] Various small studies have examined self-reported age of menarche in relation to psychosis onset but with conflicting results. In a Spanish sample (n=42), there was no significant correlation between age of menarche and age of psychosis onset.[52] In a Chilean health record study of 105 female patients with schizophrenia, patients had a slightly later age of menarche (13.0 years), than the local population (12.5 years), which was statistically significant.[53] However, there was no correlation between age of menarche and age of illness onset. A North American sample of 68 patients with schizophrenia-spectrum disorders found no correlation between age of menarche and illness onset, though worse negative symptoms and functional impairment were associated with later age of menarche.[54] A Turkish sample of 259 female patients with schizophrenia found a negative association between age of menarche and first onset of psychotic symptoms: patients who had a younger age at menarche tended to have later onset of psychosis.[55] This inverse association was also found in an earlier Canadian sample of 35 women with schizophrenia.[56]

The time around the first menstrual period, which is associated with highly variable fluctuations in ovarian hormones coincides with a rising incidence of psychotic disorders. Menarche has anecdotally been linked to isolated psychotic episodes and as the first presentation of menstrual psychosis (see Chapter 2). While there is some evidence that earlier age of menarche (and thus earlier exposure to higher levels of oestrogen) is associated with later age of psychosis onset, this finding has not been replicated consistently across samples. Following menarche, the rhythm of hormonal cycles that govern menstruation begins. The effect of these cycles on psychotic illness will be examined next.

1.4.4 Menstrual cycle

While a possible link between the menstrual cycle and psychosis has been speculated, a paucity of high-quality research in this area has meant that the link has not been well-characterised, with the bulk of evidence being anecdotal case-reports of psychotic episodes linked to the menstrual cycle. A systematic search and analysis of these case-reports is provided in Chapter 2, while Chapter 3 presents case identified through electronic health records.

Aside from discrete episodes of psychosis being linked with the menstrual cycle, the potential for established psychotic disorders to be exacerbated by the cycle should be considered. In contrast to the brief episodes of menstrual psychosis, menstrual exacerbation of psychotic disorders involves the worsening of symptoms or relapses at certain phases of the menstrual cycle, without full and complete recovery between menstrual episodes. Notably, up to two thirds of patients with schizophrenia self-report fluctuation in symptoms linked to their menstrual cycle.[48]

I previously conducted a systematic review and meta-analysis of menstrual exacerbation of psychotic disorders.[57] To examine the effect of the menstrual cycle on the outcome of psychiatric admission across studies, I extracted admissions that took place during perimenstrual (day 24 to day 5) and non-perimenstrual (day 6 to day 23). Across the 12 studies that examined psychiatric admissions, the rate of admissions during the perimenstrual phase was 1.5 times higher than the baseline rate, as shown in Figure 3.

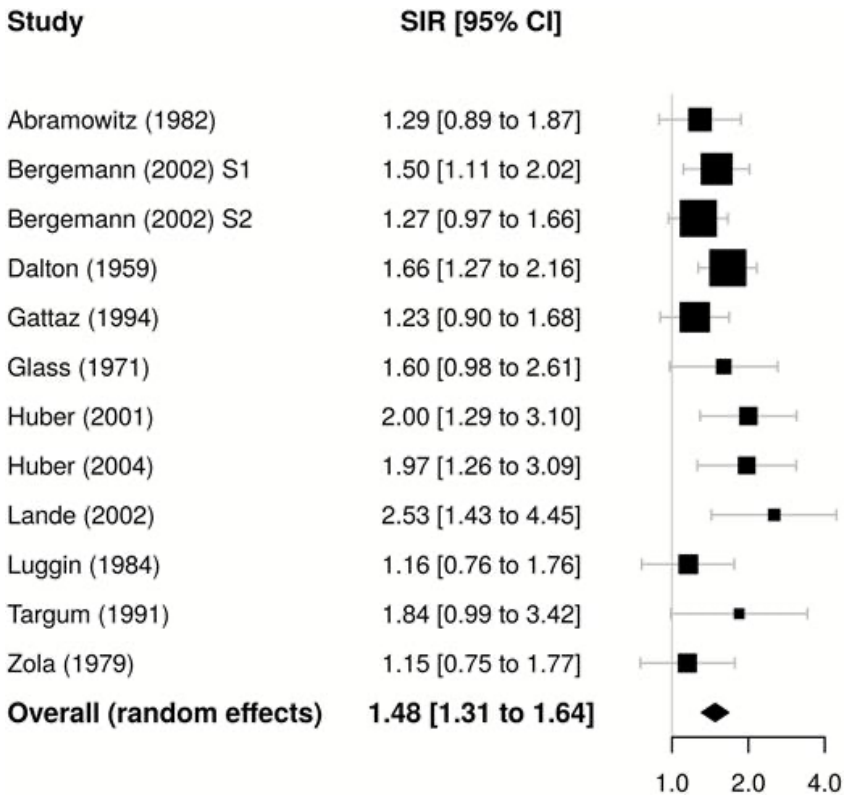


Figure 3. Pooled standardised incident ratios (SIR) of observed/expected rates of psychiatric admissions during the perimenstrual phase (day 24 – day 5) of a 28-day cycle. Reproduced from Reilly et al. 2020,[57] under CC-BY.

Of the six studies that examined psychotic symptoms in relation to the menstrual cycle, four showed perimenstrual deterioration. However, these studies were limited by examining symptom scores at only two or three timepoints in the cycle. Fully characterising symptom changes throughout the cycle warrants measurement of symptoms with greater temporal resolution, ideally through daily symptom ratings.

These preliminary findings suggest that patients with established psychotic disorders experience a worsening of their illness during the perimenstrual phase, a time when levels of both oestradiol and progesterone are falling, in keeping with the oestrogen hypothesis. More intensive measurement of symptoms in relation to the cycle using smartphone questionnaires will be discussed in Chapter 6.

1.4.5 Postpartum

Of all reproductive life-events, childbirth is perhaps most recognised as having the potential to precipitate episodes of psychosis. While the absolute rate of postpartum psychosis is rare (1-2 cases per 1000 births),[58] the relative risk of admission for psychosis within the first postpartum

month is high; up to 20 times the baseline risk.[59] By contrast, the risk of psychiatric admission during pregnancy is lower than baseline.[59]

The risk of postpartum relapse is particularly high in bipolar disorder; 17% will experience relapse following childbirth, which rises to 66% in patients who were medication-free during pregnancy.[60] While primiparity is a risk factor for first onset of postpartum psychosis,[61] after an initial episode, the relapse rate in subsequent pregnancies is 29%.[60] In more than half of cases, first episode postpartum psychosis will be the start of an illness with episodes outside the postpartum period,[62] mainly within the bipolar spectrum.[63]

The temporal relationship between childbirth and psychosis onset is striking. The rate of psychiatric admission is highest in the first month following childbirth,[59] while approximately three quarters of women report symptoms beginning within three days of delivery.[64] In a Danish record-linkage study, the period of highest risk of psychiatric admission was 10 – 19 days postpartum.[65] On retrospective interview, the most commonly reported early symptoms were elated mood, decreased sleep, increased energy and talkativeness.[64] During postpartum episodes, common symptoms include delusions, ideas of reference, and hallucinations in visual or auditory modalities.[66] Most participants meet diagnostic criteria for bipolar disorder with psychotic symptoms.[66]

While the close temporal association with the fall in oestrogen and progesterone at parturition suggests a hormonal trigger, causality has not been demonstrated. Indeed, while hormonal treatment in the form of allopregnanolone is now approved for postpartum depression,[67] hormonal approaches are not recognised as treatments for postpartum psychosis.[68] One small open-label trial of transdermal oestradiol on relapse rates in 29 women at risk of postpartum psychosis was negative.[69] Another potential precipitant for postpartum psychosis is sleep deprivation,[70] with immune dysfunction,[71] and genetic predisposition[72] additionally implicated in the aetiology.

A potential link between postpartum psychosis and psychotic episodes linked to the menstrual cycle is explored in Chapter 2. Notably, despite both these precipitants of psychosis being rare, a number of cases are reported to have experienced psychotic episodes at both these reproductive events. Comparison will also be made between the phenomenology of postpartum and menstrual-related psychotic episodes. The possibility of a hormone-sensitive subtype of psychosis, vulnerable to relapses as reproductive events across the lifespan will be discussed in Chapter 6.

1.4.6 Menopause

Increased incidence of psychosis around the age of menopause was part of the earliest epidemiological evidence to support oestrogen hypothesis. The landmark ABC Schizophrenia study[73] identified an interesting sex difference in the onset of schizophrenia, a 'second peak' in women. This finding, shown in Figure 4 below, shows a slightly earlier and steeper increase of schizophrenia incidence in men which steadily declines from a peak in early adulthood. By contrast, the incidence in women has a later and broader initial peak and then a smaller secondary peak around the age of 45 – 49 years. The similarity with the average age of menopause was evident and led researchers to speculate that the protective effect of oestrogen resulted in decreased incidence in women compared with men prior to the menopause and a reversal of this post-menopause, increased incidence in women compared with men. They further predicted that severity of schizophrenia should worsen following the menopause.



Figure 4. Distribution of age at onset of schizophrenia (first-ever sign of mental disorder) by sex; ICD 9-295, 297, 298.3, 298.4 (ABC Schizophrenia Study). Reproduced under CC-BY licence from Häfner 2019.[74]

The primary finding of a clear secondary peak has not been universally replicated in larger samples, such as a Finish nationwide cohort study[75] or a meta-analysis of incidence rates in England.[76] However, both these studies did clearly show a reversal in the sex difference in

schizophrenia incidence: the disorder was common in men prior to the age of 40 and more common in women after the age of 40. Furthermore, from the age of 45, women with schizophrenia have more relapses than their male peers and require higher doses of antipsychotic medication.[77]

A limitation of research into the menopause and psychosis is a reliance of age as a proxy marker rather than validated staging of the menopause transition.[78] Given that the normal age of menopause spans more than a decade, it is plausible than accurate menopausal staging would show even stronger associations with new onset and worsening of psychotic illness.

1.4.7 Association between endogenous oestradiol and symptoms

Given the association of hormonal transitions with psychosis risk, it is intuitive to examine the relationship between endogenous hormone measures and symptoms of psychosis. This approach is not without its difficulties. Levels of hormones fluctuate across the menstrual cycle within individuals and show marked variation between individuals. Riecher-Rössler et al.[45] measured oestradiol levels in 32 acutely unwell female inpatients with schizophrenia. Significant correlations between oestradiol levels and psychopathology were found, with lower oestradiol being associated with more severe symptoms. However, this correlation was not replicated in other small samples from South Korea (n=30),[79] USA (n=23),[80] Croatia (n=31),[81] or Iran (n=66).[82] Brand et al. analysed oestradiol levels in female patients with schizophrenia spectrum disorders, separated by those prescribed prolactin-raising (n=27) or prolactin-sparing (n=21) antipsychotics.[83] They found a significant correlation between oestradiol and verbal fluency in the prolactin-raising group, and a correlation with depression/anxiety symptoms in the prolactin-sparing group.

The largest study to date included 125 female patients and measured oestradiol at three timepoints in the menstrual cycle: at follicular, ovulatory and luteal phases.[84] Oestradiol showed negative correlation with positive symptoms measured by the Positive and Negative Syndrome Scale (PANSS) but there was no correlation with total PANSS score or total Brief Psychiatric Rating Scale (BPRS) score.

While there are some studies reporting correlation of endogenous oestradiol with more severe psychotic symptoms, there is little consistency. Causative effects cannot be inferred from these studies. Other endogenous hormones, such as progesterone, LH and FSH also fluctuate across the menstrual cycle and could contribute to psychiatric symptoms. Furthermore, oestradiol is suppressed by hyperprolactinaemia. Given the tendency of dopamine-blocking agents to

elevate prolactin, the relationship between oestradiol and psychotic symptoms could be confounded by this medication.

1.4.8 Effect of exogenous hormones in psychosis

If the menopause does confer increased risk for psychosis, could this be ameliorated through the administration of HRT? This is a well-established and effective treatment for menopausal vasomotor symptoms.[34] It has also been shown to prevent perimenopausal depression in a randomised trial.[85] Typically, for patients who have not undergone hysterectomy, it involves administration of a combination of oestradiol and progesterone. In a Finnish nationwide cohort study,[86] use of HRT was associated with 16% reduced risk of relapse in female patients with schizophrenia, using a within-person design to control for potential confounders. Crucially, the effect was only seen when hormone therapy was initiated before the age of 56 years.

Multiple trials of oestradiol have been conducted in schizophrenia, the largest (n=200) using it as an adjunctive treatment to antipsychotics in pre-menopausal women.[87] The trial met its primary outcome of the PANSS positive scale with a standardised mean difference of 0.38. A similar effect size was obtained when combining the trial with other smaller randomised studies. Interestingly the effect was entirely driven by participants aged 39 years or older, whereas oestradiol was not superior to placebo in younger participants.

While the protective effect of exogenous oestradiol is promising, particularly when commenced close to the natural age of menopause, the finding requires further replication in randomised controlled trials and in independent observational datasets. Many unanswered questions remain. The most effective formulation of HRT is not known. Whether there is a 'critical window' for initiating hormone therapy, as has been suggested for dementia,[88] is plausible, but the ideal age requires further investigation and may vary between individuals.

Whether other types of exogenous female ovarian hormones could be beneficial at other life-stages is unknown. While the combined oral contraceptive is a recognised treatment for premenstrual dysphoric disorder (PMDD),[11] and is recommended for premenstrual exacerbation of other conditions,[11] there is a notable lack of evidence in psychotic disorders. Anecdotally, combined oral contraceptives have been used to prevent further episodes of psychosis linked to the menstrual cycle, which will be examined in Chapters 2 and 3.

1.5 The menstrual cycle as a transdiagnostic modifiable risk factor

The menstrual cycle is emerging as a risk factor for various mental disorders including psychosis, depressive disorders, bipolar disorder, and emotionally unstable personality

disorder.[89] Severe mental health outcomes are additionally associated with cycle phase: meta-analyses have found that the perimenstrual phase has an increased risk of psychiatric admission for all diagnoses and menstruation is associated with an increased rate of suicide attempts and completed suicide.[90] Substance misuse including alcohol and nicotine increase perimenstrually.[91] Perimenstrual exacerbation is not limited to mental disorders: conditions such as epilepsy,[92] migraine[12] and asthma[93] have all shown worsening during this phase of the cycle. Thus, the menstrual cycle may be a transdiagnostic risk factor for both psychiatric, neurological and physical disorders, mental health outcomes and substance use, summarised in Figure 5 below.

Transdiagnostic risk across the menstrual cycle

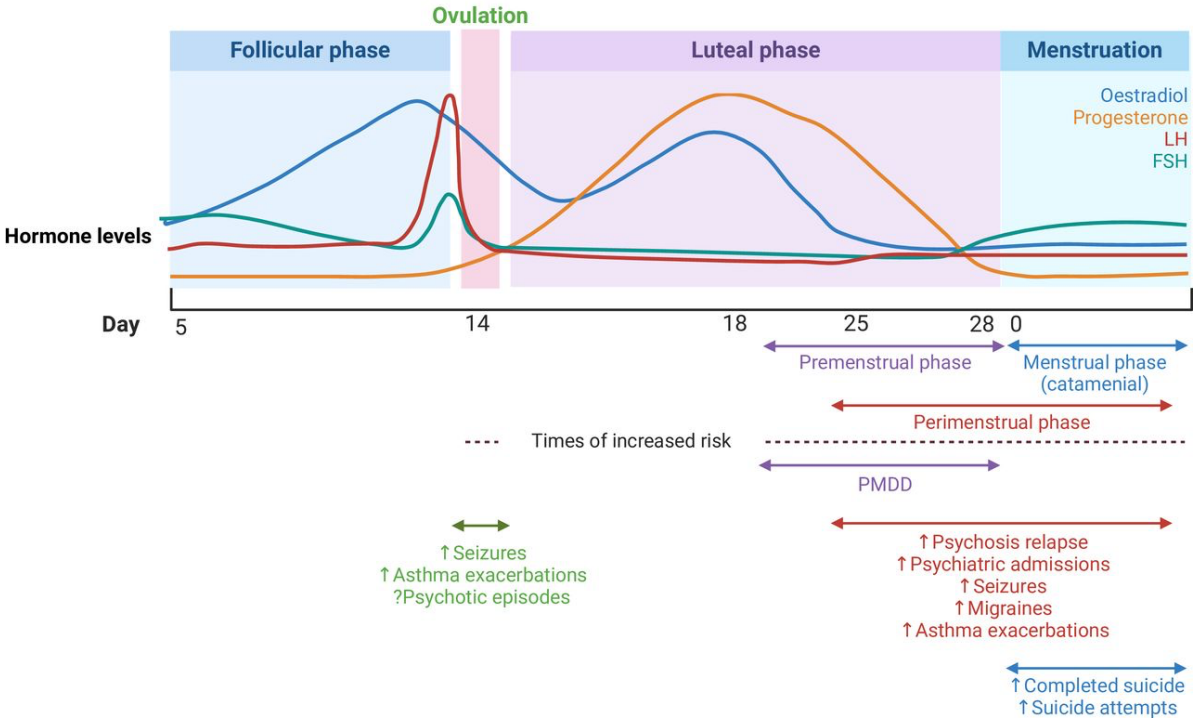


Figure 5. Schematic representation of hormone fluctuations during the menstrual cycle with associated risk for various disorders. The list of disorders provided is indicative and not comprehensive. The cycle is standardised to 28 days with ovulation at 14 days; in practice, this shows marked interindividual and intraindividual variation. Cycle phase definitions can vary between studies; here the premenstrual phase is day 18 – day 28, menstrual (catamenial) phase day 1 – day 5, perimenstrual phase day 24 – day 5. FSH, follicle stimulating hormone; LH, luteinising hormone; PMDD, premenstrual dysphoric disorder. Created with BioRender.com. Reproduced under CC-BY from Marwick et al. 2025.[94]

If the menstrual cycle is identified as a potential risk factor for an individual, clinical intervention is possible. This might range from increasing awareness of times in the cycle which associated

with higher risk, to adjusting doses of medication to control symptoms which show menstrual exacerbation. An additional strategy is to stabilise the cyclical fluctuation of ovarian hormones. This can be achieved through the prescription of oral contraceptives continuously or through the administration of gonadotrophin-releasing hormone analogues and subsequent add-back of oestradiol and progesterone. These strategies have been validated in PMDD and are advocated for premenstrual exacerbation of other disorders.[11] The last-line treatment for PMDD is surgical intervention, which typically involves hysterectomy with bilateral oophorectomy, with addback oestradiol. While this option is reserved for patients with severe symptoms in whom other treatment options have not been tolerated, it offers a permanent solution to severe premenstrual symptoms.

1.6 Methodological approaches

This thesis has taken two broad methodological approaches. The first was to characterise episodes of psychosis linked to the menstrual cycle ('menstrual psychosis'). The purpose of this was to provide a systematic description of this phenotype in terms of patient demographics, symptomatology, treatment-response and outcome. Cases were systematically identified from the historical and modern case-report literature, as well as from electronic health records from a large mental health trust. Comparisons were made between cases of menstrual psychosis and patients experiencing episodes of psychosis not linked to the menstrual cycle. Ultimately, I aimed to examine whether there is a phenotype of menstrual psychosis that represents a distinct psychiatric syndrome.

The second approach was to examine menstrual cycle characteristics and hormones in female patients with psychosis. The purpose was to determine whether there is evidence of menstrual dysfunction in psychosis more generally. Data was used from studies of individuals at different stages of psychotic illness. This includes younger patients at CHR-P (Chapter 5) or experiencing their first psychotic episode (FEP) (Chapter 5), as well as older patients with more established psychotic disorders (Chapter 4). Examining patients at the time of their first episode has the advantage that participants are less exposed to the social and lifestyle deprivation that is too often associated with chronic psychotic disorders and may contribute to hormonal dysfunction. Including participants with a putatively prodromal syndrome (CHR-P) has the benefit of minimising the effects of antipsychotic medication, which can have a profound effect on hormonal pathways. Including an older group of middle-aged women through the UK Biobank has the strength of utilising a larger sample around the age of perimenopause, many of whom will have experienced the long-term consequences of chronic psychosis. The range of measures collected in these two datasets allows examination of self-reported menstrual cycle

characteristics (regularity, age of menarche, age of menopause), as well as hormone measures (most notably oestradiol). The effect of oestradiol on cognitive and psychotic symptoms was additionally examined.

Finally, the limitations of both these approaches are discussed and ways to overcome them in future research was proposed. I described an ongoing study (Chapter 6.2 Future directions) which aims to monitor daily symptom changes across the cycle in female patients in the early stages of psychosis.

1.7 Notes on terminology

The Kraepelin division of psychosis into dementia praecox (what we now call schizophrenia) and manic-depressive insanity (bipolar disorder) remains remarkably influential in psychiatry, a century after Emil Kraepelin's death.[95] This divide has been challenged, in terms of overlapping genetic risk,[96] shared pathophysiological mechanisms,[97] lack of discrete diagnostic boundaries[98] and shared pharmacological strategies (namely antipsychotic medication).[99] Nevertheless there are important reasons to maintain Kraepelin's dichotomy by keeping schizophrenia and bipolar disorder as separate categories. Firstly, postpartum psychosis is proposed to be a type of bipolar disorder,[100] based on its symptomatology,[101] long-term course,[62] and response to lithium.[68] In keeping with this, bipolar disorder has a comparatively higher risk of postpartum relapse.[102] Secondly, episodes of psychosis linked to the menstrual cycle have been proposed as being on the bipolar spectrum too,[103] which will be discussed in detail in Chapters 2 and 3. Thirdly, risk of new-onset mania appears to be increased around the menopause transition.[104] In places, I referred to schizophrenia-spectrum disorders, which encompass the ICD-10 chapter of Schizophrenia, schizotypal and delusional disorders (F20-F29).[105]

In keeping with early intervention in psychosis terminology, I used FEP (first episode psychosis) to refer to the first presentation of psychotic illness, irrespective of eventual diagnosis or long-term outcome. Notably, within the broad FEP group, diagnoses of schizophrenia and bipolar disorder show greater stability over time than other disorders within the non-affective and affective psychosis spectrums.[106] Since the 1990s, a major research focus has been in identifying an at risk syndrome for psychosis.[107] At various junctures this has been conceptualised as prodromal psychosis, at risk mental state, or ultra-high risk for psychosis. In this thesis I used CHR-P (clinical high risk for psychosis),[108] which is now the preferred terminology in most settings.

Menstrual psychosis will be used for psychotic episodes associated with the menstrual cycle, encompassing pre-menstrual psychosis (onset in the pre-menstrual phase) and catamenial psychosis (onset with menstruation). HRT (hormone replacement therapy) will be used in preference to menopausal hormone therapy, in keeping with both the British Menopause Society[109] and the National Institute for Health and Care Excellence (NICE).[29]

2 Phenotypic analysis of menstrual psychosis case reports

2.1 Introduction

Descriptions of psychotic episodes associated with the menstrual cycle have been published since the early 1800s. While many of these predate modern psychiatry, they document characteristic patterns of illness: brief episodes of psychosis with complete recovery within two weeks of onset.[110] These episodes are distinct from the menstrual exacerbation of an underlying psychotic disorder[57] as they occur in the context of normal functioning. Cases of menstrual psychosis can be categorised based on their timing in relation to the cycle.[110] These include premenstrual (onset in the ten days before menstruation), catamenial (onset with menstruation), midcycle (onset around ovulation, approximately two weeks before menstruation), and epochal (bipolar episodes lasting the whole cycle with switches in polarity linked to menstruation). Classification can also be based on association with events in the reproductive life-cycle, such as menarche, postpartum and menopause. A descriptive summary of cases were published in a 2008 monograph, 'Menstrual Psychosis and the Catamenial Process'[111] which identified approximately 80 cases with strong evidence of episodes being related to the menstrual cycle and 200 possible cases where the association was weaker.

The illness course, symptomatology and effects of treatment have been described for typical cases. Many include onset of episodes during adolescence with some occurring around the time of menarche. Symptoms generally have an abrupt onset and can include affective disturbance (elation, lability, depression) in addition to psychotic symptoms. Like postpartum psychosis, symptoms may include confusion and perplexity, with a fluctuating, 'kaleidoscopic' quality.[112] The prominence of affective presentation and similarity in clinical presentation to postpartum psychosis has led to speculation that it should be considered as part of the bipolar spectrum.[103] Cases should be distinguished from PMDD, which presents with affective disturbance (irritability, anxiety, depression, lability)[113] in the two weeks prior to menstruation, though without symptoms of mania or psychosis. Unlike other psychotic presentations, there is precedent to treat episodes of menstrual psychosis using hormonal strategies, including combined oral contraceptives,[114] transdermal oestradiol[115] and gonadotrophin releasing hormone analogues.[116]

While there are anecdotal descriptions of the phenomenology and management of menstrual psychosis, there has not been a systematic analysis of the most frequently reported symptoms, the age of onset, or the proportion of cases that respond to hormonal treatment.

2.2 Aims

The first aim was to systematically identify cases of menstrual psychosis (defined as brief psychotic episodes linked to the cycle with full recovery between episodes). This involved searching historical literature, previous reviews, and modern electronic databases. The second aim was to characterise the phenotype of menstrual psychosis, in terms of age distribution, symptomatology, cycle phase associated with episodes and relation to other reproductive life events. The third aim was to systematically describe the response to hormonal treatment.

The study was pre-registered with PROSPERO (CRD42023408345), available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=408345

2.3 Methods

2.3.1 Inclusion criteria

Case reports and case series were considered for inclusion where the study authors reported a link between episodes of psychosis and the menstrual cycle. Cases with any psychotic or catatonic symptom were considered. Cases of menstrual exacerbation of a chronic psychotic disorder (without recovery between episodes) were excluded, as were reviews and editorials.

2.3.2 Search strategy

The following databases were searched: MEDLINE, Embase, and PsycINFO. There were no language restrictions, with non-English reports translated using Google Translate. References of included papers, previous reviews[103,110,117] and previous monographs[111,118] were manually searched. An example of the combination of search terms which were searched in the title, abstract, headings, keywords for each database is given below:

((psychosis OR psychotic OR schizophren OR schizoaffective OR bipolar affective OR bipolar disorder OR mania OR manic OR catatoni*) AND (menstrua* OR catamenia* OR monthly OR cyclic* OR menses OR menarche))*

Study screening was performed in duplicate by two independent researchers (the author, in combination with a medical student), with disagreement resolved by discussion. The initial screening of titles and abstracts identified potentially relevant studies, with full texts of these then retrieved and assessed for eligibility. Published cases were supplemented with

anonymised unpublished case reports provided by Professor Ian Brockington, recognised as the foremost expert of this condition.

2.3.3 Data extraction

Clinical and demographic details extracted for cases included age of onset, age of menarche, country, ethnicity, psychiatric diagnosis, relation of episodes to reproductive life events (menarche and childbirth), menstrual phase of episode onset, and number of episodes linked to the cycle. The Association for Methodology and Documentation in Psychiatry (AMDP) symptom checklist[119] was used to extract symptomatology. This consists of 153 symptoms, grouped into symptom domains, covering the full range of psychopathology. If a symptom was not mentioned specifically, it was considered absent. Symptom domains were pre-defined by the AMDP checklist; the domain was considered as present if any symptom in the domain was recorded. A full list of AMDP symptoms and domains is provided in the Appendices. The evidence of association with the menstrual cycle, was graded for each case using criteria adapted from Brockington 2017:[118]

- Very strong evidence: seven or more episodes clearly linked to the cycle with dates of episodes and menstruation provided.
- Strong evidence: seven or more episodes clearly linked to the cycle.
- Medium evidence: five to six episodes or many unnumbered episodes clearly linked to the cycle.
- Low evidence: three to four episodes clearly linked to the cycle or many unnumbered episodes with uncertain link to the cycle. Menstrual relapses following postpartum onset.
- Very low evidence: one to two episodes clearly linked to the cycle. More episodes with uncertain link.

Individual hormonal treatments were categorised as combined (oestrogen and progestogen), oestrogen-only, progestogen only, androgens, thyroid hormone, gonadotrophin releasing hormone agonists, clomiphene, oophorectomy (including irradiation of ovaries). If a treatment was reported in less than five patients or had an unclear description, it was categorised as ‘other’. Response to treatment was categorised as full (episodes were prevented in the absence of antipsychotics), partial (improvement in episodes, possibly in combination with antipsychotics), none (no response or worsening) or unknown. When patients were prescribed multiple hormonal treatments, responses to each were recorded separately.

2.3.4 Data analysis

Case characteristics were presented descriptively as medians and interquartile ranges (IQR) for continuous variables and as proportions for categorical variables. To reduce the large number of symptoms which were absent, any symptom with near zero variance (using a cutoff ratio of 95:5 between the most common value to the second most common value) was excluded.[120] Correlations between continuous variables were calculated using Pearson's coefficient. Correlation between pairs of symptoms was calculate using Pearson's coefficient, corrected at the false discovery rate of 5%, owing to the large number of symptoms.

2.4 Results

2.4.1 Identification of cases

A total of 10,558 records were retrieved from the electronic database search (see Figure 6). After assessing 166 full texts for eligibility, 82 studies were included, comprising data from 112 individual patients. An additional 206 published cases (including historical cases) were identified from previous reviews,[110,111,118] as well as 99 anonymised unpublished cases from Professor Brockington. The total number of cases available for analysis was therefore 417. The full list of cases with references is given in the Appendices.

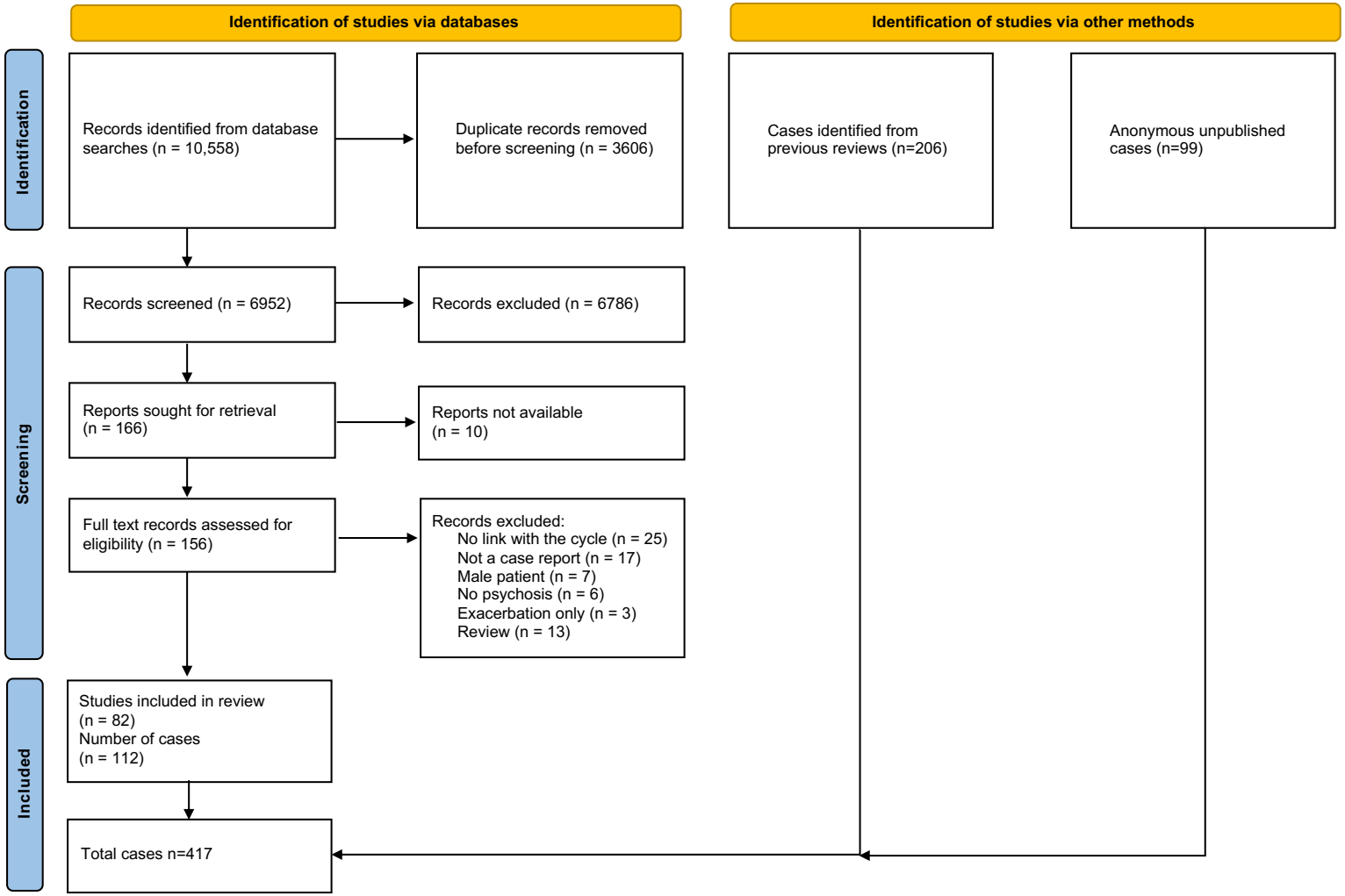


Figure 6. PRISMA flow chart of menstrual psychosis systemic review case selection.

The frequency of published cases over time is shown in Figure 7. The earliest reported case was in 1816, with more than half of cases reported before 1959. Approximately half of published cases were from Europe (n=207, 49.6%). The country with most published cases was Germany (n=66, 15.8%), followed by the USA (n=54, 12.9%), Japan (n=45. 10.8%), the UK (n=43, 10.3%), and France (n=41, 9.8%). A global map showing published cases is shown in Figure 8.

Strength of evidence was rated very strong (requiring seven or more dated menstrual episodes) in 13 cases (3.1%), strong (requiring seven or more menstrual episodes) in 46 (11.0%), medium (requiring 5 – 6 menstrual episodes) in 129 (30.9%), low (3 – 4 menstrual episodes) in 149 (35.7%) and very low (1 – 2 menstrual episodes) in 80 (19.1%).

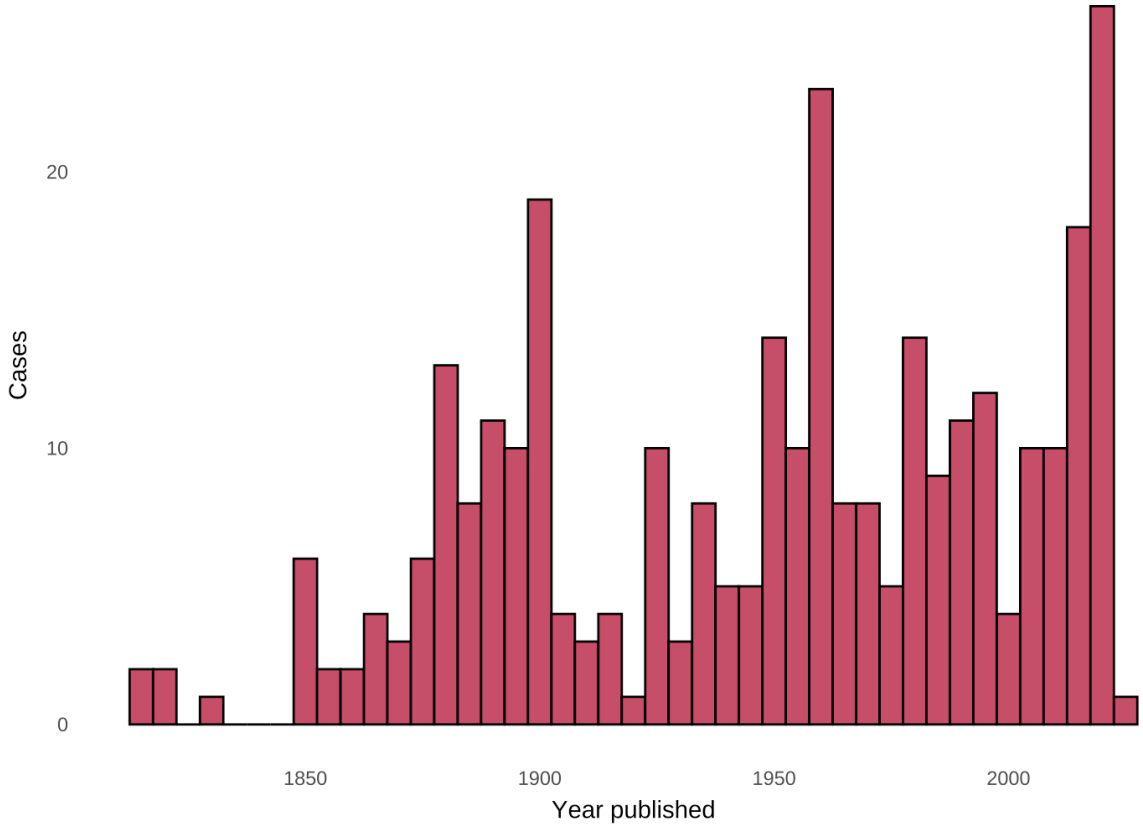


Figure 7. Year of publication for case reports of menstrual psychosis.

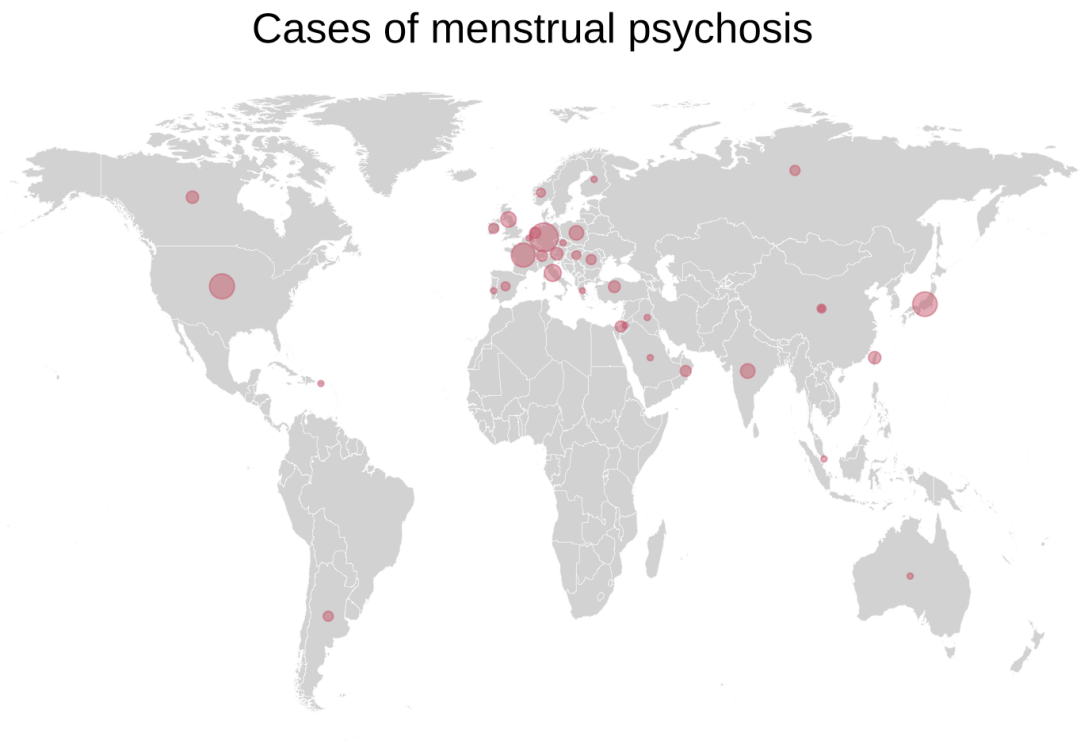


Figure 8. Map of menstrual psychosis case reports, size of circle is proportionate to the number of cases in each country.

2.4.2 Characteristics of cases

Most cases had onset of episodes in the premenstrual (n=230, 55.2%) or catamenial (n=89, 21.3%) phase, or a combination of these phases (n=26, 6.2%). In addition to episodes of menstrual psychosis, 66 cases (15.8%) experienced psychotic episodes relating to childbirth. In 23 (5.5%) this was early-onset postpartum psychosis (occurring within the first two weeks) and in 22 (5.3%) this was late-onset postpartum psychosis. Onset of psychosis occurred around the time of menarche (either before or soon after the first menstrual period) in 55 cases (13.2%). The median number of episodes linked to the cycle was 5 (IQR 3 – 9). There was no correlation between number of episodes and year of publication (r=-0.04, 95% CI -0.18 – 0.1, p=0.547). The modal age of onset was 14 years, the median was 19 years (IQR 15 – 26 years) and the age distribution is shown in Figure 9. Some information was poorly reported: only 101 (24.2%) case reports described the psychiatric diagnosis and only 13 (3.1%) reported race or ethnicity. By contrast, age of onset was reported for 360 cases (86.3%).

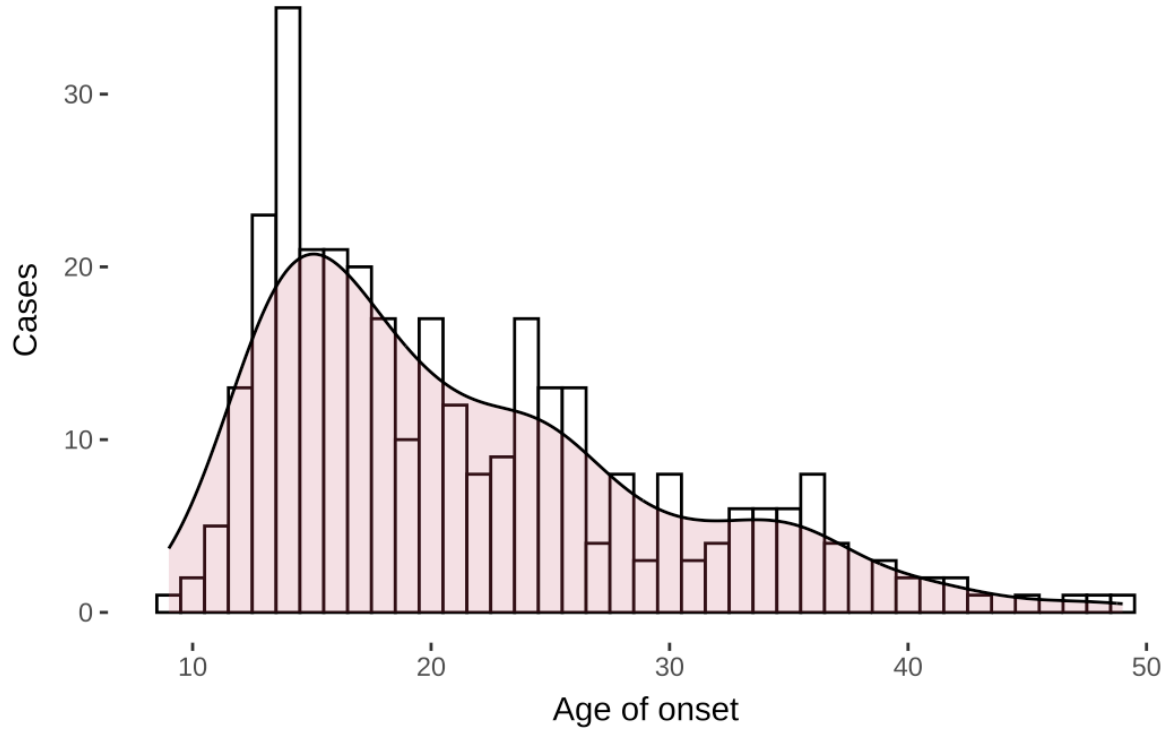


Figure 9. Age distribution of first episode linked to the cycle in menstrual psychosis case reports.

2.4.3 Symptomatology

Frequencies of AMDP symptom domains are shown in Figure 10. The most common symptom domain was disturbance of affect (n=292, 70.0%), followed by disorders of drive and psychomotor activity (n=246, 59.0%), delusions (n=172, 41.2%), disorders of perception (n=164, 39.3%) and disorders of consciousness (n=142, 34.1%).

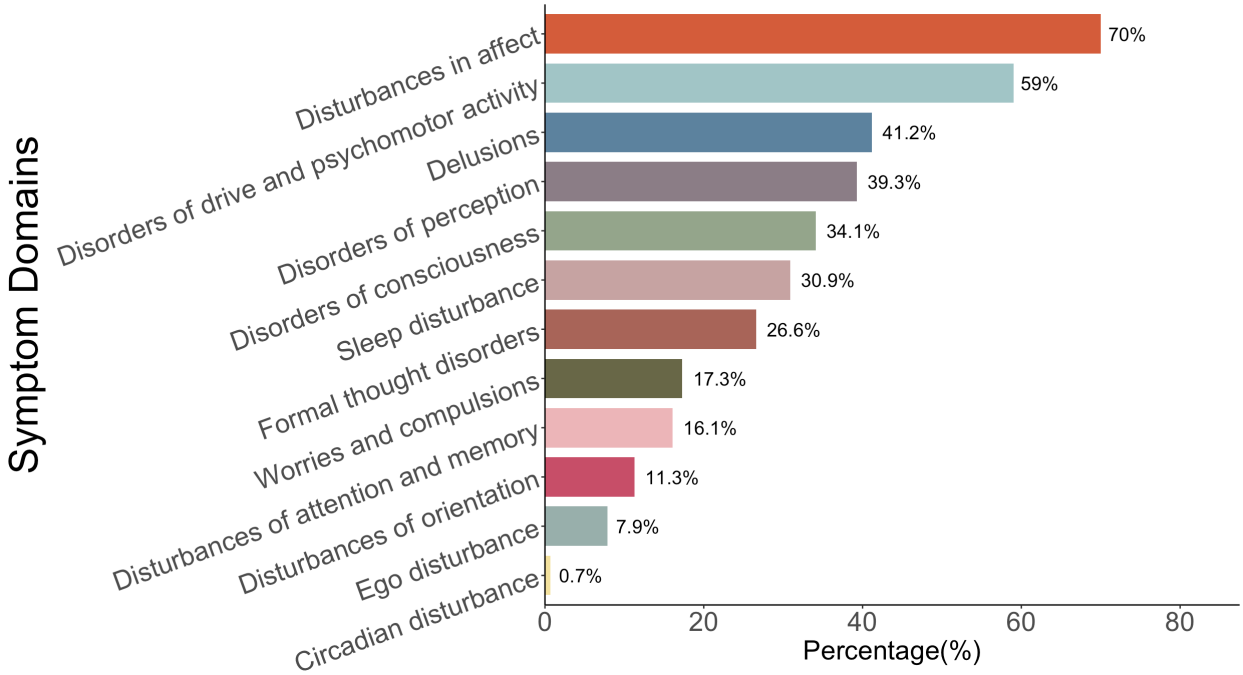


Figure 10. Proportion of AMDP in Psychiatry symptom domains in menstrual psychosis case reports.

Removing symptoms with near zero variance reduced the number from 153 to 39. Proportions of reported symptoms are shown in Figure 11. The most common individual symptom was depressed mood (n=150, 36.0%), followed by motor restlessness (n=134, 32.1%), auditory verbal hallucinations (n=128, 30.7%), euphoria (n=108, 25.9%), clouded consciousness (n=107, 25.7%).

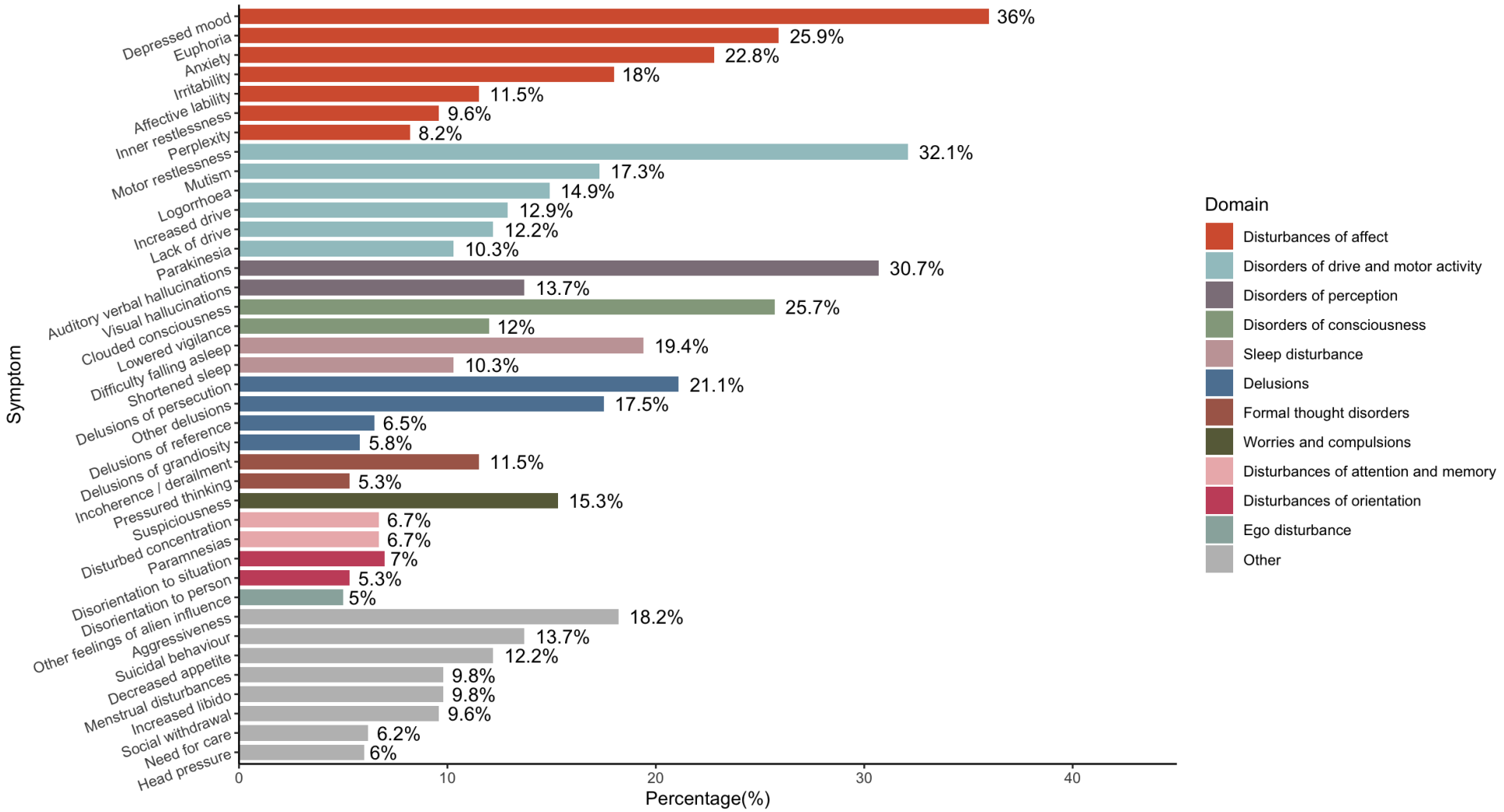


Figure 11. Proportion of individual symptoms as measured by the AMDP in menstrual psychosis case reports, grouped by symptom domain.

There was a weak positive correlation of total number of symptoms reported and year in which the case report was published (r=0.14, 95% CI 0.03 – 0.24, p=0.015). A heatmap of individual symptom correlations is shown in Figure 12. The largest positive correlations were between increased drive and euphoria (r=0.44, 95% CI: 0.36 – 0.51, p<0.0001), decreased appetite and shortened sleep (r=0.41, 95% CI: 0.32 – 0.48, p<0.0001), logorrhoea and euphoria (r=0.34, 95% CI: 0.25 – 0.42, p<0.0001) and decreased appetite and mutism (r=0.33, 95% CI: 0.24 – 0.42, p<0.0001).

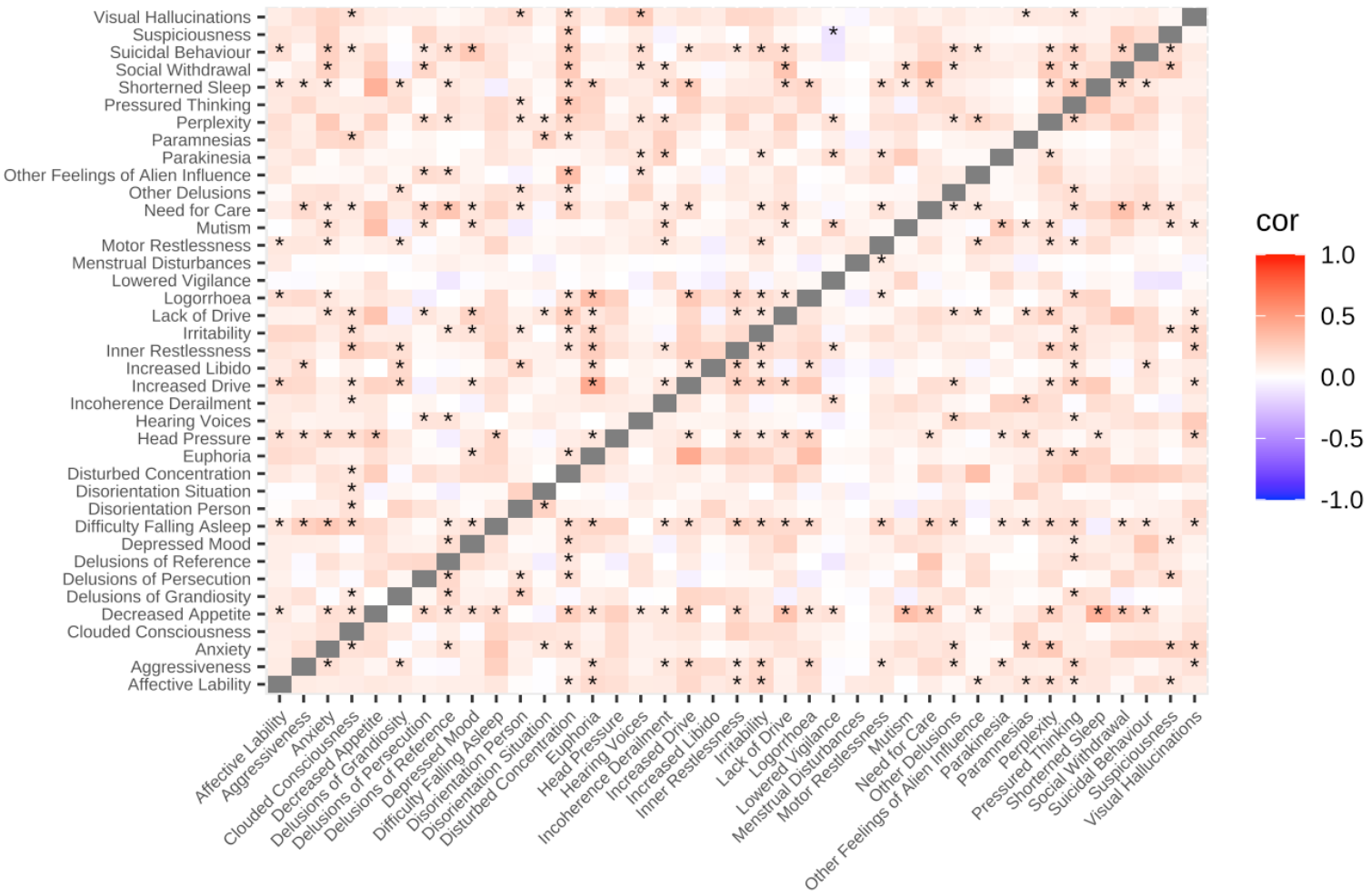


*Figure 12. Heatmap of individual symptom correlation in menstrual psychosis case reports, *indicates statistical significance at false discovery rate of 5%.*

2.4.4 Response to hormone treatments

Around a third of cases (n=130, 31.2%) received at least one treatment that targeted hormonal mechanisms (either through the administration of exogenous hormones or removal of the ovaries). The most common individual hormonal treatment was the combined oral contraceptive (n=47, 11.3%), followed by progesterone (n=31, 7.4%) and thyroid hormone (n=10, 2.4%). The most common type of hormone treatment was the combination of oestrogen and progestogen (n=59,14.1%), followed by progestogen alone (n=48, 11.5%), with the full list shown in Figure 13.

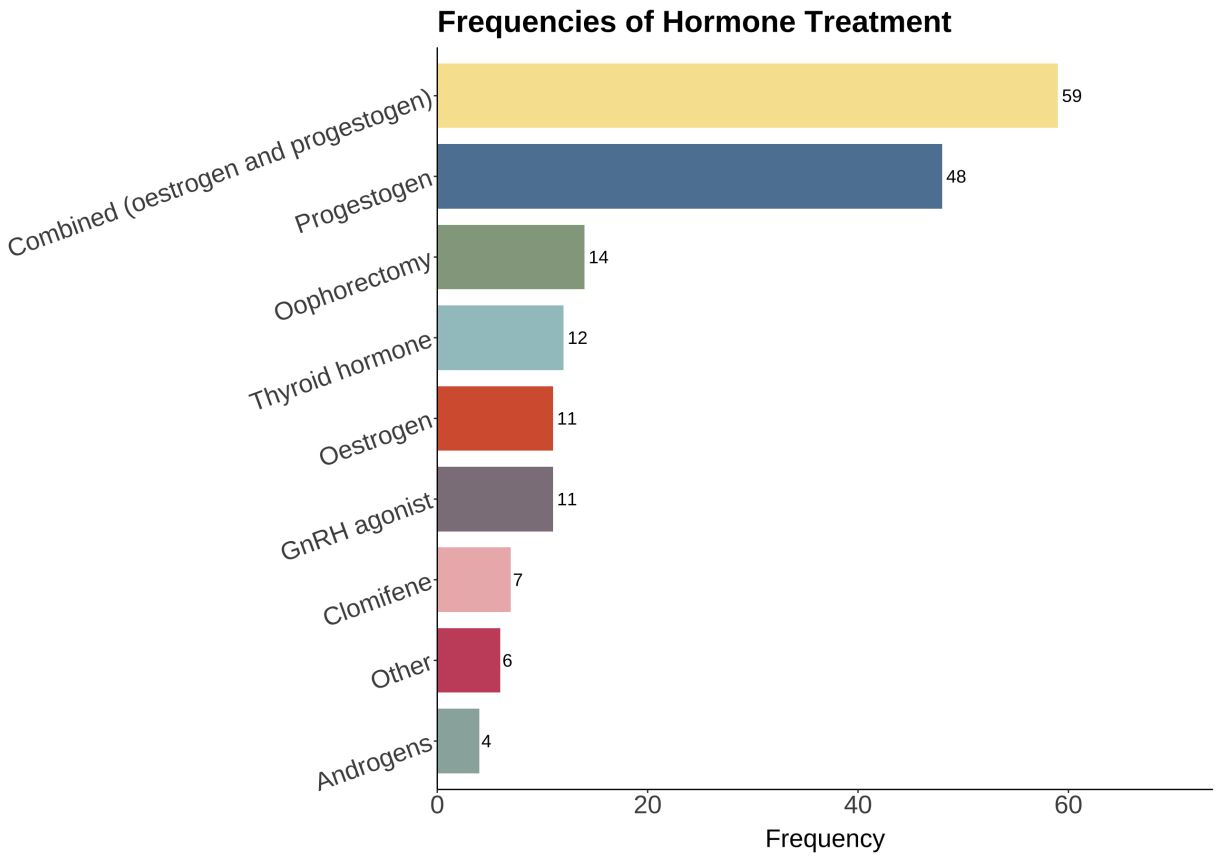


Figure 13. Frequencies of different types of hormonal treatments in menstrual psychosis case reports.

Of the 130 patients who trialled at least one hormonal treatment, 54 (41.5%) had a complete response (prevention of episodes in the absence of antipsychotic medication) to at least one treatment, 45 (34.6%) had a partial response, 19 (14.6%) had no response and in 12 (9.2%) the response was not described. The responses to different types of treatment are shown in Figure 14. Of the most frequent types of treatments, combined hormone therapy showed at least a partial response in 60% of cases, while progestogen-alone showed at least a partial response in

67%. Although not part of the hypothalamic-pituitary-gonadal axis, thyroid hormone was used in 12 cases and had at least a partial response in 10 of these. All case reports describing thyroid hormone treatment were from 1967 or earlier. Oophorectomy or irradiation of the ovaries had a favourable response in half of cases receiving this intervention, with the other half of cases having an unknown or non-response.

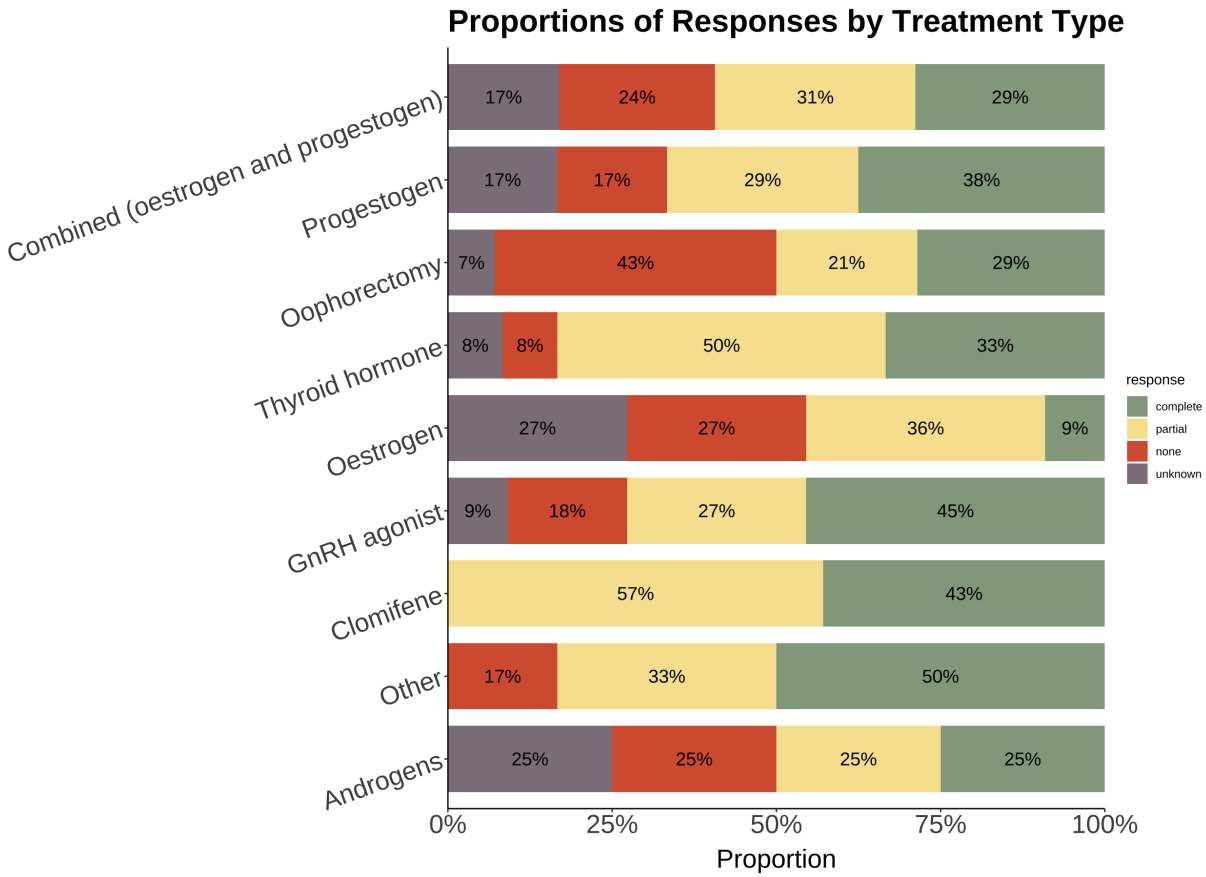


Figure 14. Responses to different types of hormonal treatments in menstrual psychosis case reports.

2.5 Discussion

This was the first systematic search of menstrual psychosis and the largest analysis of cases conducted to date. Menstrual psychosis is predominately a disorder of adolescence, with both the modal and median onset before 20 years of age. Indeed, 59 cases occurred at the time of menarche, suggesting this time of hormonal fluctuation confers a higher risk of psychotic episodes. The modal age of onset of 14 years is clearly lower than that of both schizophrenia (20.5 years), or bipolar disorder (19.5 years).[49] In most cases the onset of episodes was in either

the premenstrual or catamenial phase. This timing of increased risk within the cycle is similar to that for the relapse of an existing psychotic disorder.[57]

The psychopathology of menstrual psychosis suggests a bipolar diathesis: the most commonly reported symptom domain was disturbance of affect, with the most frequent individual symptom being depressed mood. A link is suggested with postpartum psychosis, which is also characterised by affective symptoms, sudden onset, and a subsequent diagnosis of bipolar disorder.[101] Postpartum psychosis is a more widely recognised, but comparably rare condition, occurring in 1-2 per 1000 births.[58] It is therefore striking that one in six cases of menstrual psychosis also experienced psychotic episodes during the postpartum period.

Cases spanned 20 decades, beginning long before psychiatric diagnostic systems were implemented and before antipsychotic medications or exogenous hormonal treatments had been introduced. Despite this, there was no correlation between the year of publication and the number of psychotic episodes linked to the menstrual cycle for each case. However, over time the number of symptoms reported for each case increased, perhaps reflecting a greater lexicon of symptomatology available to the modern psychiatrist. The criteria for 'very strong' evidence of a link to the menstrual cycle were strict, requiring at least seven well described episodes dated and linked to the cycle. Only 13 cases met this requirement. Most of these were reported before the era of antipsychotic medication, with the median published year of 1934. No cases after the year 2000 met the requirement for very strong evidence.

Despite ovarian hormone fluctuation being implicated in menstrual psychosis and hormonal therapies being available since the 1930s, less than a third of reports describe a trial of exogenous hormones. The most frequent hormonal treatment, combined oral contraceptives, is a recommended treatment for premenstrual exacerbation of mental disorders in UK guidelines.[11] This treatment represents a reasonable choice, given the familiarity of oral contraceptives to both patients and clinicians, their known side-effect profile, their place in treatment of premenstrual disorders,[121] and favourable response in almost two thirds of cases reported here. Furthermore, if episodes of menstrual psychosis are triggered by fluctuating hormone levels, suppressing ovulation and providing a stable level of oestrogen and progestogen is a rational treatment strategy.

The next most common treatment, use of a progestogen alone (including both synthetic progestins and progesterone), is not currently recommended for the treatment of premenstrual disorders.[122] Despite this, more than two thirds of cases reported a favourable response, suggesting that it should be re-considered as an intervention in treatment guidelines. Older

case reports, published before 1970, describe trials of thyroid hormone resulting in a favourable response in half of patients. This is in keeping with thyroid-status being linked to schizophrenia since the late 19th century and thyroid hormones being used as an experimental treatment.[123]

There are indications that ovarian hormone fluctuation is not the underlying cause in all cases. Administration of gonadotrophin-releasing hormone analogues, which suppress oestradiol and progesterone and can be used as a diagnostic test for premenstrual disorders[124] showed no improvement in approximately one fifth. Similarly, oophorectomy or ovarian irradiation, which results in low levels of both oestrogen and progesterone showed no response in 43% of cases. It is possible that some patients have coincidental episodes of psychosis which are not related to ovarian hormones. This is supported by brief monthly psychotic episodes being reported in patients who are not experiencing menstrual cycles: during amenorrhoea,[125] pregnancy,[126] post-menopause[127] and in male adolescents.[128] In this respect, we should bear in mind a prescient letter from psychiatrist John Lewis Crammer to The Lancet in 1960, 'All cycles are not menstrual'.[129]

2.5.1 Strengths and limitations

Although a systematic review of case reports allowed quantitative analysis of cases and the largest synthesis to date, this approach has important limitations. Overall, the strength of evidence associated with the cycle was either low or very low in more than half of cases. This reflects cases tending to have a small number of psychotic episodes associated with the cycle. As approximately half the cases were reported before the advent of modern diagnostic classification systems, the description of symptoms may not reflect current psychiatric practice. Case reports rely on a clinician recognising menstrual psychosis and then publishing a description. As such they are unlikely to be representative of the underlying patient population, a limitation which will be addressed in the next Chapter. Furthermore, symptom data was extracted from written case reports, rather than direct interview with patients, with presence/absence of a symptom relying on it being correctly reported. Future studies should aim for more systematic assessment of symptomatology to more robustly characterise the condition.

2.5.2 Conclusion

Menstrual psychosis is a condition which has been described in hundreds of case reports. It has a peak onset in adolescence and most frequently presents as an affective psychosis. Most cases have episodes which begin in the premenstrual or catamenial phase. Many cases have been successfully treated using hormonal therapies, often using the combined oral

contraceptive. Nevertheless, case reports are anecdotal forms of evidence, which are merely descriptive, have inherent bias, may be unrepresentative of the underlying patient population and have no comparison group. To address these limitations, the next Chapter will use an alternative approach, identifying cases through searching electronic health records of a large mental health service.

3 Identification and analysis of menstrual psychosis cases using electronic health records

3.1 Introduction

An alternative approach to examining case-reports is to systematically search electronic health records for cases meeting the clinical criteria of menstrual psychosis. This method of identifying cases does not rely on a clinician to publish the clinical details and is therefore not subject to this form of publication bias. Thus, cases identified through electronic health records may be more representative of the underlying patient population. Furthermore, a control group of patients experiencing psychotic episodes not linked to the menstrual cycle can be extracted from the same local population and used as a comparator. The clinical characteristics from the case report literature can also be compared with unpublished cases from electronic health records to determine whether there are systemic differences between published and unpublished cases. To do this, I harmonised data extraction from each cohort.

Cases were extracted from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre) Case Register[130] which contains structured data (for example, age, sex, ethnicity, ICD-10 diagnosis) as well as free-text from clinical notes which can be screened using a list of search-terms. I have previously used similar methodology to characterised cases of psychosis linked to cannabis withdrawal.[131]

3.2 Aims

The first aim was to identify menstrual psychosis cases by examining a large number of electronic health records using the Clinical Record Interactive Search (CRIS) of South London and Maudsley NHS Foundation Trust.[130] The second aim was to rate the strength of evidence for association with the menstrual cycle and describe clinical characteristics of this population relative to a matched patient group. The third aim was to compare cases identified through electronic health record search to case reports identified in the preceding Chapter.

3.3 Methods

3.3.1 Electronic health record search

The study utilised data from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre Case Register, serving a catchment area of over 1.2 million residents in South East London and containing anonymised records of over 400,000 patients receiving secondary mental healthcare.[130] The project was approved under CRIS Ethics (Oxfordshire Research Ethics

Committee, reference 23/SC/0257), with the subproject ID 23-038 gaining approval by the CRIS Oversight Committee.

The entirety of the case register (over 400,000 electronic records) was searched from inception (the records became fully electronic in April 2006) to April 2024. Keywords were used to search the free-text fields of clinical records, for example (premenstrual, menstrual, catamenial, menses) combined with (psychosis, psychotic, mania, manic, bipolar, schizophrenia, schizoaffective). Next, a search of cases with a recorded ICD-10[105] diagnostic codes for psychotic disorders was performed, using the search terms 'premenstrual' and 'menstrual'. A full list of the terms used is provided in the Appendices.

3.3.2 Case screening

Initial screening was performed by the author, with all possible cases for inclusion checked by a second psychiatrist. Clinical records, including emergency assessments, progress notes, ward rounds, clinic letters, and discharge summaries were manually reviewed. The same inclusion criteria were used as the previous Chapter: (i) acute psychotic episodes; (ii) of less than two weeks in duration; (iii) in synchrony with the cycle; (iv) with full recovery between episodes. Patients who had menstrual exacerbation of a chronic psychotic disorder (worsening of psychosis associated with the cycle but not discrete psychotic episodes) were excluded.

3.3.3 Data extraction

The same strength of evidence ratings were performed as the previous Chapter, in duplicate, with disagreement resolved by discussion. Each case was graded as having very strong, strong, medium, low, or very low evidence of association with the menstrual cycle. Routinely collected data such as age, ethnicity, ICD-10 diagnosis, and index of multiple deprivation (IMD) score were automatedly extracted from structured fields in the health record. Ethnicity was grouped into Asian, Black, Mixed race, Other, White, or Missing. Individual symptoms and symptom domains were extracted through manual inspection of the clinical record, using the AMDP symptom checklist,[119] as in the previous Chapter, with the full list of symptoms available in the Appendices. Response to treatment was categorised in the same way as the previous Chapter as complete, partial or no response.

3.3.4 Identification of controls

Up to four controls were identified for each case, from the same set of health records. For some cases, less than four adequately matched controls could be identified within the population. All controls were female; they were then matched by ethnicity, age of illness onset (within a two-year period), and primary ICD-10 diagnosis. Patients who had any mention of menstrual

exacerbation of illness were excluded from being controls. For both cases and controls, three clinical outcomes were automatedly extracted from the health records: the total number of inpatient admissions, inpatient bed-days and number of face-to-face contacts.

3.3.5 Data analysis

All analyses were carried out using R Statistical Software version 4.4.0. The presence/absence of individual symptoms was compared between groups using logistic regression. To reduce a large number of symptoms which were absent in both cases and controls, any symptom with near zero variance (using a cutoff ratio of 95:5 between the most common value to the second most common value) was excluded from the analysis.[120] Symptom domains were pre-specified, taken from the AMDP system; if any individual symptom was present, the symptom domain was categorised as present. To control for multiple comparisons, the false discovery rate was set at 5% using the Benjamini-Hochberg procedure.[132] Continuous variables were compared using t-tests if normally distributed and Mann-Whitney U tests if not. Categorical variables were compared using chi squared tests.

3.4 Results

3.4.1 Identification of cases

The clinical record search returned 544 unique patient records, see Figure 15. Of these, 421 were excluded: 322 had no evidence of psychotic symptoms, 70 had no link with the menstrual cycle and 29 were irrelevant records. Of the 123 records in which a patient, family member or clinician reported a link between symptoms and the cycle, 77 were an exacerbation of an underlying mental disorder, 4 were likely PMDD or premenstrual syndrome (PMS), 4 provided insufficient information, and 38 met criteria for menstrual psychosis. Of these, a single case had very strong evidence, 2 had strong evidence, 8 had medium evidence, 10 had low evidence and 17 had very low evidence. In 22 cases, the diagnosis ‘menstrual psychosis’ was explicitly mentioned in the clinical record.

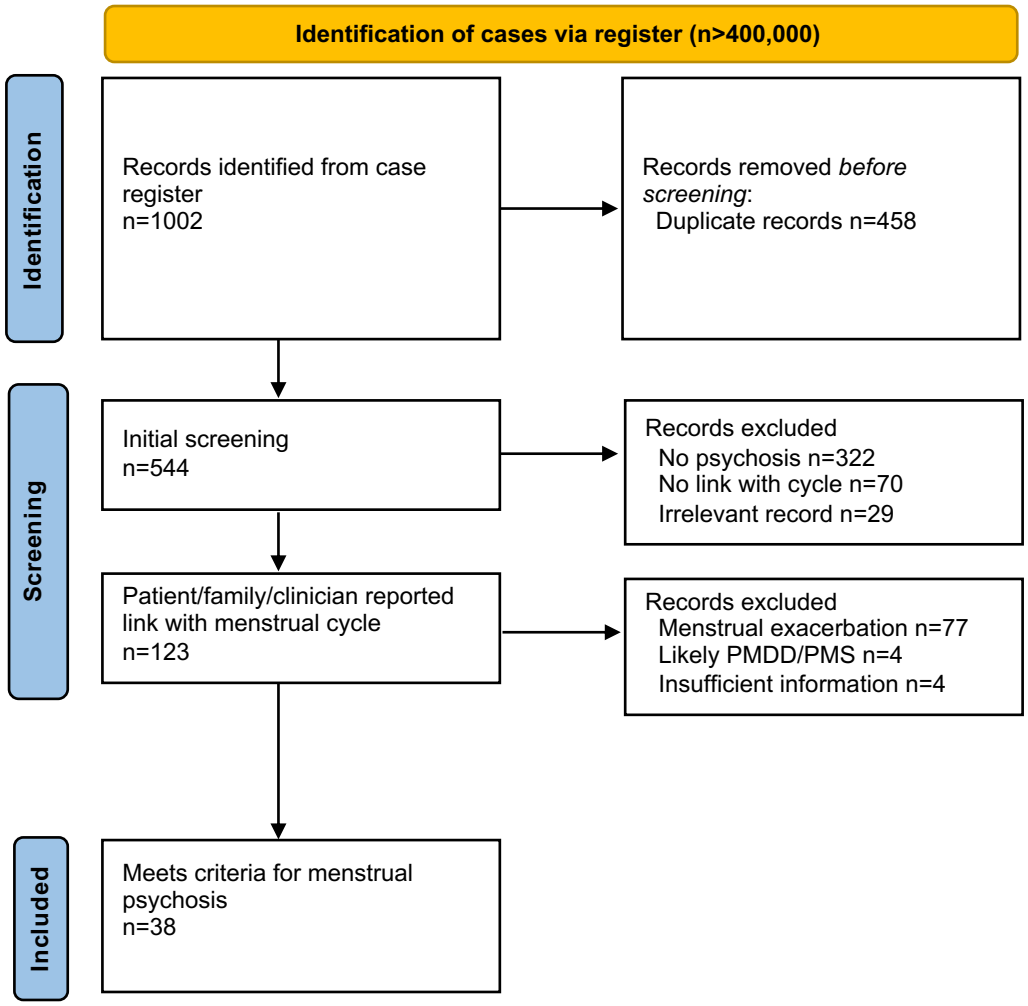


Figure 15. Flow diagram of menstrual psychosis cases identified by search of electronic health records. PMDD – premenstrual dysphoric disorder, PMS – premenstrual syndrome.

3.4.2 Characteristics of cases

Cases had a modal age of onset of 14 years and a median age of onset of 17 years (IQR 14 – 26 years). Seven had onset around the time of menarche (either before or soon after the first menstrual period). In terms of menstrual cycle phase, 24 (63.2%) had premenstrual onset, 11 (28.9%) had catamenial onset, one had episodes both premenstrually and catamenially, one had unclear onset, and one had midcycle onset. The median number of psychotic episodes associated with the cycle was 3 (IQR 2 – 4). The most common ethnicity was Black (n=15, 39.5%), with most cases being non-White (n=23, 60.5%). The most common clinical diagnosis

was bipolar disorder (n=13, 34.2%). Four cases had a documented clinical diagnosis of postpartum psychosis in their health record.

3.4.3 Response to hormone treatments

In more than half of cases (n=21, 55.3%), hormone treatment had been initiated, mainly in the form of a combined oral contraceptive (n=20), in all cases as an adjunct to antipsychotic medication. In 15 cases this resulted in a partial or complete response (defined as the prevention of further episodes).

3.4.4 Case-control comparison

Symptom data were extracted from 38 cases and 112 matched controls. The total number of individual symptoms was similar between groups (cases mean 14.6, SD 7.2, controls mean 14.8, SD 6.6, p=0.840). Removing symptoms with near zero variance reduced the number of symptoms from 153 to 56. The proportions of symptoms domains (defined by the presence of at least one individual symptom in that domain) present in cases and controls are shown in Table 1. All cases displayed at least one affective symptom. Hallucinations were present in 28 cases (73.7%), while disorders of drive and psychomotor activity were present in 23 (60.5%).

After correcting for multiple comparisons, cases had a higher proportion of disorders of consciousness (OR 4.7, 95% 2.1 – 10.73, p<0.001), but a lower proportion of worries/compulsions (OR 0.34, 95% CI: 0.16 – 0.73, p=0.033) relative to controls, as shown in Table 1 and displayed as a forest plot in Figure 2. After correcting for multiple comparisons, cases had higher odds of incoherence/derailment (OR 5.48, 95% CI: 1.83 – 17.57, p=0.037), clouded consciousness (OR 4.23, 95% CI: 1.88 – 9.65, p=0.019) and labile affect (OR 3.09, 95% CI: 1.45 – 6.76). Conversely, cases had lower odds of suicidal behaviour (OR 0.2, 95% CI: 0.08 – 0.46, p<0.001), depressed mood (OR 0.21, 95% CI: 0.09 – 0.45, p<0.001), self-harm (OR 0.24, 95% CI: 0.08 – 0.62, p=0.048) and suspiciousness (OR 0.32, 95% CI: 0.15 – 0.69, p=0.037).

*Table 1. Logistic regression of symptom domains by menstrual psychosis case-control status. P values are corrected for multiple comparisons using the Benjamini-Hochberg procedure. OR – Odds Ratio, 95% CI – 95% Confidence Interval. *Indicates statistical significance at false discovery rate of 5%. Proportion of cases with Disturbances of affect reduced to 0.99 to allow calculation of OR.*

	Proportion				
Symptom domain	Cases (n=38)	Controls (n=112)	OR	95% CI	Corrected p value
Disturbances of affect	0.99	0.96	3.5	0.37 – 466.5	0.628
Disorders of perception	0.74	0.79	0.76	0.33 – 1.85	0.736
Disorders of drive and psychomotor activity	0.61	0.69	0.7	0.33 – 1.51	0.649
Formal thought disorders	0.58	0.42	1.9	0.91 – 4.06	0.305
Sleep disturbance	0.58	0.62	0.86	0.41 – 1.83	0.755
Delusions	0.53	0.39	1.72	0.82 – 3.63	0.337
Disorders of consciousness	0.47	0.16	4.7	2.1 – 10.73	<0.001*
Worries and compulsions	0.47	0.72	0.34	0.16 – 0.73	0.033*
Disturbances of attention and memory	0.37	0.44	0.75	0.35 – 1.58	0.718
Ego disturbances	0.24	0.21	1.2	0.48 – 2.82	0.755
Disturbances of disorientation	0.21	0.11	2.22	0.80 – 5.89	0.305

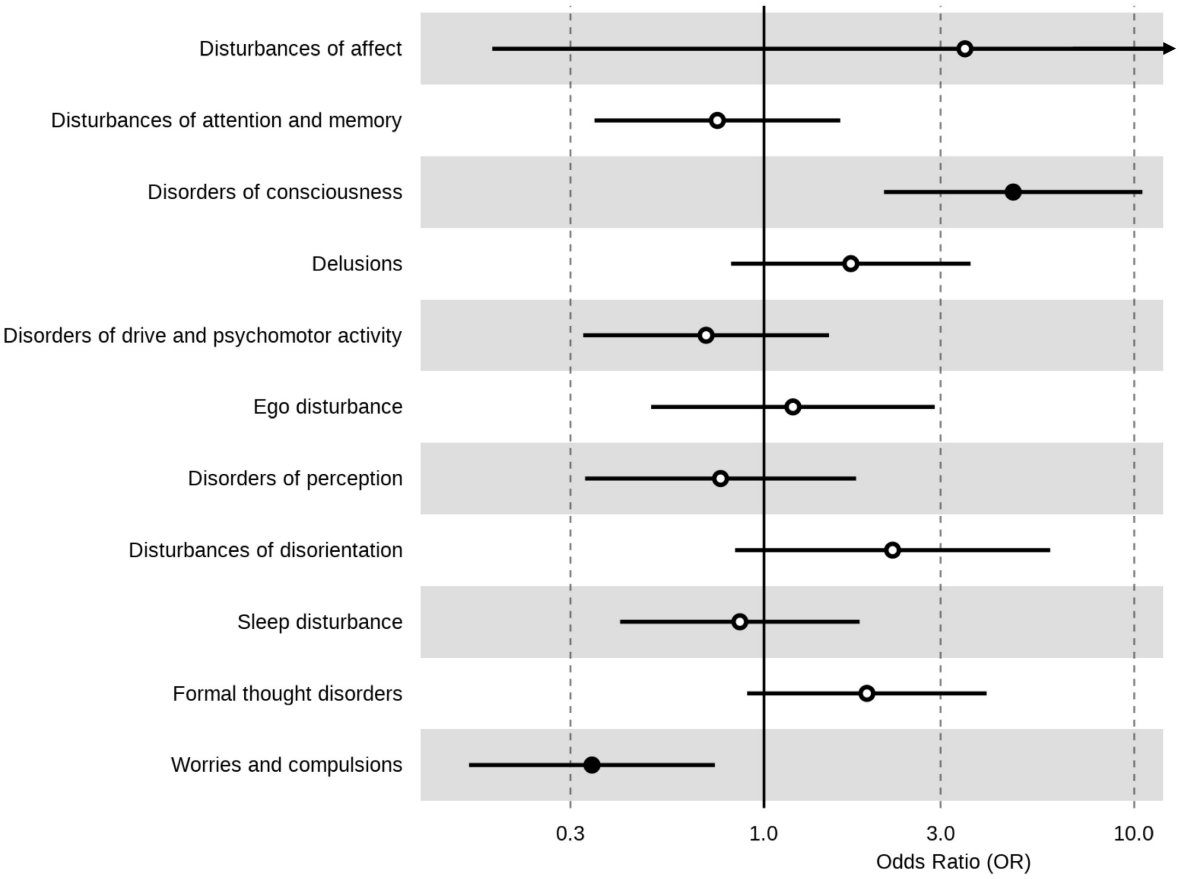


Figure 16. Forest plot of the association of symptom domains with menstrual psychosis case-control status. Odds Ratio >1 indicates higher likelihood in cases, Odds Ratio <1 indicates higher proportion in controls. Black circle indicates statistical significance corrected at the False Discovery Rate of 5%.

The proportions of individual symptoms in cases and controls are shown in Table 2. The most common symptom in cases was auditory verbal hallucinations (n=26, 68.4%), affective lability (n=24, 63.2%), anxiety in (n=24, 63.4%), euphoria (n=19, 50.0%) and motor restlessness (n=19, 50%). Logistic regression results are shown in Table 2 and as forest plot in Figure 18. After correcting for multiple comparisons, cases had higher odds of incoherence/derailment (OR 5.48, 95% CI: 1.83 – 17.57, p=0.037), clouded consciousness (OR 4.23, 95% CI: 1.88 – 9.65, p=0.019) and labile affect (OR 3.09, 95% CI: 1.45 – 6.76). Conversely, cases had lower odds of suicidal behaviour (OR 0.2, 95% CI: 0.08 – 0.46, p<0.001), depressed mood (OR 0.21, 95% CI: 0.09 – 0.45, p<0.001), self-harm (OR 0.24, 95% CI: 0.08 – 0.62, p=0.048) and suspiciousness (OR 0.32, 95% CI: 0.15 – 0.69, p=0.037).

*Table 2. Logistic regression of individual symptoms by menstrual psychosis case-control status. P values are corrected for multiple comparisons using the Benjamini-Hochberg procedure. OR – Odds Ratio, 95% CI – 95% Confidence Interval. *Indicates statistical significance at false discovery rate of 5%*

Symptom	Proportion Cases (n=38)	Controls (n=112)	OR	95% CI	Corrected p value
Clouded consciousness	0.45	0.16	4.23	1.88 – 9.65	0.019*
Disorientation to situation	0.16	0.09	1.91	0.61 – 5.57	0.576
Disturbed concentration	0.34	0.44	0.67	0.30 – 1.42	0.594
Disturbed short-term memory	0.03	0.07	0.35	0.02 – 2.01	0.594
Retarded thinking	0.13	0.07	1.97	0.56 – 6.33	0.587
Pressured thinking	0.29	0.23	1.35	0.57 – 3.04	0.672
Flight of ideas	0.08	0.12	0.65	0.14 – 2.17	0.706
Tangential thinking	0.34	0.23	1.72	0.76 – 3.81	0.501
Incoherence/derailment	0.24	0.05	5.48	1.83 – 17.57	0.037*
Suspiciousness	0.45	0.71	0.32	0.15 – 0.69	0.037*
Delusions of reference	0.11	0.11	0.98	0.26 – 3.03	0.982
Delusions of persecution	0.37	0.29	1.46	0.66 – 3.15	0.594
Delusions of grandiosity	0.13	0.13	0.98	0.30 – 2.75	0.982
Other delusions	0.29	0.19	1.77	0.74 – 4.07	0.501
Auditory verbal hallucinations	0.68	0.73	0.79	0.36 – 1.81	0.709
Visual hallucinations	0.37	0.29	1.46	0.66 – 3.15	0.594
Bodily hallucinations	0.08	0.12	0.6	0.13 – 1.97	0.67
Olfactory and gustatory hallucinations	0.08	0.04	1.83	0.36 – 7.87	0.656
Thought broadcasting	0.08	0.09	0.87	0.19 – 3.05	0.946
Other feelings of alien influence	0.13	0.1	1.39	0.41 – 4.13	0.709
Perplexity	0.34	0.21	2.01	0.88 – 4.51	0.392
Blunted affect	0.29	0.22	1.42	0.60 – 3.21	0.656
Depressed mood	0.39	0.76	0.21	0.09 – 0.45	<0.001*
Hopelessness	0.13	0.25	0.45	0.14 – 1.19	0.473
Anxiety	0.63	0.67	0.85	0.40 – 1.85	0.814
Euphoria	0.5	0.38	1.67	0.79 – 3.52	0.501
Irritability	0.47	0.57	0.67	0.32 – 1.41	0.594
Inner restlessness	0.08	0.17	0.42	0.09 – 1.33	0.501
Feelings of inadequacy	0.18	0.11	1.88	0.65 – 5.11	0.565
Exaggerated self-esteem	0.18	0.14	1.35	0.48 – 3.49	0.706
Incongruent affect	0.18	0.14	1.35	0.48 – 3.49	0.706
Affective lability	0.63	0.36	3.09	1.45 – 6.76	0.037*
Lack of drive	0.05	0.29	0.14	0.02 – 0.49	0.063
Increased drive	0.11	0.19	0.51	0.14 – 1.46	0.576
Motor restlessness	0.5	0.46	1.15	0.55 – 2.42	0.825
Parakinesia	0.13	0.09	1.55	0.45 – 4.69	0.671
Mutism	0.21	0.07	3.47	1.18 – 10.2	0.123
Logorrhoea	0.08	0.09	0.87	0.19 – 3.05	0.946
Social withdrawal	0.16	0.24	0.59	0.21 – 1.48	0.594

Aggressiveness	0.34	0.43	0.69	0.31 – 1.47	0.594
Suicidal behaviour	0.21	0.57	0.2	0.08 – 0.46	<0.001*
Self-harm	0.13	0.38	0.24	0.08 – 0.62	0.048*
Lack of insight	0.34	0.18	2.39	1.03 – 5.46	0.199
Need for care	0.18	0.18	1.04	0.38 – 2.60	0.982
Attacks of anxiety	0.13	0.12	1.06	0.32 – 3.01	0.982
Acceleration of thinking	0.39	0.19	2.83	1.26 – 6.34	0.068
Impulsivity	0.29	0.21	1.49	0.63 – 3.39	0.594
Difficulty falling asleep	0.18	0.34	0.44	0.17 – 1.04	0.355
Interrupted sleep	0.24	0.27	0.85	0.34 – 1.95	0.825
Shortened sleep	0.29	0.23	1.35	0.57 – 3.04	0.672
Early morning wakening	0.05	0.1	0.51	0.08 – 2.02	0.652
Tiredness	0.03	0.12	0.21	0.01 – 1.09	0.473
Decreased appetite	0.18	0.32	0.48	0.18 – 1.13	0.444
Menstrual disturbances	0.05	0.05	0.98	0.14 – 4.48	0.982
Head pressure	0.16	0.08	2.15	0.67 – 6.42	0.501
Increased libido	0.13	0.12	1.06	0.32 – 3.01	0.982

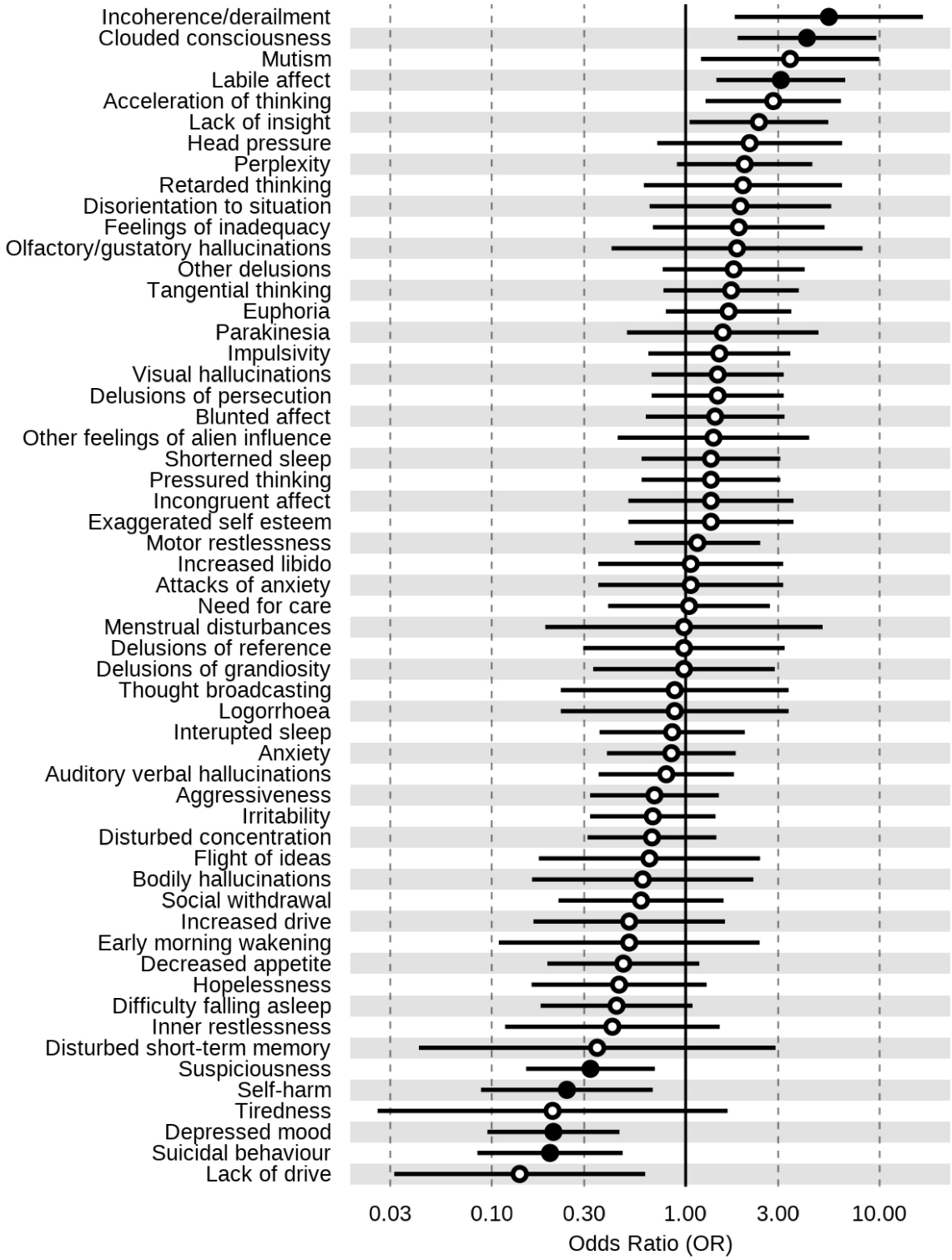


Figure 17. Forest plot of the association of individual symptoms with menstrual psychosis case-control status. Odds Ratio >1 indicates higher proportion in cases, Odds Ratio <1 indicates higher proportion in controls. Black circle indicates statistical significance corrected at the false discovery rate of 5%.

Follow-up information was available for 33 (89.5%) cases and 107 (91.5%) controls. There were no statistically significant differences in matching variables, or in IMD score (Table 3). There were no group differences in the total number of inpatient admissions, number of inpatient bed-days, or number of clinical contacts.

Table 3. Comparison of menstrual psychosis cases and controls. SD – standard deviations, IMD – index of multiple deprivation, IQR – interquartile range. Groups were compared using t-test for age and IMD score, chi squared test for ethnicity and diagnosis, and Mann-Whitney U test for admissions, contacts and bed days.

	Case (n=33)	Control (n=107)	p value
Age, mean (SD)	22.7 (10.8)	24.5 (10.7)	0.165
Ethnicity, number			
Asian	2 (6.1%)	4 (3.8%)	0.943
Black	14 (42.2%)	41 (38.1%)	
Missing	2 (6.1%)	9 (8.4%)	
Mixed race	2 (6.1%)	4 (3.7%)	
Other	1 (3.0%)	5 (4.7%)	
White	12 (36.4%)	44 (41.1%)	
Diagnosis (ICD-10), number			
Acute and transient psychotic disorders (F23)	9 (27.3%)	30 (28.0%)	0.957
Bipolar disorder (F32)	12 (36.4%)	32 (29.9%)	
Depressive disorder (F32.3)	2 (6.1%)	7 (6.5%)	
Nonorganic psychosis (F29);	6 (18.2%)	25 (23.4%)	
Schizophrenia (F20)	4 (12.1%)	13 (12.1%)	
IMD score, mean (SD)	23.2 (8.9)	26.0 (10.4)	0.168
Clinical outcomes			
Number of admissions, median (IQR)	2 (1 – 3)	2 (1 – 4)	0.660
Number of contacts, median (IQR)	54 (22 – 146)	48.5 (11 – 153)	0.547
Number of bed days, median (IQR)	131 (36 – 154)	80 (28 – 264)	0.971

3.4.5 Comparison with case-reports

Comparison between electronic health record cases and with case-reports is shown in Table 4. There was no difference in age between groups (p=0.325). Case reports had a greater number of episodes associated with the cycle than cases from electronic health records, while the total number of symptoms extracted was higher in electronic health record cases.

Table 4. Comparison of menstrual psychosis case reports and menstrual psychosis cases from electronic health records, using Mann-Whitney U-test. EHR – electronic health records, IQR – interquartile range. *Indicates statistical significance at the level of p<0.05.

	Case reports (n=417)	EHR (n=38)	p value
Age, median (IQR)	19 (15 – 26)	17 (14 – 25.5)	0.325
Number of episodes associated with cycle, median (IQR)	5 (3 – 9)	3 (2 – 4)	<0.0001*
Number of symptoms extracted, median (IQR)	5 (3 – 9)	14 (10 – 19)	<0.0001*

Logistic regression for symptom domains is shown in Table 5. In the univariable analyses, symptom domains of disturbances of attention and memory, ego disturbance, disorders of perception, sleep disturbance, formal thought disorders and worries/compulsions were more common in cases detected from electronic health records. However, when adjusting for total number of symptoms, none of these remained statistically significant. Instead, the only symptom domain which was different between groups was disorders of drive and psychomotor activity, which was more common in case reports (adjusted OR 0.10, 95% CI: 0.03 – 0.26, p<0.001), as shown in Figure 18.

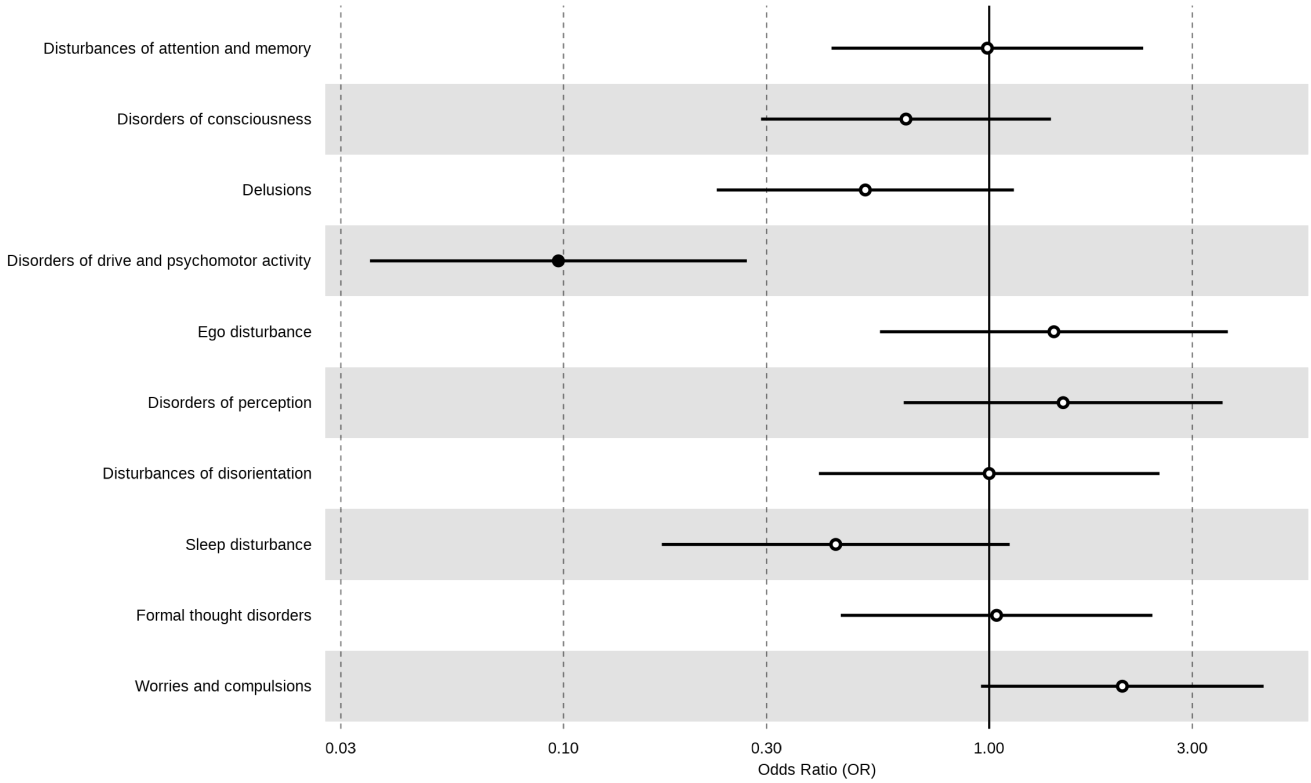


Figure 18. Forest plot showing the association of AMDP symptom domains between menstrual psychosis case reports and menstrual psychosis cases from electronic health records, adjusted for total number of symptoms. Odds Ratio >1 indicates higher proportion in cases from electronic health records, Odds Ratio <1 indicates higher proportion in case reports. Black circle indicates statistical significance corrected at the false discovery rate of 5%.

*Table 5. Logistic regression of AMDP symptom domains comparing menstrual psychosis case reports to menstrual psychosis cases identified by electronic health records. P values are corrected for multiple comparisons using the Benjamini-Hochberg procedure. EHR – electronic health records, OR – Odds Ratio, 95% CI – 95% Confidence Interval. *Indicates statistical significance at false discovery rate of 5%† indicates test not performed due to 100% of cases having this symptom domain*

			Unadjusted		Adjusted for total number of symptoms	
AMDP Domain	Proportion case reports	Proportion EHR	OR (95% CI)	p value	OR (95% CI)	p value
Disorders of consciousness	0.34	0.47	1.74 (0.89 – 3.41)	0.142	0.64 (0.29 – 1.38)	0.568
Disturbances of disorientation	0.11	0.21	2.1 (0.86 – 4.66)	0.129	1 (0.37 – 2.39)	0.992
Disturbances of attention and memory	0.16	0.37	3.05 (1.47 – 6.13)	0.004*	0.99 (0.41 – 2.26)	0.992
Formal thought disorders	0.27	0.58	3.79 (1.93 – 7.59)	<0.001*	1.04 (0.44 – 2.39)	0.992
Worries and compulsions	0.17	0.47	4.31 (2.16 – 8.58)	<0.001*	2.06 (0.95 – 4.38)	0.272
Delusions	0.41	0.53	1.58 (0.81 – 3.11)	0.216	0.51 (0.23 – 1.13)	0.272
Disorders of perception	0.39	0.74	4.32 (2.11 – 9.57)	<0.001*	1.49 (0.64 – 3.6)	0.656
Ego disturbances	0.08	0.24	3.61 (1.51 – 8.03)	0.004*	1.42 (0.53 – 3.52)	0.724
Disturbances of affect	0.70	1.0	NA	NA	NA	NA
Disorders of drive and psychomotor activity	0.59	0.61	1.07 (0.55 – 2.14)	0.939	0.1 (0.03 – 0.26)	<0.001*
Sleep disturbance	0.31	0.58	3.07 (1.57 – 6.13)	0.003*	0.44 (0.17 – 1.11)	0.272

Logistic regression for individual symptoms is shown in Table 6 showing both crude rates and adjusted for total number of symptoms. Multiple symptoms were more common in the cases detected from electronic health records including acceleration of thinking, labile affect, tangential thinking, pressured thinking, disturbed concentration, perplexity, anxiety, auditory verbal hallucinations, exaggerated self-esteem, suspiciousness, irritability, visual hallucinations, shortened sleep, need for care, euphoria, clouded consciousness and aggressiveness. However, after adjusting for total number of symptoms, only acceleration of thinking (adjusted OR 11.2, 95% CI 4.4 – 29.0, $p<0.001$), affective lability (adjusted OR 7.0, 95% CI 3.2 – 15.6, $p<0.001$), and tangential thinking (adjusted OR 6.8, 95% CI 2.8 – 16.4, $p<0.001$) remained statistically significant. Lack of drive was the only symptom more common in case reports (adjusted OR 0.07, 95% CI 0.01 – 0.3, $p=0.020$), as shown in Figure 19.

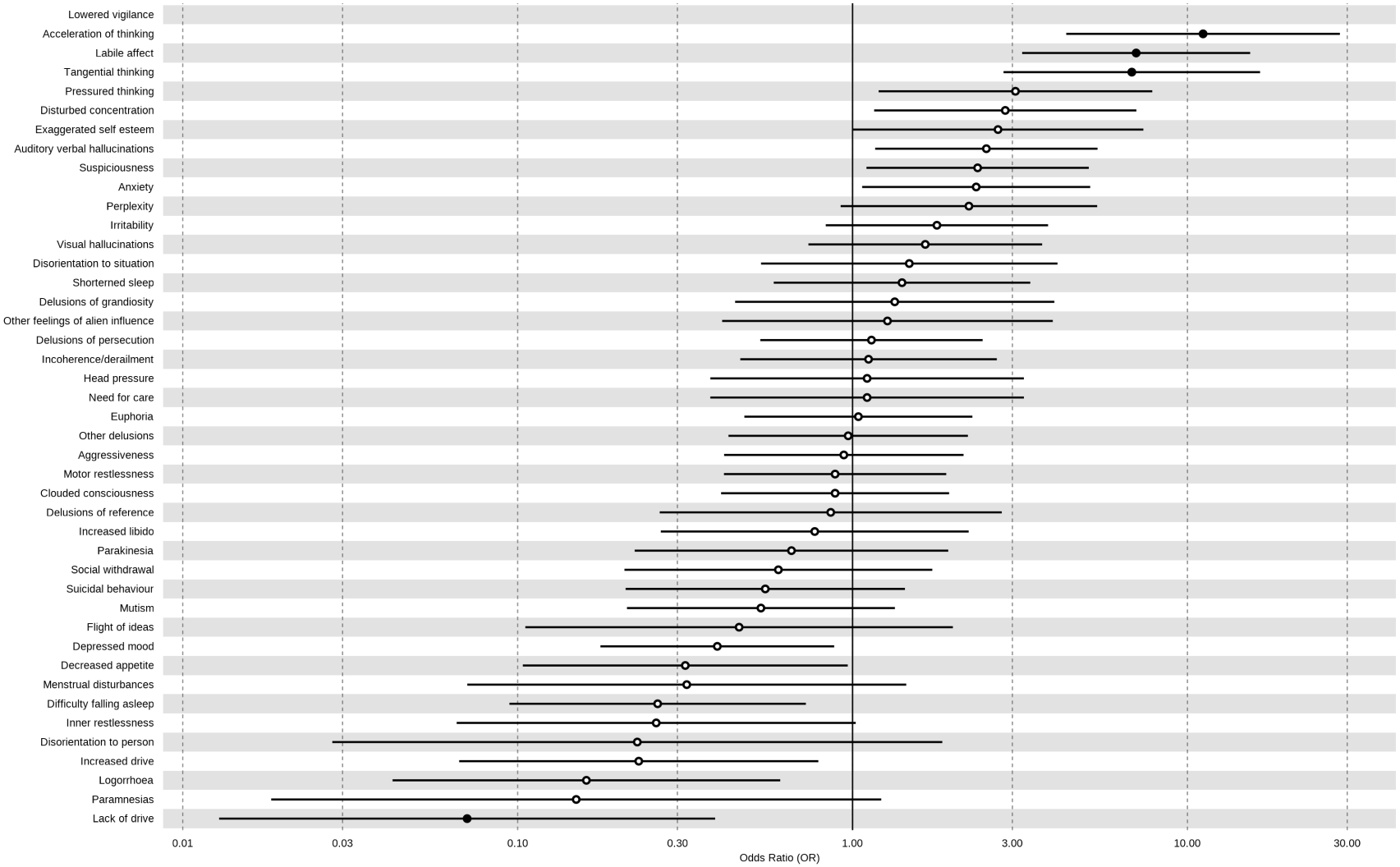


Figure 19. Forest plot showing the association of AMDP individual symptoms with between case reports and cases from electronic health records, adjusted for total number of symptoms. Odds Ratio >1 indicates higher proportion in cases from electronic health records, Odds Ratio <1 indicates higher proportion in case reports. Black circle indicates statistical significance corrected at the false discovery rate of 5%.

*Table 6. Logistic regression of AMDP individual symptoms comparing menstrual psychosis case reports to menstrual psychosis cases identified by electronic health records. P values are corrected for multiple comparisons using the Benjamini-Hochberg procedure. EHR – electronic health records, OR – Odds Ratio, 95% CI – 95% Confidence Interval. *Indicates statistical significance at false discovery rate of 5%, †indicates test not performed due to zero counts*

			Unadjusted		Adjusted for total number of symptoms	
AMDP symptom	Proportion Case reports	Proportion EHR	OR (95% CI)	p value	OR (95% CI)	p value
Lowered vigilance	0.12	0.0	NA†	NA†	NA†	NA†
Clouded consciousness	0.26	0.45	2.35 (1.18 – 4.61)	0.034*	0.88 (0.39 – 1.91)	0.917
Disorientation to situation	0.07	0.16	2.51 (0.89 – 6.13)	0.106	1.48 (0.49 – 3.85)	0.653
Disorientation to person	0.05	0.03	0.49 (0.03 – 2.42)	0.583	0.23 (0.01 – 1.23)	0.332
Disturbed concentration	0.07	0.34	7.22 (3.28 – 15.52)	<0.001*	2.85 (1.12 – 6.98)	0.091
Paramnesias	0.07	0.03	0.38 (0.02 – 1.84)	0.457	0.15 (0.01 – 0.81)	0.184
Pressured thinking	0.05	0.29	7.31 (3.14 – 16.46)	<0.001*	3.05 (1.15 – 7.7)	0.091
Flight of ideas	0.05	0.08	1.7 (0.39 – 5.28)	0.505	0.46 (0.09 – 1.72)	0.496
Tangential thinking	0.04	0.34	12.2 (5.3 – 28.1)	<0.001*	6.80 (2.77 – 16.39)	<0.001*
Incoherence/ derailment	0.12	0.24	2.39 (1.01 – 5.17)	0.068	1.12 (0.43 – 2.62)	0.917
Suspiciousness	0.15	0.45	4.47 (2.21 – 8.92)	<0.001*	2.36 (1.09 – 4.99)	0.091
Delusions of reference	0.07	0.11	1.7 (0.48 – 4.67)	0.457	0.86 (0.23 – 2.55)	0.917
Delusions of persecution	0.21	0.37	2.18 (1.06 – 4.34)	0.061	1.13 (0.51 – 2.41)	0.917
Delusions of grandiosity	0.06	0.13	2.48 (0.80 – 6.47)	0.144	1.33 (0.40 – 3.73)	0.850
Other delusions	0.18	0.29	1.92 (0.88 – 3.95)	0.144	0.97 (0.41 – 2.15)	0.949
Auditory verbal hallucinations	0.31	0.68	4.89 (2.44 – 10.3)	<0.001*	2.50 (1.17 – 5.55)	0.091
Visual hallucinations	0.14	0.37	3.68 (1.76 – 7.46)	<0.001*	1.65 (0.72 – 3.61)	0.397
Other feelings of alien influence	0.05	0.13	2.86 (0.91 – 7.55)	0.09	1.27 (0.37 – 3.66)	0.894
Perplexity	0.08	0.34	5.86 (2.69 – 12.4)	<0.001*	2.22 (0.88 – 5.29)	0.184
Depressed mood	0.36	0.40	1.16 (0.58 – 2.27)	0.702	0.39 (0.17 – 0.87)	0.091
Anxiety	0.23	0.63	5.81 (2.93 – 12.0)	<0.001*	2.34 (1.06 – 5.23)	0.113

Euphoria	0.26	0.50	2.86 (1.45 – 5.63)	0.006*	1.04 (0.47 – 2.27)	0.94
Irritability	0.18	0.47	4.10 (2.06 – 8.15)	<0.001*	1.78 (0.81 – 3.82)	0.304
Inner restlessness	0.10	0.08	0.81 (0.19 – 2.38)	0.750	0.26 (0.05 – 0.88)	0.139
Exaggerated self esteem	0.05	0.18	4.48 (1.65 – 11.02)	0.006*	2.73 (0.95 – 7.15)	0.137
Affective lability	0.12	0.63	13.18 (6.47 – 27.82)	<0.001*	7.0 (3.21 – 15.61)	<0.001*
Lack of drive	0.12	0.05	0.40 (0.06 – 1.36)	0.338	0.07 (0.01 – 0.31)	0.021*
Increased drive	0.13	0.11	0.79 (0.23 – 2.08)	0.702	0.23 (0.06 – 0.7)	0.091
Motor restlessness	0.32	0.50	2.11 (1.08 – 4.14)	0.061	0.89 (0.41 – 1.89)	0.917
Parakinesia	0.10	0.13	1.32 (0.43 – 3.29)	0.648	0.65 (0.20 – 1.76)	0.653
Mutism	0.17	0.21	1.28 (0.53 – 2.78)	0.633	0.53 (0.20 – 1.28)	0.347
Logorrhoea	0.15	0.08	0.49 (0.12 – 1.42)	0.361	0.16 (0.03 – 0.53)	0.059
Social withdrawal	0.10	0.16	1.77 (0.64 – 4.22)	0.347	0.60 (0.19 – 1.63)	0.562
Aggressiveness	0.18	0.34	2.33 (1.11 – 4.70)	0.049*	0.94 (0.4 – 2.08)	0.922
Suicidal behaviour	0.14	0.21	1.68 (0.69 – 3.70)	0.338	0.55 (0.19 – 1.38)	0.397
Need for care	0.06	0.18	3.4 (1.28 – 8.10)	0.025*	1.11 (0.35 – 3.06)	0.92
Acceleration of thinking	0.03	0.40	20.27 (8.68 – 48.4)	<0.001*	11.2 (4.37 – 29.0)	<0.001*
Difficulty falling asleep	0.19	0.18	0.94 (0.37 – 2.09)	0.881	0.26 (0.09 – 0.68)	0.070
Shortened sleep	0.10	0.29	3.54 (1.59 – 7.49)	0.004*	1.41 (0.56 – 3.3)	0.653
Decreased appetite	0.12	0.18	1.62 (0.63 – 3.68)	0.388	0.32 (0.10 – 0.9)	0.129
Menstrual disturbances	0.10	0.05	0.51 (0.08 – 1.75)	0.465	0.32 (0.05 – 1.17)	0.304
Head pressure	0.06	0.16	2.94 (1.03 – 7.29)	0.061	1.11 (0.34 – 3.08)	0.920
Increased libido	0.10	0.13	1.39 (0.46 – 3.47)	0.603	0.77 (0.24 – 2.07)	0.862

3.5 Discussion

This electronic health record study identified 38 possible cases of menstrual psychosis between 2006 and 2024, a condition which had previously only been reported by single case reports or small case series. Notably, none of these cases had previously been published as a case report, despite a diagnosis of menstrual psychosis being recorded for the majority (57.9%) of cases. While auditory verbal hallucinations was the most frequently recorded symptom, the symptoms that were more common in cases than controls were incoherence/derailment, clouded consciousness and affective lability. Despite these differences in clinical presentation, cases did not differ from controls in clinical outcomes.

In this study, the majority of cases had either low or very low evidence of a link to the menstrual cycle, according to criteria from Brockington.[118] However, these criteria were developed from historical case reports, typically of a well-described relapsing psychotic disorder over many years. Many historical cases had relatively large numbers of discrete psychotic episodes timed in relation to the cycle, probably because they were published prior to the advent of antipsychotic medications. In this sample, which relied on observations and history documented as part of routine clinical care, it is likely that some cases were rated as having low or very low evidence because there was insufficient information recorded to demonstrate an association between an episode and the menstrual cycle. This is in line with the absence of a diagnosis of 'menstrual psychosis' in 16 of 38 cases, suggesting that the condition is still under-recognised.

Almost all cases identified through electronic health records (92.1%) had onset of episodes in the premenstrual (in the days before menstruation) or catamenial (with onset of menstruation) phase of the cycle. This is in keeping with my previous meta-analysis showing an exacerbation of chronic psychotic disorders during the perimenstrual phase (either before or during menstruation).[57] I did not identify any cases that were epochal (bipolar disorder with change of polarity), suggesting this onset was rarer or even more difficult to detect. The premenstrual phase is characterised by a steep fall in plasma levels of oestradiol and progesterone, which remain low during menstruation.[133] Psychotic episodes associated with this time in the cycle is therefore in keeping with an increased risk of psychosis at other times of hormone decline, such as the postpartum and menopause transition.

Using the previous definition of menstrual psychosis,[110] I restricted cases to patients in whom brief episodes of psychosis were linked to the menstrual cycle, with complete resolution between episodes. Chronic psychotic disorders with menstrual exacerbation were therefore

excluded. That 80 cases were excluded for this reason, suggests the menstrual cycle has an influence on psychotic disorders more broadly.[57] Thus, while discrete psychotic episodes linked to the cycle may be rare, a greater number of individuals with psychosis may be vulnerable to cyclical hormonal fluctuations.

These findings support the characterisation of menstrual psychosis as a polymorphic psychotic disorder,[110] with affective symptoms (most frequently labile affect) present in almost all cases. This is consistent with the proposal that the condition is part of the bipolar spectrum,[103] as has been suggested for postpartum psychosis.[72] Four of the cases I identified additionally experienced postpartum psychosis (another rare condition), suggesting shared underlying pathophysiological mechanisms, such as a sensitivity to falling oestradiol levels. There are similarities in symptomatology; the clouded consciousness that was characteristic of our cases is also seen in postpartum psychosis, where it has been called 'extreme confusion'.[101]

Symptoms typical of menstrual psychosis from the case report literature[110] were common in electronic health record cases, such as hallucinations (73.7%) and delusions (52.6%). The symptom of confusion (clouded consciousness) was less frequent (44.7%) but was more prevalent in cases than controls. Mutism, another feature reported in case reports, was present in a minority of cases (21.1%) and had a higher proportion in cases, though this was not statistically significant when adjusted for multiple comparisons. The only symptom from case reports absent in the electronic health record sample was stupor (coded in the AMDP system as lowered vigilance), though this was reported in a minority (12%) of case reports.

The adolescent peak age of onset for menstrual psychosis contrasts with the typical age of onset for psychosis in early adulthood (age 20 – 21 years).[49] Because the median age of onset was 17 years, half of the cases could be expected to initially present to child and adolescent, rather than adult mental health services. Seven cases had onset around menarche, suggesting that this hormonal transition can act as a trigger for psychotic episodes.

Case reports summarised in the previous Chapter suggest that the hormonal therapies such as the combined oral contraceptive can prevent recurrence of menstrual psychosis, to the extent that antipsychotic medication can be successfully discontinued.[114,134,135] This strategy was employed in more than half of the cases, with the majority of these having a favourable response. While transdermal oestradiol has shown potential as an adjunctive symptomatic treatment for schizophrenia[87] and menopausal hormone therapy appears to prevent psychosis relapse,[86] oral contraceptives have had less attention as a treatment for psychosis. In contrast, these medications have an established evidence-base for other menstrual mood disorders.

Combined oral contraceptives have been shown to be effective in treating PMDD,[121] where they are considered as first-line pharmacological management.[11]

Interestingly, there were no significant differences in clinical outcomes between cases and matched controls from the same population. However, the measures of outcome comprised generic indices of access to secondary mental health care and it is possible that differences would be evident if outcomes were more specific to psychosis, such as commonly used rating scales.[136] It is possible that, in matching for age and diagnosis, cases and controls were overmatched, obscuring true differences between menstrual psychosis and episodes of psychosis unrelated to the menstrual cycle. Psychosis in early adolescence is itself rare,[137] to the extent that I was unable to identify the maximum number of four controls for each case.

3.5.1 Strengths and limitations

By accessing a large dataset of mental health records, it was possible to identify cases of menstrual psychosis that had not been published as case reports. This allowed identification of more cases of menstrual psychosis than any previous single study, and enabled comparison of the clinical features to those of a well-matched patient group. However, the timing of episodes in relation to the menstrual cycle was determined by information documented by clinicians in the health record. Evaluating the timing of psychiatric symptoms in relation to the menstrual cycle is prone to error, particularly when symptoms not recorded prospectively.[138] Furthermore, it relies on the clinician being aware that symptoms may be related to the cycle. Thus, it is likely that the number of cases identified in the course of routine care is an underestimation and does not provide a reliable index of the incidence or prevalence of menstrual psychosis. Unlike case reports, which typically require informed written consent from each patient, I was unable to report information which could lead to the identification of individuals for ethical reasons. Thus, I was unable to describe the illness course, symptomatology, or treatment response in any single patient. Instead, these measures were all reported as a group aggregates. While I drew controls from the same population as the cases and excluded controls with evidence of menstrual exacerbation in their record, I cannot rule out the possibility that some controls had menstrual worsening that was not detected or recorded. Because the number of cases identified was modest, I attempted to increase statistical power by selecting up to four matched controls per case, such that the total sample size was n=140. Nevertheless, I may still have limited ability to detected significant group differences.

3.5.2 Conclusion

This Chapter further supports the notion that menstrual psychosis is a condition which typically emerges in early adolescence, has an episode course, and is associated with an affective and confusional presentation. Unreported cases can be identified using electronic health records, suggesting that the case-report literature represents only a small proportion of women experiencing menstrual psychosis. Cases from electronic health record provided a richer description of symptoms but were otherwise similar in characteristics to case-reports.

I have described a phenotype in which brief psychotic episodes occur in synchrony with the menstrual cycle. Whether patients diagnosed with psychotic disorders more broadly have menstrual dysfunction will be considered in the next two Chapters.

4 Sex hormones and menstrual cycle characteristics in women with schizophrenia using the UK Biobank

4.1 Introduction

The oestrogen hypothesis proposes that hypo-oestrogenism, a 'chronic oestrogen deficiency syndrome', is an inherent part of schizophrenia.[39] Supporting this, historical studies, prior to the introduction of antipsychotic medication, reported hypo-oestrogenism on vaginal smears from women diagnosed with dementia praecox.[39] Modern studies must contend with the confounding effect of antipsychotic medication which elevates prolactin and can lead to secondary hypogonadism.[139] While some studies report lower oestradiol in schizophrenia[45–47] these have included relatively small samples (n<100) and have lacked appropriate control subjects. By contrast, a meta-analysis which included 523 female schizophrenia patients[140] suggested that testosterone is higher than in controls. A possible symptom of suppressed oestradiol levels, menstrual cycle irregularity, has been reported in up to 41% of female patients with schizophrenia,[48] though this was not compared to a control group. Other menstrual cycle characteristics such as age of menarche and age of menopause have been less examined.

Cognitive deficits are considered a core part of schizophrenia and are not responsive to current treatments.[141] In older women, endogenous oestradiol levels are associated with performance across a range of cognitive domains,[142] while there is some evidence that HRT can benefit cognition, if commenced early in the menopause transition.[143] Two small studies[144,145] suggest that oestradiol is positively correlated with cognitive performance in schizophrenia, with higher levels associated with better functioning. It has been speculated, based on pre-clinical models, that treatments targeting the oestrogen system could have cognitive benefits in schizophrenia,[146] though evidence from clinical trials is inconclusive.[87]

While hypo-oestrogenism has long been regarded as part of the schizophrenia disease process, this has not been confirmed in studies using large samples and appropriate control subjects. Whether hypo-oestrogenism is related to the pathophysiology of schizophrenia, or merely a consequence of antipsychotic medication or other secondary lifestyle factors is not known. It is important to determine whether oestradiol levels are suppressed in schizophrenia and whether these are associated with cognitive deficits, as this could potentially be corrected using exogenous hormone replacement.

This Chapter used data from the UK Biobank, a large open-access study which recruited approximately 500,000 participants aged 40-69 between 2006-2010. Participants with mental disorders, including schizophrenia, can be identified both through self-reported diagnosis

(assessed as part of a mental health questionnaire) and through linkage of hospital-based ICD diagnoses.[147] As part of the assessment process, female participants reported age of menarche, age of menopause, menstrual cycle regularity, medication use and lifestyle factors. They also completed a touchscreen cognitive battery. Blood measures, including oestradiol levels were taken as part of the assessment. Genetic markers, including polygenic risk scores (PRS) for schizophrenia[148] and bipolar disorder[149] are available. These provide measures of common genetic variants contributing to the risk of each disorder. As such they can be used to assess whether the genetic liability of each disorder is associated with outcomes.[150] By limiting this genetic risk to subjects who do not have a diagnosis of schizophrenia or bipolar disorder, the confounding factors associated with each diagnosis itself (such as psychotropic medication and lifestyle factors) are mitigated.

4.2 Aims

The first aim was to examine menstrual cycle characteristics, including menstrual cycle regularity, age of menarche and age of menopause, among female patients with schizophrenia. These characteristics were compared to other mental disorders (depression and bipolar disorder) as well as participants who reported no psychiatric illness. The second aim was to examine oestradiol levels in schizophrenia, compared to controls with other mental disorders and those who did not have a mental disorder. I aimed to determine whether genetic risk of schizophrenia and bipolar disorder was associated with oestradiol levels and whether oestradiol was associated with cognitive performance, both through levels of oestradiol level and in terms of menstrual cycle phase.

4.3 Methods

The study was conducted under UK Biobank Ethical Approval under the application *Sex hormones, cognition, and risk for mental illness,* Project ID 171904. The design was a cross-sectional comparison between female patients with schizophrenia, bipolar disorder, depression, or no psychiatric disorder. All data were taken from the baseline study visit.

4.3.1 Data collection

A touchscreen questionnaire was administered to UK Biobank participants as part of their baseline assessment. This included questions about sociodemographic characteristics, including IMD, highest level of education and ethnicity, as well as lifestyle factors such as smoking status and alcohol intake. Participants were specifically asked whether they were currently taking 'hormone replacement therapy', the 'oral contraceptive pill' or the 'minipill'. Age of menarche was determined by the item: 'how old were you when your periods started?' Age of

menopause by: 'how old were you when your periods stopped?' Time since last menstrual period by: 'how many days since your last menstrual period?' Parity was taken from the item, 'How many children have you given birth to? (Please include live births only)'

Oestradiol and testosterone were measured using chemiluminescent immunoassay-competitive binding, using two step-competitive analysis on a Beckman Coulter Unicel Dxl 800 with a minimum detection limit of 175 pmol/L.[151] Enhanced PRS for schizophrenia and bipolar disorder were provided from the UK Biobank dataset[152] and used as markers of genetic risk for these disorders. These are derived using external genome-wide association studies[148,149] and are calculated by aggregating the effect of many common variants associated with each disorder.[153] The scores are standardised to a normal distribution with a mean of 0 and SD of 1. The enhanced PRS for age of menopause was used as a measure of genetic component of menopausal age.[154]

The UK Biobank used a fully automated touchscreen questionnaire to administer cognitive tests. The following baseline tests were used: fluid intelligence (verbal and numerical reasoning), numeric memory (working memory), pairs matching (visual declarative memory), reaction time (processing speed). Despite being a brief assessment, these cognitive tests show moderate-high test-retest reliability and substantial concurrent validity with reference tests.[155]

4.3.2 Data processing

The baseline assessment provided data on sociodemographic factors, medications, self-reported menstrual cycle length and regularity, and self-reported ages of menarche and menopause. Participants were considered post-menopausal if they reported 'yes' to the question 'Have you had your menopause (periods stopped)', or were 55 years or older, or had a bilateral oophorectomy.[156] Menstrual cycle irregularity was coded if participants reported an irregular cycle, or if their cycle length was less than 21 days or greater than 35 days.[157] Days since last menstrual period was assumed to refer to the end of menstruation. Days 0 – 5 were coded as early follicular, 6 – 10 as late follicular, 11 – 14 as midcycle, 15 – 18 as early luteal and 19 – 24 as midluteal and days >24 as late luteal.[156] The cycle phase was coded as early follicular if the participant responded that they were menstruating on the day of assessment.

Psychiatric diagnoses were determined using a combination of ICD diagnoses obtained from hospital-linkage, self-reported diagnoses and diagnoses based on symptom measures.[147] A diagnosis of schizophrenia was recorded if there was any ICD-10 (F20-F29) or ICD-9 (code 295) diagnosis of a schizophrenia spectrum disorder in the participant's hospital records, or if they reported a diagnosis of schizophrenia or any other psychotic illness as part of the mental health

questionnaire (see Appendices for these items). Bipolar disorder was recorded in the absence of a schizophrenia diagnosis, in the presence of any ICD-10 (F30-F31) or ICD-9 (code 296) diagnosis of bipolar disorder, or if there was a report of mania, hypomania, bipolar or manic depression as part of the mental health questionnaire, or if answers to the symptom questionnaire indicated a diagnosis of bipolar I or bipolar II disorder. Major depressive disorder was recorded in the presence of any ICD-10 (F32-F33) or ICD-9 (code 311) diagnosis of depressive disorder, or self-report of depression but not mania, hypomania, bipolar or manic-depression on mental health questionnaire, or if answers to the symptom questionnaire indicated a diagnosis of probable recurrent major depression severe, probable recurrent major depression moderate, or single probable major depression episode. Participants were categorised as having no mental disorder if they did not meet criteria for any of the above categories and they indicated that they did not have a mental disorder on the mental health questionnaire. Participants reported current medication, which was categorised in terms of antidepressants or antipsychotics, taken from the list provided by Davis et al.[147] Antipsychotics were further classified as prolactin-sparing or prolactin-raising based on the Maudsley Prescribing Guidelines,[158] as shown:

- Prolactin-sparing: aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine iloperidone, lumateperone, pimavanserin, quetiapine, xanomeline
- Prolactin-raising: lurasidone, olanzapine, ziprasidone, amisulpride, paliperidone, risperidone, sulpiride, first generation antipsychotics

Hormone assays of oestradiol, testosterone and sex hormone binding globulin were taken from the baseline visit. Levels that were below the limit of detection were imputed at 3/4 of the minimal reporting value: 175pmol/L for oestradiol, 0.35 nmol/L for testosterone, 0.33 nmol/L for sex hormone binding globulin, as per Tin Tin et al.[156] To examine the biologically active forms of the hormones, free concentrations of oestradiol and testosterone were calculated, using formula provided by Tin Tin et al.[159] This calculates the free hormone concentration from the total hormone concentration, accounting for the binding to albumin and sex hormone binding globulin.

$$[F] = [T] / (1 + K_A[A] + K_S[S])$$

where:

- [T] is the total hormone concentration
- [F] is the free hormone concentration

- [A] is the albumin concentration
- [S] is the SHBG concentration
- K_A and K_S are the association constants for albumin and sex hormone binding globulin

The association constants given are:

- Oestradiol, $K_A=6.0\times10^4$ and $K_S=0.68\times10^9$
- Testosterone, $K_A=3.\times10^4$ and $K_S=1.0\times10^9$

Measures from the cognitive battery were used as recommended by Fawns-Ritchie and Deary:[155]

- Fluid intelligence – fluid intelligence score
- Numeric memory – maximum digits remembered correctly
- Pairs matching – number of incorrect matches in round
- Reaction time – mean time to identify matches

4.3.3 Data analysis

All analyses were performed within the UK Biobank Research Analysis Platform, using R statistical software. Continuous variables were presented as means and SDs if normally distributed or otherwise as medians and IQRs. Categorical variables were presented as proportions. ANOVAs were conducted to examine group differences in continuous variables. Variables that were not normally distributed were log-transformed prior to analysis. When overall effects were significant, Tukey's post hoc tests were used to identify specific between-group differences. Chi-square tests were applied to compare proportions. Pearson correlations were calculated to assess associations between continuous variables, with non-normally distributed measures log-transformed beforehand. Linear regression models were used to examine differences between diagnostic groups, using the healthy control group as the reference. All analyses included relevant covariates and results are presented for both unadjusted and adjusted models. Model residuals were examined to assess heteroscedasticity.

4.3.3.1 Menstrual cycle characteristics

Self-reported age at menarche was examined in the whole female sample. Age at menopause was examined in postmenopausal participants. Menstrual cycle regularity was examined in premenopausal participants who were not prescribed exogenous hormones (oral contraceptives or HRT) and were not pregnant. Linear regression models were used to examine

the association between diagnostic group and age of menarche, using IMD and ethnicity as covariates. For age of menopause, the model was adjusted for current age, body mass index (BMI), IMD, smoking status, ethnicity, education, alcohol status, age at menarche and parity (number of live births).

To examine the effect of genetic risk for schizophrenia and for bipolar disorder on age of menopause, independent of confounding factors associated with these disorders, enhanced PRS for these disorders were taken from participants who did not have a diagnosis of either disorder. These scores were then examined in relation to age at menopause, and with enhanced PRS for age of menopause using Pearson's correlations.

4.3.3.2 Hormone analysis

Oestradiol and testosterone were examined in premenopausal participants. Linear models examining the effect of diagnostic group on oestradiol levels were performed, with age, BMI, IMD (deprivation), smoking status (smoker/non-smoker), ethnicity, education (whether they obtained a college or university qualification), and alcohol status (drinker/non-drinker) as covariates. To standardise oestradiol levels by menstrual cycle phase, a linear model was fitted for oestradiol, using cycle phase as a categorical variable. The residuals from this model were then added to the mean log oestradiol value and the result exponentiated to give a standardised value.[160] The same procedure was used to produce standardised values of testosterone. In participants with schizophrenia, hormone levels were compared between antipsychotic medication groups (prolactin-raising versus prolactin-sparing). Values of free oestradiol and free testosterone were examined in relation to cognitive performance, as the unbound fractions represent the biologically active forms of these hormones. Genetic risk using enhanced PRS for schizophrenia and bipolar disorder was examined in relation to oestradiol using Pearson correlations in participants without either of these diagnoses (in order to remove the confounding effects of illness).

4.4 Results

4.4.1 Description of cohort

The total cohort consisted of 273,156 female participants (characteristics shown in Table 7), including 2,106 participants with schizophrenia, 1,909 with bipolar disorder, and 57,928 with depression. A further 62,156 individuals were classified as having no mental disorder, while for 149,048 the presence of a mental disorder was unknown. There were statistically significant differences between diagnostic groups in terms of age (at time of baseline assessment), BMI, IMD, smoking status, ethnicity and education. Participants with each mental disorder were

slightly younger, with higher BMI and IMD scores. Individuals in the mental disorder groups were more likely to smoke, more often of non-white ethnicity, and less likely to have attained a college or university degree.

Among the 195,092 post-menopausal participants (Table 8), diagnostic groups differed with respect to BMI, smoking status, college education, and non-white ethnicity. In contrast, no differences in age were observed across diagnostic groups. In the 69,675 pre-menopausal participants (Table 9) there were significant differences between diagnostic groups in terms of age, BMI, IMD, smoking and non-white ethnicity. In pre-menopausal patients with schizophrenia, 95 reported a prolactin-raising antipsychotic at baseline, 50 had a prolactin-sparing antipsychotic, and 469 did not have any medication reported.

Table 7. Characteristics of UK Biobank female cohort (n=273,156). Differences between groups tested using ANOVA for continuous variables and chi squared test for categorical variables. SD - standard deviation, IMD – index of multiple deprivation

	Diagnostic group					
	Healthy controls (n=62,156)	Schizophrenia (n=2,106)	Bipolar Disorder (n=1,909)	Depression (57,928)	Unknown (149,048)	p value
Age at assessment, mean (SD)	55.6 (7.5)	55.4 (8.2)	54.9 (8.0)	55.2 (7.9)	57.2 (8.2)	<0.001
BMI, mean (SD)	26.1 (4.6)	27.8 (5.9)	28.3 (6.1)	27.7 (5.6)	27.3 (5.2)	<0.001
IMD, mean (SD)	14.1 (11.4)	20.9 (16.2)	20.6 (15.3)	18.2 (14.2)	17.8 (14.3)	<0.001
Age at menarche, mean (SD)	12.9 (1.5)	13.1 (1.7)	12.9 (1.7)	12.9 (1.6)	13.0 (1.6)	<0.001
Current smoker, number (percentage)	3,046 (4.9%)	342 (16.2%)	367 (19.2%)	6,882 (11.9%)	13,847 (9.3%)	<0.001
White ethnicity, number (percentage)	60,254 (96.9%)	1,922 (91.3%)	1,763 (92.4%)	55,576 (95.9%)	138,898 (93.2%)	<0.001
College degree, number (percentage)	18,094 (29.1%)	461 (21.9%)	451 (23.6%)	11,910 (20.6%)	20,807 (14.0%)	<0.001

Table 8. Characteristics of post-menopausal UK Biobank cohort (n=195,092). Differences between groups tested using ANOVA for continuous variables and chi squared test for categorical variables. SD - standard deviation, IMD – index of multiple deprivation

	Diagnostic group					
	Healthy controls (n=43,051)	Schizophrenia (n=1,422)	Bipolar disorder (n=1,265)	Depression (n=39,051)	Unknown (110,292)	p value
Age at assessment, mean (SD)	59.3 (5.2)	59.6 (6.0)	59.1 (6.0)	59.3 (5.6)	60.9 (5.5)	0.185
BMI, mean (SD)	26.2 (4.5)	27.8 (5.8)	28.4 (5.7)	27.7 (5.5)	27.5 (5.1)	<0.001
IMD, mean (SD)	13.8 (11.1)	20.2 (15.4)	20.2 (15.4)	17.7 (14.0)	17.4 (14.1)	<0.001
Age at menopause, mean (SD)	50.4 (4.3)	49.4 (5.0)	49.3 (5.0)	49.7 (4.8)	49.8 (4.7)	<0.001
Current smoker, number (percentage)	1,903 (4.4%)	220 (15.5%)	110 (8.7%)	4,210 (10.8%)	9,551 (8.7%)	<0.001
White ethnicity, number (percentage)	42,039 (97.7%)	1,322 (93.0%)	1,198 (94.7%)	37,820 (96.9%)	104,491 (94.7%)	<0.001
College degree, number (percentage)	11,163 (25.9%)	267 (18.8%)	145 (11.5%)	6,970 (17.9%)	12,684 (11.5%)	<0.001

Table 9. Characteristics of pre-menopausal UK Biobank cohort (n=69,675). Differences between groups tested using ANOVA for continuous variables and chi squared test for categorical variables. SD - standard deviation, IMD – index of multiple deprivation

	Diagnostic group					
Variable	Healthy controls (n=17,311)	Schizophrenia (n=614)	Bipolar disorder (n=587)	Depression (n=16,756)	Unknown (n=34,407)	p value
Age at assessment, mean (SD)	47.1 (3.9)	46.7 (4.0)	46.5 (3.8)	46.6 (3.9)	46.5 (3.9)	<0.001
BMI, mean (SD)	25.7 (4.8)	27.9 (6.3)	28.3 (6.7)	27.6 (6.0)	26.8 (5.4)	<0.001
IMD, mean (SD)	14.7 (11.9)	22.4 (17.1)	21.1 (15.0)	19.2 (14.7)	18.8 (15.0)	<0.001
Cycle length in days, mean, (SD)	26.9 (2.9)	27.0 (3.2)	27.3 (3.1)	26.8 (3.0)	26.7 (3.0)	0.0464
Current smoker, number (percentage)	1,030 (6.0%)	109 (17.8%)	140 (24.0%)	2,273 (14.2%)	3,830 (11.2%)	<0.001
White ethnicity, number (percentage)	16,460 (95.3%)	528 (87.0%)	515 (88.0%)	15,660 (93.9%)	30,167 (88.3%)	<0.001
College degree, number (percentage)	6,890 (39.8%)	184 (30.0%)	177 (30.2%)	4,859 (29.0%)	8,464 (24.6%)	<0.001
Irregular menses, number (percentage)	3,012 (17.4%)	103 (16.8%)	100 (17.0%)	2,916 (17.4%)	5,367 (15.6%)	0.981
Oestradiol, pmol/L, median (IQR)	437.6 (293.4 – 699.6)	396.6 (269.4 – 604.9)	426.6 (282.4 – 651.5)	427.3 (285.6 – 674.5)	434.7 (292.2 – 686.5)	0.004
Testosterone, nmol/L, median (IQR)	1.07 (0.74 – 1.44)	1.12 (0.71 – 1.46)	1.07 (0.697 – 1.47)	1.08 (0.72 – 1.46)	1.09 (0.76 – 1.47)	0.892

4.4.2 Menstrual cycle characteristics

The mean age of menarche was 13.0 years, and the range was 7 – 18 years. In the unadjusted model, women with schizophrenia had a slightly older age at menarche compared to healthy controls, while depression was associated with a younger age at menarche, see Table 10. There was no difference in age of menarche between women with bipolar disorder and healthy controls. After adjustment for IMD and ethnicity, schizophrenia remained associated with later menarche (β=0.11, 95% CI: 0.04 – 0.18, p=0.003) and depression remained associated with earlier menarche (β=-0.04, 95% CI: -0.06 – -0.02, p <0.001). Among covariates, IMD showed a statistically significant but negligible effect. Ethnicity was generally not associated with age at menarche, except for those identifying as Mixed ethnicity, who had earlier menarche compared with White ethnicity.

*Table 10. Linear regression of diagnostic group on age of menarche in UK Biobank. Results presented for unadjusted model and adjusting for IMD and ethnicity. CI – Confidence Interval, IMD – index of multiple deprivation, * indicates statistical significance at the 5% level.*

	Unadjusted		Adjusted	
Variable	β coefficient (95% CI)	p value	β coefficient (95% CI)	p value
Diagnosis (reference – healthy controls)				
Schizophrenia	0.13 (0.06 – 0.20)	<0.001*	0.11 (0.04 – 0.18)	0.003*
Bipolar disorder	-0.02 (-0.09 – 0.06)	0.655	-0.03 (-0.11– 0.04)	0.424
Depression	-0.03 (-0.05 – -0.01)	0.001*	-0.04 (-0.06 – -0.02)	<0.001*
IMD			0.00 (0.00 – 0.002)	<0.001*
Ethnicity (reference – White)				
Asian			-0.00 (-0.09 – 0.08)	0.921
Black			0.05 (-0.04 – 0.14)	0.267
Mixed			-0.20 (-0.31 – -0.09)	<0.001*
Other			-0.08 (-0.19 – 0.03)	0.150

The median age of menopause was 49.9 years, and the range was 35 to 65 years. In the unadjusted linear regression, each psychiatric diagnosis was associated with earlier age of menopause when compared to healthy controls (Table 11). After adjusting for age, BMI, IMD, smoking status, ethnicity, college education, alcohol use and parity, the association between mental disorders and earlier age of menopause remained statistically significant. In the adjusted models, women with schizophrenia experienced menopause earlier than healthy controls (β=-0.84, 95% CI: -1.21 – -0.47, p<0.001), as did those with bipolar disorder (β=-0.83, 95% CI: -1.23 – -0.43, p<0.001) and those with depression (β=-0.49, 95% CI: -0.60 – -0.39, p<0.001). Later menopause was associated with older current age, higher educational attainment, and greater parity. Smoking and greater deprivation were linked to earlier menopause. Age at menarche showed no significant association in the adjusted model. The only ethnic group which showed a significant association was 'Other' which experienced menopause earlier than those reporting White ethnicity.

*Table 11. Linear regression of diagnostic group on age of menopause in post-menopausal UK Biobank participants. Results presented for unadjusted model and adjusting for age, BMI, IMD, smoking, ethnicity, college education, alcohol use, age of menarche and parity. CI – Confidence Interval, BMI – body mass index, IMD – index of multiple deprivation. * Indicates statistical significance at the 5% level.*

	Unadjusted		Adjusted	
Variable	β coefficient (95% CI)	p value	β coefficient (95% CI)	p value
Diagnosis (reference – healthy controls)				
Schizophrenia	-0.98 (-1.25 – -0.71)	<0.001*	-0.84 (-1.21 – -0.47)	<0.001*
Bipolar disorder	-1.10 (-1.39 – -0.81)	<0.001*	-0.83 (-1.23 – -0.43)	<0.001*
Depression	-0.63 (-0.70 – -0.56)	<0.001*	-0.49 (-0.60 – -0.39)	<0.001*
Current age			0.14 (0.13 – 0.15)	<0.001*
BMI			-0.005 (-0.01 – 0.005)	0.350
IMD			-0.01 (-0.02 – -0.008)	<0.001*
Current smoker			-1.05 (-1.22 – -0.87)	<0.001*
Ethnicity (reference – White)				
Asian			-0.31 (-0.73 – 0.11)	0.152
Black			-0.43 (-1.02 – 0.16)	0.150
Mixed			-0.33 (-1.04 – 0.38)	0.360
Other			-0.61 (-1.17 – -0.05)	0.031*
College education			0.47 (0.36 – 0.59)	<0.001*
Current drinker			0.45 (0.33 – 0.56)	<0.001*
Age of menarche			0.01 (-0.005 – 0.03)	0.157
Parity (number of live births)			0.11 (0.07 – 0.15)	<0.001*

As expected, in the whole sample there was moderate positive correlation between schizophrenia and bipolar disorder enhanced PRS (r=0.38, 95% CI: 0.37 – 0.38, p<0.001). There was no significant correlation between enhanced PRS for schizophrenia and enhanced PRS for age of menopause (r=-0.0013, 95% CI: -0.009 – 0.007, p=0.762), or between risk scores for bipolar disorder and age of menopause (r=0.0006, 95% CI: -0.008 – 0.009, p=0.880). In post-menopausal participants without a history of either schizophrenia or bipolar disorder

(n=32,765), there was no significant correlation between PRS for schizophrenia and age of menopause (r=-0.002, 95% CI: -0.013 – 0.0086, p=0.682), or between bipolar disorder and age of menopause (r=-001, 95% CI: -0.02 – 0.001, p=0.079).

There was no difference the proportion of individuals experiencing menstrual cycle irregularity between diagnostic groups. Unexpectedly, cycle irregularity was numerically lower in patients with schizophrenia (16.8%) than among those with no psychiatric diagnosis (17.4%). There was no difference in cycle irregularity between antipsychotic medication groups.

4.4.3 Comparison of oestradiol between groups

Oestradiol results were available for 41,882 pre-menopausal participants. Missing values showed borderline statistical significance by diagnostic group Table 12. Levels of oestradiol below the limit of detection were imputed at 3/4 of the lower limit (131.25 pmol/L), this affected 18,598 values in the premenopausal sample. The median value was 433.5 pmol/L (IQR 290.4 – 686.0 pmol/L).

Table 12. Reportability of oestradiol values by diagnostic group in UK Biobank. Chi squared test p=0.06

	Diagnostic group				
	Healthy controls	Schizophrenia	Bipolar disorder	Depression	Unknown
Reportable	10,542 (60.9%)	355 (57.8%)	332 (56.6%)	10,029 (59.9%)	20,624 (59.9%)
Missing	2,182 (12.6%)	82 (13.4%)	94 (16%)	2,154 (12.9%)	4,683 (13.6%)
Too Low	4,587 (26.5%)	177 (28.8%)	161 (27.4%)	4,573 (27.3%)	9,100 (26.4%)

A one-way ANOVA demonstrated a significant effect of menstrual cycle phase on oestradiol levels in the 31,225 women who had paired observations on oestradiol and menstrual cycle phase ($p<0.0001$), shown in Figure 20. The highest level was at the midcycle phase, representing the surge in oestradiol before ovulation. The lowest oestradiol levels were at the late luteal and early follicular phases, the time around menstruation, which is associated with increased relapse of psychosis.[57] Given the effect of menstrual cycle phase on oestradiol levels, standardised oestradiol levels were calculated by regressing baseline oestradiol on cycle phase and using the resulting residuals (standardised oestradiol levels) in subsequent analyses to remove phase-driven variation. The median standardised oestradiol was 430.6 pmol/L (IQR 294.3 – 677.6 pmol/L).

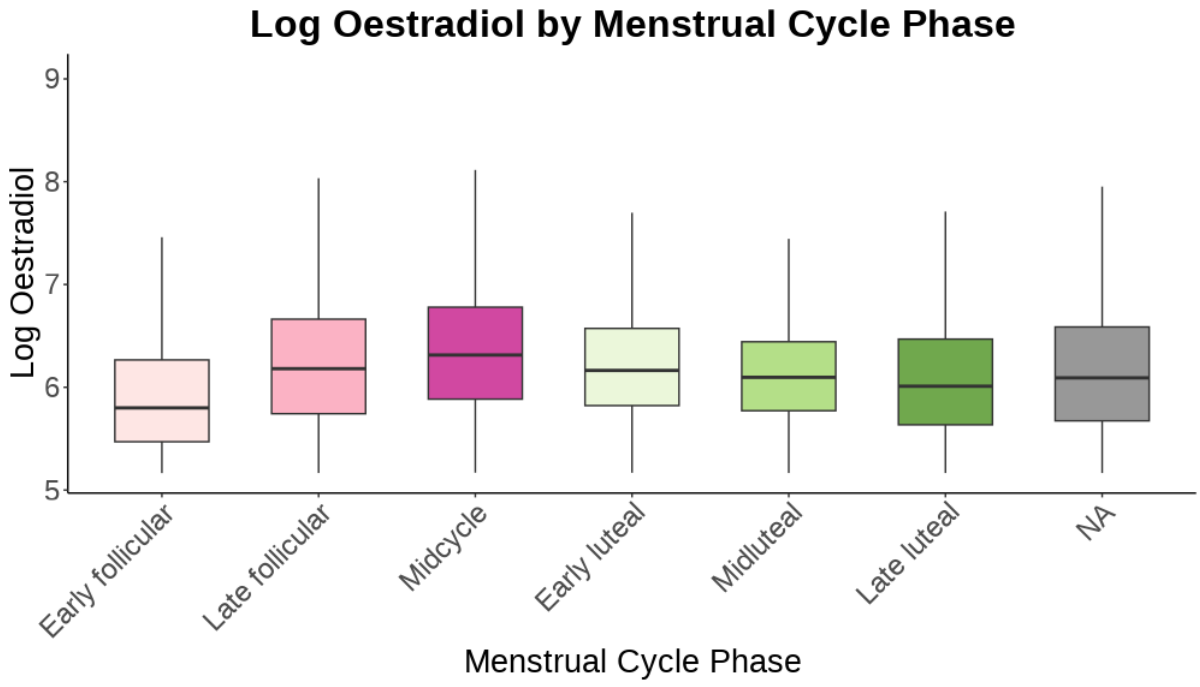


Figure 20. Boxplot of log oestradiol values by menstrual cycle phase in UK Biobank. NA – indicates unknown menstrual cycle phase.

After standardising by menstrual phase, participants with schizophrenia (β=-39.8, 95% CI: -76.9 – -2.76, p=0.035), bipolar disorder (β=-47.1, 95% CI: -85.5 – -8.58, p=0.017) and depression (β 10.7, 95% CI:-20.5 – -0.99, p=0.031) had lower oestradiol levels than healthy controls in the unadjusted regression model (Table 13). However, in the model adjusted for age, BMI, IMD score, smoking status, alcohol status, college education, and ethnicity, none of the diagnostic groups remained significant. Among the covariates, age, smoking and BMI showed a negative association with oestradiol. Ethnicity, college education, alcohol use and IMD score did not show association with oestradiol.

*Table 13. Linear regression of diagnostic group on oestradiol level, standardised by menstrual phase in UK Biobank. Results presented for unadjusted model and adjusting for age, BMI, IMD, smoking, ethnicity, college education and alcohol use. CI – Confidence Interval, BMI – body mass index, IMD – index of multiple deprivation. * Indicates statistical significance at the 5% level.*

	Unadjusted		Adjusted	
Variable	β coefficient (95% CI)	p value	β coefficient (95% CI)	p value
Diagnosis (reference – healthy controls)				
Schizophrenia	-39.8 (-76.9 – -2.76)	0.035	-24.7 (-63.0 – 13.6)	0.206
Bipolar disorder	-47.1 (-85.5 – -8.58)	0.017	-29.6 (-68.9 – 9.71)	0.140
Depression	-10.7 (-20.5 – -0.99)	0.031	-2.63 (-12.8 – 7.56)	0.613
Age			-11.7 (-13.6 – 9.73)	<0.001
BMI			-4.21 (-5.62 – -2.79)	<0.001
IMD			-0.39 (-0.95 – 0.16)	0.166
Current smoker			-29.5 (-53.3 – -5.86)	0.014
Current drinker			6.84 (-12.5 – 26.2)	0.489
College education			-5.95 (-22.6 – 10.7)	0.484
Ethnicity (reference – White)				
Asian			-24.7 (-74.8 – 25.5)	0.335
Black			-20.3 (-74.8 – 34.2)	0.465
Mixed			-26.2 (-92.5 – 40.1)	0.439
Other			-24.4 (-89.8 – 41.0)	0.465

In the participants diagnosed with schizophrenia, oestradiol was compared among those not prescribed anti-psychotic medications (n=469), those prescribed prolactin-raising antipsychotics (n=95) and those prescribed prolactin sparing antipsychotics (n=50). The group prescribed prolactin-raising antipsychotics had lower oestradiol levels than those prescribed no medication or prolactin sparing antipsychotics, though this was not significant in the adjusted model, see Table 14.

*Table 14. Linear regression of antipsychotic medication on oestradiol level in UK Biobank, standardised by menstrual phase. Results presented for unadjusted model and adjusting for age, BMI, IMD, smoking, ethnicity, college education and alcohol use. CI – Confidence Interval, BMI – body mass index IMD – index of multiple deprivation. * Indicates statistical significance at the 5% level.*

	Unadjusted		Adjusted	
Variable	β coefficient (95% CI)	p value	β coefficient (95% CI)	p value
Antipsychotic (reference - none)				
Prolactin-raising	-113.6 (-210.7 – -16.4)	0.022*	-113.0 (-274.0 – 48.0)	0.168
Prolactin-sparing	-7.68 (-131.1 – 115.8)	0.903	69.8 (-141.7 – 281.3)	0.516
Age			-5.70 (-19.2 – 7.80)	0.406
BMI			1.26 (-7.59 – 10.11)	0.779
IMD			-0.50 (-4.08 – 3.08)	0.784
Current smoker			140.2 (-9.47 – 289.8)	0.066
Current drinker			62.2 (-59.1– 183.5)	0.313
College education			123.0 (-1.69 – 247.7)	0.053
Ethnicity (reference – White)				
Asian			-195.5 (-525.6 – 134.7)	0.244
Black			-113.8(-365.4 – 137.8)	0.373
Mixed			-94.5 (-439.1 – 250.1)	0.589
Other			-30.3 (-369.6 – 309.0)	0.860

Enhanced PRS's were used to assess the correlation between genetic risk for psychiatric disorders and standardised hormone levels. This was performed in pre-menopausal participants with genetic data who did not have diagnosis of schizophrenia or bipolar disorder (n=15,211), in order to remove the confounding effects associated with each diagnosis. There was no correlation between enhanced PRS for schizophrenia and log standardised oestradiol

level (r=0.01, 95% CI -0.006 – 0.026, p=0.220), or between enhanced PRS for bipolar disorder and log standardised oestradiol level (r=-0.003, 95% CI -0.013 – 0.019, p=0.714).

4.4.4 Comparison of testosterone between groups

Levels of testosterone across menstrual cycle phases are shown in Figure 21 for the 26,426 pre-menopausal participants who had paired observations of testosterone and menstrual cycle phase. A one-way ANOVA showed a significant effect of menstrual phase on log-transformed testosterone (p<0.0001). Levels were highest at the midcycle phase, mirroring the pattern of oestradiol seen across the menstrual cycle.

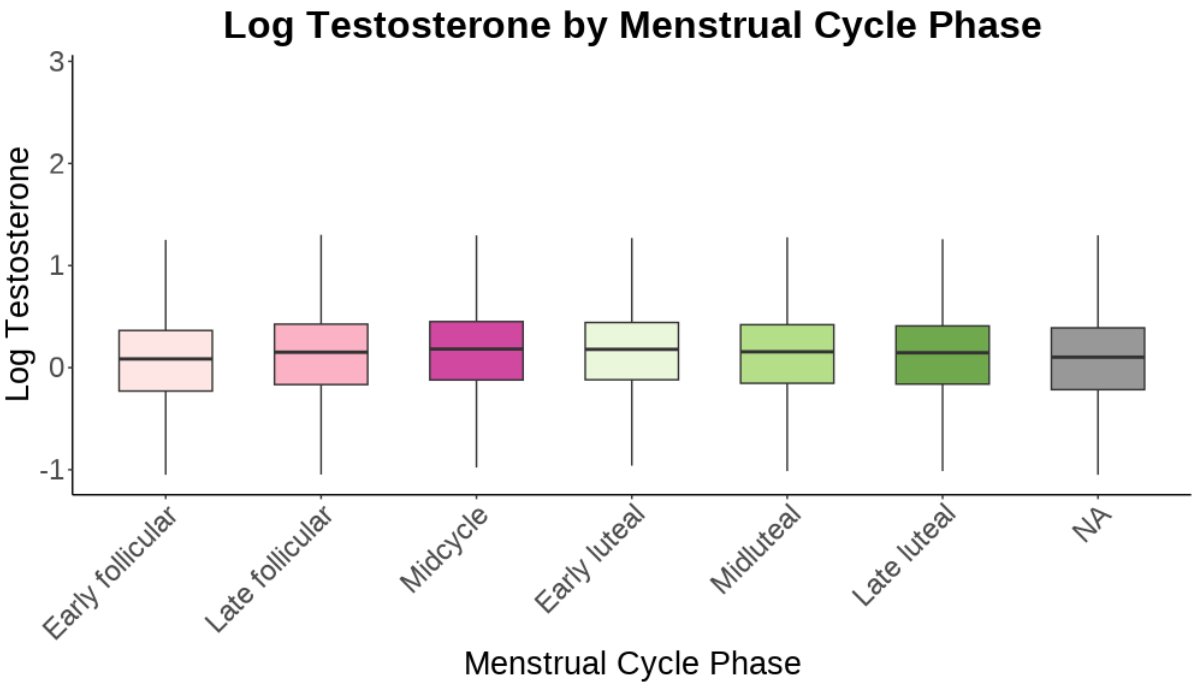


Figure 21. Boxplot of log-transformed testosterone levels across menstrual cycle phases in UK Biobank. NA – indicates unknown diagnosis.

Testosterone levels were standardised by menstrual cycle phases as for oestradiol. The median phase-standardised testosterone level was 1.07 nmol/L (IQR 0.73 – 1.45 nmol/L). In the unadjusted model, there were no associations between any psychiatric diagnostic group and testosterone (Table 15). After adjusting for covariates, bipolar disorder (β=-0.101, 95% CI: -0.185 – -0.016, p=0.020) and depression (β=-0.036, 95% CI: -0.061 – -0.012, p=0.004) were associated with lower testosterone, while schizophrenia did not show an association. As expected, age was negatively associated with testosterone. Black ethnicity was associated with lower testosterone. Smoking, alcohol use, and BMI were associated with higher testosterone.

*Table 15. Linear regression of diagnostic group on testosterone level in UK Biobank, standardised by menstrual phase. Results presented for unadjusted model and adjusting for age, BMI, IMD, smoking, ethnicity, college education and alcohol use. CI – Confidence Interval, BMI – body mass index, IMD – index of multiple deprivation. * Indicates statistical significance at the 5% level.*

	Unadjusted		Adjusted	
Variable	β coefficient (95% CI)	p value	β coefficient (95% CI)	p value
Diagnosis (reference – healthy controls)				
Schizophrenia	0.008 (-0.045 – 0.061)	0.761	-0.053 (-0.139 – 0.034)	0.231
Bipolar disorder	0.009 (-0.046 – 0.063)	0.749	-0.101(-0.185 – -0.016)	0.020*
Depression	0.010 (-0.004 – 0.024)	0.175	-0.036 (-0.061 – -0.012)	0.004*
Age			-0.018 (-0.021 – -0.015)	<0.001*
BMI			0.012 (0.010 – 0.015)	<0.001*
IMD			0.000 (-0.001 – 0.001)	0.677
Current smoker			0.122 (0.086 – 0.157)	<0.001*
Current drinker			0.036 (0.007 – 0.065)	0.017*
College education			0.017 (-0.008 – 0.043)	0.176
Ethnicity (reference – White)				
Asian			0.002 (-0.074 – 0.079)	0.950
Black			-0.221 (-0.304 – -0.139)	<0.001*
Mixed			-0.070 (-0.171 – 0.031)	0.174
Other			-0.062 (-0.163 – 0.039)	0.227

In pre-menopausal participants without a diagnosis of schizophrenia or bipolar disorder, there was no correlation between enhanced PRS for schizophrenia and standardised log testosterone level (r=-0.006, 95% CI: -0.022 – 0.009, p=0.419). There was also no correlation for PRS for bipolar disorder (r=0.0015, 95% CI: -0.013 – 0.017, p=0.847).

4.4.5 Cognitive functioning

A summary of cognitive test scores across diagnostic groups is shown in Table 16. As expected, significant differences were observed for all tests (p<0.0001). Post hoc tests showed that participants with schizophrenia, bipolar disorder and depression had lower fluid intelligence

scores than healthy controls (all $p<0.0001$). Participants with schizophrenia could remember less digits correctly than healthy controls ($p=0.0007$), made more errors in pairs matching ($p<0.0001$) and had slower reaction times ($p<0.0001$). Those with bipolar disorder made more errors during pairs matching ($p<0.0001$) and had slower reaction times than healthy controls ($p<0.0001$) but did not differ significantly in numeric memory ($p=0.08$). Participants with depression had worse numeric memory than controls ($p=0.02$), had more errors during pairs matching ($p=0.003$) and slower reaction times ($p<0.0001$). Participants with schizophrenia only differed from those with bipolar disorder in terms of slower reaction time ($p=0.035$). Participants with depression performed better than those with schizophrenia in terms of fluid intelligence ($p=0.015$), numeric memory ($p=0.010$), pairs matching ($p<0.0001$) and reaction time ($p<0.0001$).

Table 16. Cognitive test scores by diagnosis in UK Biobank. ANOVA used to compare differences between groups. SD – standard deviation.

	Diagnostic group					
	Healthy controls (n=17,311)	Schizophrenia (n=614)	Bipolar disorder (n=587)	Depression (n=16,756)	Unknown (n=34,407)	p value
Fluid intelligence score, mean (SD)	6.61 (2.06)	5.63 (2.18)	5.63 (2.21)	6.06 (2.08)	5.57 (2.12)	<0.0001
Numeric memory, maximum digits recalled correctly, mean (SD)	6.90 (1.23)	6.30 (1.66)	6.56 (1.38)	6.79 (1.28)	6.68 (1.32)	<0.0001
Pairs matching, errors in round, mean (SD)	3.42 (2.68)	4.29 (4.23)	3.99 (3.21)	3.52 (2.81)	3.76 (3.09)	<0.0001
Reaction time, milliseconds, mean (SD)	515.3 (87.5)	559.6 (134.1)	544.5 (120.4)	525.1 (101.6)	529.5 (106.1)	<0.0001

4.4.6 Sex hormones and cognitive functioning

In the entire pre-menopausal sample who had paired oestradiol and cognitive data (n=54,131), there was no association between log free oestradiol and fluid intelligence or numeric memory (Table 17). In the unadjusted model, there were significant negative associations between log free oestradiol and pairs matching (β=-0.037, 95% CI: -0.068 – -0.006, p=0.021), as well as reaction time (β=-2.536, 95% CI: -3.615 – -1.456, p<0.001), though neither remained significant when controlling for age, BMI, ethnicity, IMD, smoking status and alcohol status. In the schizophrenia group, reaction time showed a positive association in both unadjusted and adjusted (β=44.12, 95% CI: 16.16 – 72.07, p=0.002) models, implying slower reaction times were associated with higher oestradiol. In the depression group, worse numeric memory was associated with higher levels of oestradiol in the unadjusted and adjusted models (β=-0.195, 95%CI: -0.334 – -0.056, p=0.006). There were no significant associations between free testosterone and any cognitive score in either unadjusted or adjusted regression models. Similarly, there were no significant associations between free testosterone and any cognitive score within diagnostic groups.

*Table 17. Linear regression of log free oestradiol on cognitive performance in UK Biobank. Results presented for unadjusted model and adjusting for age, BMI, IMD, smoking, ethnicity, college education and alcohol use. CI – Confidence Interval, BMI – body mass index, IMD – index of multiple deprivation. * Indicates statistical significance at the 5% level.*

	Unadjusted		Adjusted	
	β coefficient (95% CI)	p value	β coefficient (95% CI)	p value
		Whole sample (n=54,131)		
Fluid intelligence	-0.025 (-0.064 - 0.014)	0.207	0.039 (-0.019 – 0.096)	0.185
Numeric memory	-0.015 (-0.060 – 0.031)	0.529	-0.022 (-0.101 – 0.057)	0.592
Pairs matching	-0.037 (-0.068 – -0.006)	0.021*	0.040 (-0.014 – 0.093)	0.146
Reaction time	-2.54 (-3.62 – -1.46)	<0.001*	-0.268 (-2.06 – 1.52)	0.770
		Healthy controls (n=4915)		
Fluid intelligence	-0.004 (-0.137 – 0.130)	0.954	0.006 (-0.124 – 0.136)	0.928
Numeric memory	-0.082 (-0.248 – 0.085)	0.335	-0.076 (-0.253 – 0.101)	0.398
Pairs matching	-0.033 (-0.131 – 0.066)	0.516	0.022 (-0.079 – 0.124)	0.665
Reaction time	-0.764 (-3.91 – 2.39)	0.635	2.38 (-0.853 – 5.61)	0.149
		Schizophrenia (n=205)		
Fluid intelligence	-0.414 (-1.01 – 0.183)	0.171	-0.286 (-0.887 - 0.316)	0.346
Numeric memory	0.385 (-0.734 – 1.50)	0.482	-0.663 (-2.11 - 0.785)	0.341
Pairs matching	0.191 (-0.777 – 1.16)	0.698	0.406 (-0.658 - 1.469)	0.453
Reaction time	33.4 (7.72 – 59.1)	0.011*	44.1 (16.2 – 72.1)	0.002*
		Bipolar disorder (n=201)		
Fluid intelligence	0.298 (-0.213 – 0.808)	0.251	0.521 (-0.010 – 1.05)	0.054
Numeric memory	-0.100 (-0.892 – 0.692)	0.799	-0.246 (-1.42 – 0.927)	0.668
Pairs matching	-0.250 (-0.853 – 0.353)	0.414	-0.199 (-0.881 – 0.482)	0.565
Reaction time	-15.8 (-38.7 – 7.07)	0.174	-19.5 (-45.5 – 6.41)	0.139
		Depression (n=5,243)		
Fluid intelligence	-0.008 (-0.111 – 0.094)	0.875	0.018 (-0.080 – 0.116)	0.713
Numeric memory	-0.170 (-0.301 – -0.038)	0.012*	-0.195 (-0.334 – -0.056)	0.006*
Pairs matching	-0.011 (-0.111 – 0.089)	0.830	0.063 (-0.042 – 0.168)	0.238
Reaction time	-3.95 (-7.56 – -0.350)	0.032	-2.13 (-5.78 - 1.51)	0.252

4.4.7 Menstrual cycle phase and cognitive functioning

Cognitive functioning was compared across menstrual cycle phases in the pre-menopausal sample (n=69,675), as shown in Table 18. There were statistically significant effects of menstrual cycle phase on fluid intelligence (p=0.008), pairs matching (p=0.002) and reaction time (p<0.0001) but not on numeric memory (p=0.427). Post hoc Tukey's tests showed that fluid intelligence was higher in the midcycle phase compared with early follicular (mean difference 0.19, 95% CI: 0.011 – 0.375, p=0.30), and late follicular (mean difference 0.29, 95% CI: 0.086 – 0.503, p=0.0008). For pairs matching, the midcycle phase had less errors than late follicular (mean difference -0.17, 95% CI: -0.31 – -0.03, p=0.010). Reaction time was fastest in the midluteal phase. This was statistically significant compared with early follicular (mean difference -6.82, 95% CI: -11.60 – -2.04, p=0.0007), and late follicular (mean difference -7.97, 95% CI: -13.48 – -2.45, p= 0.0006). The early luteal phase showed a faster reaction time than early follicular (mean difference -8.12, 95% CI: -12.14 – -4.10, p<0.0001), and late follicular (mean difference -9.27, 95% CI: -14.14 – -4.40, p<0.0001). The midluteal phase had faster reaction time than early follicular (mean difference -9.55, 95% CI: -13.53 – -5.58, p<0.0001), and late follicular (mean difference -10.70, 95% CI: -15.54 – -5.87, p<0.0001). The late luteal phase similarly had faster reactions than early follicular (mean difference -4.9, 95% CI: -9.28 – -0.62, p=0.014), and late follicular (mean difference -6.10, 95% CI: -11.23 – -0.97, p=0.0092).

There were 399 participants with schizophrenia who had menstrual cycle phase and cognitive testing. In this subgroup, there was no effect of menstrual cycle phase on fluid intelligence (p=0.251), pairs matching (p=0.597) or reaction time (p=0.533). There was a statistically significant effect of menstrual cycle phase on numeric memory (p=0.0375), though post hoc Tukey's test did not find any two-way comparisons of menstrual cycle phase to be statistically significant.

Table 18. Cognitive performance by menstrual cycle phase in pre-menopausal UK Biobank participants (n=69,675). P values calculated by one way ANOVA of menstrual cycle phase on cognitive task. Fluid intelligence measured as a score, numeric memory as maximum digits recalled, paired matching as number of errors, reaction time in milliseconds. SD = standard deviation.

	Menstrual cycle phase							
	Early follicular (n=15,610)	Late follicular (n=6,278)	Midcycle (n=4,468)	Early luteal (n=7,160)	Midluteal (n=7,393)	Late luteal (n=5,799)	Unknown (n=22,967)	p value
Fluid intelligence, mean (SD)	5.95 (2.18)	5.85 (2.15)	6.14 (2.08)	6.03 (2.14)	6.03 (2.06)	6.04 (2.10)	5.96 (2.14)	0.0008
Numeric memory, mean (SD)	6.74 (1.32)	6.76 (1.33)	6.82 (1.24)	6.86 (1.24)	6.80 (1.27)	6.77 (1.23)	6.73 (1.31)	0.427
Pairs matching, mean (SD)	3.60 (2.96)	3.66 (3.08)	3.50 (2.78)	3.62 (2.91)	3.49 (2.82)	3.63 (2.91)	3.70 (2.99)	0.002
Reaction time, mean (SD)	524.0 (102.0)	525.1 (108.4)	517.1 (95.3)	515.8 (92.3)	514.4 (93.4)	519.0 (94.2)	536.0 (105.9)	<0.0001

4.5 Discussion

This chapter examined menstrual cycle characteristics and sex hormones levels across mental disorders, using data from the UK Biobank. Participants with schizophrenia had later age of menarche and earlier age of menopause compared with healthy controls. They also had lower levels of oestradiol, though this was not significant after adjusting for relevant demographic and lifestyle factors. There was no evidence for associations of genetic liability for schizophrenia and oestradiol levels. There was a significant effect of menstrual cycle phase on cognition across participants, with best performance in the phase with highest oestradiol, though this was not demonstrated for participants with schizophrenia.

4.5.1 Menstrual cycle characteristics

In this large sample, there were small but statistically significant differences in menstrual cycle characteristics between diagnostic groups. Participants with schizophrenia reported a slightly later age of menarche than healthy controls. After adjusting for potential confounders of ethnicity and deprivation, the effect remained statistically significant. Participants with schizophrenia also reported going through menopause on average one year earlier than participants with no psychiatric diagnosis. This remained significant after controlling for potential confounders of current age, BMI, deprivation, ethnicity, education, alcohol, smoking, age of menarche and parity. Unexpectedly, irregular menstruation was not reported more commonly among patients with schizophrenia compared to healthy controls.

While previous studies have examined age of menarche in relation to psychosis onset,[52,54,55] age of menarche in patients with psychotic disorders have not generally been compared to healthy controls. Age of menarche is multi-factorial, influenced by genetics[15] and the environment. Improvements in nutrition and living standards are thought to have contributed the average age of menarche falling in the 20th century from 14 to 12 years.[16] While there was still a significant effect when controlling for ethnicity and socioeconomic status, there may have been residual confounding between groups. Slightly earlier age of menarche in participants with a diagnosis of depression is consistent with a recent meta-analysis[161] which found earlier menarche was associated with an increased risk for depressive symptoms and diagnosis of depression. Findings from a Mendelian randomisation study suggests that the association between earlier age of menarche and depression is causal[162] rather than due to reverse causation or residual confounding.

By contrast, earlier age of menopause is associated with a range of negative health outcomes and is a marker of ill health.[163] The average age of natural menopause has risen from 48.4 years

to 49.9 years in the USA from 1959 to 2018.[164] There are a number of factors associated with onset of menopause including smoking, ethnicity, alcohol use, socioeconomic status, education and parity.[165] The relationship between age of menarche and age of menopause shows a weak, non-linear association.[166] Given that women with schizophrenia tend to experience greater socioeconomic deprivation,[167] less education,[168] and are more likely to smoke,[169] these factors could potentially confound the relationship between schizophrenia diagnosis and age of menopause. However, when adjusting for these variables in the present study, the association between schizophrenia and age at menopause remained significant. Nevertheless, the possibility of residual confounding from unmeasured health, nutritional and socioeconomic factors associated with schizophrenia cannot be excluded. A lack of correlation between genetic risk (enhanced PRS) for schizophrenia and age of menopause, suggests unmeasured environmental factors may influence the association, rather than this being an inherent part of psychotic illness. Similarly, there was no correlation between PRS for schizophrenia and those for menopause age, suggesting a lack of shared genetic vulnerability.

That women with schizophrenia may have shortened reproductive lifespan is a novel finding. Though the absolute differences are small, it represents another health disparity of this disorder which is associated with multiple adverse health outcomes, including mortality[4] and reduced fertility.[170] These findings serve as a reminder for clinicians that patients with schizophrenia may experience menopause earlier than other women. Given the menopause transition is high risk for relapse of schizophrenia,[77] clinicians should be vigilant to perimenopausal worsening of symptoms and consider HRT, which is highly affect for vasomotor symptoms[34] and may even be protective against psychosis relapse.[86]

Contrary to expectation, the proportion of participants with schizophrenia who reported menstrual cycle irregularity was not different from healthy controls. Only 17% of participants with schizophrenia reported irregular menstruation, substantially lower than the 41% that been reported in the largest previous study of 139 patients with schizophrenia.[48] There are several explanations for this apparent discrepancy. UK Biobank participants were not asked directly whether they experienced irregular cycles. Instead, when asked ‘how many days is your usual menstrual cycle?’ they had the option to press ‘irregular cycle’. Furthermore, cycles which were reported as shorter than 21 days or longer than 35 days were assumed to be irregular, consistent with previous research.[48] Another explanation is that UK Biobank participants with schizophrenia may be less severely affected than clinically ascertained cases; indeed this has been demonstrated in terms of educational attainment, employment rates, lower rates of smoking, lower PRS and lower copy number variants.[171] However, even self-reported

schizophrenia diagnosis has good agreement with subsequent research interview diagnosis and has a similar genetic liability to diagnosis from hospital records.[172] Given that significant differences were found in age of menarche, age of menopause and in unadjusted oestradiol levels, more direct questioning of menstrual cycle regularity in future studies could reveal true differences between groups.

4.5.1.1 Strengths and limitations

This is the first study to demonstrate differences in self-reported age of menarche and menopause in schizophrenia compared to people without a psychiatric diagnosis. The findings suggest individuals with schizophrenia experience a later start to their reproductive lifecycle and an earlier end to this phase of life. I utilised a data available from a large sample with a standard, computerised assessment. Nevertheless, there are several limitations with this study design. Firstly, middle-aged participants were asked to recall the timing of an event, age of menarche, several decades after it occurred. Indeed, a prospective study of more than a thousand women found that self-reported age of menarche in middle age showed only moderate-strong correlation and fair agreement with prospectively ascertained age of menarche in adolescence.[173] Similarly, age of menopause is subject to recall bias. Menopause, by definition, is the cessation of menstruation for 12 months. For this question, participants were asked 'how old were you when your periods stopped?', which is far less precise than is recommended for classifying the menopause transition.[30] Furthermore, given the mean age of recruitment to UK Biobank sample was around the natural age of menopause, participants who had later age of menopause may be under-represented. While the UK Biobank is an excellent source of data, it is known to be unrepresentative of the population, with participants being healthier and wealthier across a range of outcomes.[174] Finally, given the UK Biobank was not designed to specifically examine menstrual cycle characteristics, these factors were not comprehensively assessed. This may explain why differences in menstrual cycle characteristics such as regularity were not detected; further large studies specifically designed to examine menstrual cycle characteristics are required to determine whether this finding is a true negative.

4.5.2 Hormone differences between groups

Participants with a diagnosis of schizophrenia had lower oestradiol than healthy controls. Controlling for demographic and lifestyle factors attenuated this effect, to the extent that it was no longer statistically significant. There was no difference in testosterone between schizophrenia and healthy controls. Standardising oestradiol values by menstrual cycle phase was performed to account for the variation of oestradiol across the cycle. Samples were not obtained at a standard menstrual cycle phase, meaning that participants would be at random

points of their cycle at the baseline data collection. To adjust for this variation, menstrual cycle phase was calculated from time since last menstrual period. Though this is a crude measure of cycle phase,[133] there were significant differences in oestradiol between phases, which followed the expected pattern of increasing during the follicular phase, peaking at midcycle, then declining in the luteal phase.

These findings confirm that levels of oestradiol are lower in schizophrenia than in healthy controls, replicating the results of previous research using smaller samples.[45–47] However, this may be a consequence of lifestyle factors associated with the illness, rather than inherent to psychosis. Various measured factors, such as current smoking, higher BMI, worse IMD were associated with both schizophrenia and lower oestradiol. When controlling for these factors, the effect of schizophrenia diagnosis on oestradiol levels was no longer significant.

Another potential driver of lower oestradiol levels in schizophrenia is antipsychotic medication. There is a clear biological mechanism behind this relationship, whereby prolactin-raising antipsychotics suppress secretion of FSH and LH, via inhibition of gonadotrophin releasing hormone, thereby decreasing production of oestradiol from the ovaries. Participants who reported taking prolactin-raising antipsychotic medication had lower levels of oestradiol than those who reported prolactin-sparing antipsychotics or no medication. It is likely this comparison was under-powered, only 95 participants reported treatment with prolactin-sparing antipsychotics, 50 reported prolactin-sparing and 469 did not have any medication recorded.

The failure to find a significant difference in testosterone between groups is at odds with a previous meta-analysis showing elevated testosterone in female patients with multi-episode schizophrenia.[140] However, that analysis pooled data from only three studies, with small sample sizes (all less than 100 participants with schizophrenia). Interestingly, when adjusting for lifestyle and demographic variables, both the bipolar disorder and depression groups had lower testosterone than healthy controls. This is consistent with a previous meta-analysis showing lower testosterone in female patients with depression[175] but contradicts a previous small study which found higher testosterone in female patients with bipolar disorder.[176]

4.5.2.1 Strengths and limitations

Compared to previous research, this study benefits from a large sample size and standardisation of hormone measurement. However, the blood sampling was not standardised to menstrual cycle phase, requiring post-hoc adjustment of values, based on timing of last menstrual period (an unreliable measure of menstrual cycle phase). Furthermore, hormones were quantified by immunoassay, which is less accurate than mass spectrometry, particularly

when concentrations of hormones are low.[177] As may be expected in an age range encompassing the natural age of menopause, more than a quarter of the pre-menopausal sample had oestradiol levels below the limit of detection. To mitigate this, values of these samples were imputed at 3/4 of the lower detection limit of 175 pmol/L. Finally, the UK Biobank has a limited number of hormones available for analysis. It was not possible to examine the effect of prolactin directly in relation to testosterone or oestradiol, despite this having a plausible role in the causal pathway. Instead, I used the proxy of self-reported prolactin-raising antipsychotic medication.

4.5.3 Cognitive functioning

There were marked differences in cognitive performance by diagnostic groups; participants with mental disorders did less well than healthy controls. Those with schizophrenia also performed worse than those with depression on all cognitive tests, and had a slower reaction time than participants with bipolar disorder.

In the whole female sample, there was negligible correlation between free oestradiol level and cognitive performance; only reaction time showed a significant negative association, though this was not significant when adjusting for covariates. In participants with schizophrenia specifically, free oestradiol was positively correlated with reaction time (higher oestradiol was associated with slower reaction). There were no correlations between free testosterone and fluid intelligence, numeric memory and reaction time.

The lack of association between oestradiol and cognition is in contradiction to the prevailing consensus that oestradiol is generally pro-cognitive.[178] Animal models suggest that acute administration of oestradiol enhances memory consolidation.[179] In humans, the 'critical window hypothesis' proposes that exogenous oestradiol, in the form of HRT, can reduce the future risk of Alzheimer's disease, if given early in the menopause transition.[88]

By contrast, in the pre-menopausal sample there were robust effects of menstrual cycle phase on cognitive performance in fluid intelligence, pair matching and reaction time. The midcycle phase (associated with peaking oestradiol) showed the best performance in fluid intelligence, numeric memory and reaction time. Within the schizophrenia group, menstrual cycle phase was significantly associated with numeric memory only but none of the post hoc pairwise between phases contrasts were statistically significant.

The discrepancy between menstrual cycle phase being associated with performance across cognitive domains, while free oestradiol did not show an association, is notable. These findings suggest that single-timepoint measures of oestradiol cannot capture the dynamic fluctuation of

such hormones over time. The menstrual cycle is characterised by rising and falling levels both in the follicular phase and luteal phase. It is impossible to infer from a single measurement whether the participant's oestradiol is rising or falling or their menstrual cycle phase.

While it is generally assumed that phases of the cycle with higher oestradiol are associated with better cognitive performance, the evidence to date has been inconsistent.[180] A recent meta-analysis of 102 studies, n=3,943 and 730 comparisons, including domains of executive function, intelligence and attention, did not find robust evidence of menstrual cycle phase on cognitive performance.[181] One explanation as to why differences in cognitive performance were detected in the UK Biobank is that all previous studies included in that meta-analysis were small (the largest study had a sample size n=207, while most were less than 100 participants) and used younger samples (the oldest sample had a mean age of 36 years). By contrast, even in pre-menopausal participants, the UK Biobank has a mean age which is 10 years older and a sample size that is an order of magnitude larger than all previous studies combined.

4.5.3.1 Strengths and limitations

The UK Biobank provides standardised computerised cognitive tests, conducted at the same baseline assessment in which blood sampling and menstrual cycle questions are administered. This allows the examination of sex hormones and menstrual cycle phase on cognition using a large sample size across psychiatric diagnoses.

Nevertheless, since the UK Biobank was not specifically designed to examine menstrual cycle hormones in relation to cognition, there are inherent limitations. Blood samples were not timed to menstrual cycle phase, these were essentially taken at random points in the cycle, while other relevant hormones such as FSH, LH and progesterone were not measured. As such, it cannot be determined from a single measurement of oestradiol whether this hormone is rising or falling, or whether the participant is in the follicular or luteal phase. This may explain a lack of association between free oestradiol and cognitive performance.

Menstrual cycle phase had to be inferred based on a relatively vague question on when the participant last had a menstrual period. While menstrual cycle phase was determined through self-reporting of last menstrual period, there was some validity to these groupings, with oestradiol peaking at midcycle, as expected. This phase also showed consistently better cognitive performance across domains. While an effect of menstrual phase could not be identified in the subgroup of participants with schizophrenia (n=399), this may have been due to a lack of statistical power, compared with the whole pre-menopausal sample (n=69,675).

4.5.4 Conclusion

Women with schizophrenia have differences both in the onset and cessation of their reproductive years, which is likely driven by factors associated with chronic severe mental disorders. Similarly lower levels of oestradiol in schizophrenia were largely explained when adjusting for covariates associated with lifestyle and demographics. There was no convincing evidence that oestradiol was associated with cognitive performance or genetic liability for schizophrenia. Overall, this does not support the conception of schizophrenia as an inherently hypo-oestrogenic state.

5 Sex hormones in the PSYSCAN early psychosis study

5.1 Introduction

While Chapter 4 provided evidence of lower oestradiol in participants with schizophrenia, this included older participants who had been exposed to an accumulation of confounding factors associated with chronic mental illness. This Chapter examines the effect of oestradiol using the PSYSCAN study which includes individuals experiencing FEP, those at CHR-P and healthy controls. By including participants at an earlier stage of illness, the long-term confounding factors associated with chronic mental illness are minimised.

Previous research suggests that antipsychotic-naïve patients with FEP[182] or at CHR-P[183,184] have higher prolactin levels compared with healthy control subjects. However, the evidence to date has been derived from relatively small samples and has unknown clinical significance. Up to 90% of patients receiving D2 selective antipsychotic exhibit hyperprolactinaemia,[42] and a previous meta-analysis shows that overall more than two thirds of both female and male antipsychotic-treated patients with schizophrenia have elevated prolactin levels.[43] Raised prolactin levels inhibit the downstream secretion of sex hormones via a central hypothalamic mechanism involving the suppression of gonadotrophin releasing hormone.[44] Hence, a potential effect of hyperprolactinaemia may be to suppress oestradiol in females. In both FEP and CHR-P, raised prolactin is associated with worse cognitive performance.[185]

PSYSCAN is a naturalistic multi-centre study including both FEP[186] and CHR-P[187] cohorts. Participants were recruited between 2016 and 2019, from diverse academic and clinical centres at 19 sites across the globe: Melbourne, Edinburgh, Utrecht, Hong Kong, Naples, Galway, London, Marburg, Zurich, Toronto, Maastricht, Seoul, Sao Paulo, Copenhagen, Madrid, Tel Hashomer, Heidelberg, Cantabria, Amsterdam and Vienna. At the baseline assessment, participants underwent a range of biological assessments, including blood sampling. They also completed a number of psychiatric symptom scales and a computerised cognitive battery, PsyCog.[188] Hormone measures were obtained from obtained frozen blood samples, post hoc. These were used to obtain measurements of oestradiol and testosterone, as well as FSH, LH and prolactin.

5.2 Aims

The first aim was to compare sex hormone levels (oestradiol and testosterone) and prolactin between FEP, CHR-P and healthy control groups. The second aim was to examine the relationship between prolactin levels and sex hormone levels in each group. The third aim was

to examine the relationship between cognitive functioning and symptomatology with these hormones in each group.

5.3 Methods

PSYSCAN was approved by local research ethics committees of all participating centres and conducted in compliance with the Declaration of Helsinki. All participants provided written informed consent. Approval to use data from the consortium for this secondary analysis was given by the PSYSCAN executive committee.

5.3.1 Participant recruitment and inclusion criteria

Individuals experiencing FEP (defined as DSM-IV diagnosis schizophrenia, schizoaffective or schizophreniform disorder on structured clinical interview,[189] within three years of onset) were recruited from 16 institutions with established early intervention in psychosis services. Participants with CHR-P were recruited from ten sites with established at-risk services. They had to meet Comprehensive Assessment of At-Risk Mental State (CAARMS) criteria[190] for CHR-P. This could consist of (i) attenuated psychotic symptoms, (ii) brief limited psychotic episodes, or (iii) trait vulnerability (first degree relative with psychosis or personal history of schizotypal personality disorder) with functional decline, or basic symptoms assessed using the Schizophrenia Proneness Instrument.[191] They were excluded if exposed to antipsychotic medication at a minimally effective dose for FEP, for 30 cumulative days, in the three months prior to assessment. Healthy controls were recruited through local advertisement. Exclusions for this group were a lifetime diagnosis of DSM-IV Axis-I psychiatric disorder, diagnosis of CHR-P, psychotic disorder in a first-degree relative, history of antipsychotic use, or current use of psychotropic medication. All participants were aged between 14 and 40 years. Exclusion criteria for all participants were: any previous neurosurgery or neurological disorder, previous head injury resulting in unconsciousness lasting at least one hour, pregnancy, estimated IQ <70.

5.3.2 Data collection

Participants underwent a baseline assessment in which a semi-structured interview was used to obtain sociodemographic characteristics, psychiatry history and medication use. The Structured Clinical Interview for DSM-IV disorders[189] was used to determine psychiatric diagnosis. IQ was determined using the abbreviated version of the Wechsler's Adult Intelligence Scale.[192] Symptomatology was rated using the PANSS (positive, negative and general subscales)[136] for the FEP group and using the CAARMS[190] (divided into positive and negative subscales) for the CHR-P group. The Hamilton Depression Rating Scale (HDRS)[193] was used to assess depressive symptomatology in each group.

The PsyCog[1] battery was used to assess cognitive performance. This is a nonverbal, brief (mean testing time 36 minutes), computerised assessment using four tasks: emotion recognition, paired associated learning, rapid visual information processing (attention), and spatial span (visuospatial working memory). This tool shows good test-retest reliability and discriminates both FEP and CHR-P groups from healthy controls with medium-to-large and small-to-medium effect sizes, respectively.[194] A global composite score across cognitive domains was calculated by taking the mean of sample normed Z-scores across each domain.[194]

Blood sampling was performed during the baseline assessment. Frozen samples were transferred to the University of Turku, Finland for hormone assays. Analysis of the steroid hormones (including oestradiol and testosterone) was performed using a UHPLC-QqQ mass spectrometer. Analysis of the peptide hormones FSH, LH and prolactin was performed by a commercial immunoassay.

5.3.3 Data analysis

The analysis was restricted to female participants, who were not prescribed exogenous hormones (for example, hormonal contraception). All analyses were performed using R statistical software. Continuous variables were presented as means and SD if normally distributed or as medians and IQRs if not. Categorical variables were presented as proportions. Differences between diagnostic groups were examined using ANOVA for continuous variables or chi squared tests for categorical variables. Variables with skewed distributions were log transformed. Correlations were examined using Pearson's test. The effect of group (FEP, CHR-P) on hormone levels was examined using linear models, with healthy controls as the reference category. Results were presented both unadjusted and adjusted for age, BMI and ethnicity. For linear models, residuals were checked for homoscedasticity.

The association of oestradiol and prolactin with symptomatology was examined within groups using Pearson's correlations of log transformed values. PANSS was used to quantify severity of psychotic symptomatology in the FEP group, in terms of positive, negative and general subscales. To adjust for the effect of antipsychotic medication in the FEP group, linear regression models were used, with chlorpromazine equivalents as a covariate. For the CHR-P group, the CAARMS positive score was calculated as in Tognin et al. 2025[187] by multiplying the severity and frequency ratings for each of the four positive-symptom items and summing these products to obtain a total score. Negative symptoms were scored using the same procedure across the corresponding CAARMS negative-symptom items. In FEP, CHR-P, and healthy control

groups, hormone measures were examined in relation to depressive symptomatology using the HDRS.

These hormones were also examined in relation to cognition using PsyCog scores. Pearson's correlations using log transformed values were performed in both the whole sample and within diagnostic groups. Finally, linear models were used to adjust for the effect of diagnostic group within the whole sample.

5.4 Results

5.4.1 Description of cohort

There were 199 female participants with available baseline blood samples. Of these, 25 were excluded for the use of exogenous sex hormones, leaving a sample of 175 women (70 FEP, 67 CHR-P, 38 healthy controls) whose characteristics are shown in Table 19. There were differences between groups in terms of age, with the FEP group being older, as well as in BMI, with the CHR-P group having lower BMI. There were no significant differences in the proportion of white participants between groups.

Table 19. Characteristics of female patients in PSYSCAN (n=175). Differences between groups were tested using ANOVA for continuous variables and chi squared tests for categorical variables. FEP – first episode psychosis, CHR-P – clinical high risk for psychosis, SD – standard deviation, BMI – body mass index.

	FEP (n=70)	CHR-P (n=67)	Healthy Control (n=38)	p value
Age, mean (SD)	26.26 (6.00)	22.06 (4.77)	23.15 (4.11)	<0.0001
BMI, mean (SD)	24.03 (4.84)	22.07 (6.16)	23.92 (4.66)	0.028
White ethnicity, number (percentage)	50 (71.6%)	42 (62.7%)	19 (50.0%)	0.068

5.4.2 Comparison of hormones between groups

The distributions for each hormone (oestradiol, testosterone, FSH, LH and prolactin) were positively skewed. The median and IQRs were therefore reported for each group (Table 20). There were no differences between diagnostic groups in terms of oestradiol, testosterone, FSH or LH. There was a significant difference in prolactin across groups. In the unadjusted regression model, there was a significant effect of FEP status on prolactin, which retained significance after adjusting for age, BMI and ethnicity (β=22.1, 95% CI: 2.0 – 42.2, p=0.03). There was no difference in oestradiol or testosterone between groups in unadjusted or adjusted models.

Table 20. Hormone values by group in PSYSCAN. Differences between groups were tested using ANOVA with log transformed values. CHR-P – clinical high risk for psychosis, FEP – first episode psychosis, IQR interquartile range.

	FEP (n=70)	CHR-P (n=67)	Healthy Controls (n=38)	p value
Oestradiol, pmol/L, median (IQR)	162.05 (105.35 – 336.85)	252.4 (100.65 – 455.45)	155.25 (78.62 – 366.00)	0.560
Testosterone, nmol/L, median, (IQR)	1.08 (0.80 – 1.35)	1.11 (0.76 – 1.34)	1.06 (0.77 – 1.32)	0.980
FSH, IU/L, median (IQR)	36.2 (25.7 – 47.3)	33.1 (23.3 – 43.5)	32.2 (20.9 – 42.8)	0.232
LH, IU/L, median (IQR)	30.0 (18.2 – 41.4)	36.8 (23.3 – 61.2)	24.6 (13.7 – 51.1)	0.318
Prolactin, ng/mL, median, (IQR)	16.9 (6.25 – 36.34)	8.06 (4.28 – 21.44)	10.3 (4.81 – 14.84)	0.0003

*Table 21. Linear regression of group status on oestradiol, prolactin and testosterone levels in PSYSCAN. Results presented for unadjusted model and adjusting for age, BMI, and ethnicity. FEP – first episode psychosis, CHR-P – clinical high risk for psychosis, CI – Confidence Interval, BMI – body mass index. * Indicates statistical significance at the 5% level.*

	Unadjusted		Adjusted	
Variable	β coefficient (95% CI)	p value	β coefficient (95% CI)	p value
			Oestradiol	
Group (reference – healthy controls)				
FEP	-57.7 (-171.7 – 56.3)	0.319	21.7 (-95.9 – 139.2)	0.717
CHR-P	27.1 (-87.8 – 142.0)	0.642	93.0 (-21.3 – 207.2)	0.110
Age			1.55 (-6.34 – 9.45)	0.698
BMI			-2.71 (-10.6 – 5.13)	0.496
Ethnicity (reference – White)				
Asian			55.1 (-68.1 – 178.3)	0.378
Black			14.4 (-130.7 – 159.5)	0.845
Mixed			-164.9 (-469.9 – 140.1)	0.287
Other			62.9 (-90.0 – 215.8)	0.418
			Testosterone	
Group (reference – healthy controls)				
FEP	-0.040 (-0.382 – 0.303)	0.820	0.104 (-0.294 – 0.499)	0.609
CHR-P	0.069 (-0.279 – 0.416)	0.697	0.056 (-0.333 – 0.443)	0.110
Age			-0.021 (-0.048 – 0.005)	0.114
BMI			-0.002 (-0.029 – 0.025)	0.889
Ethnicity (reference – White)				
Asian			0.455 (0.039 – 0.871)	0.032*
Black			0.154 (-0.336 – 0.644)	0.536
Mixed			-0.162 (-1.19 – 0.867)	0.756
Other			0.128 (-0.389 – 0.645)	0.625

			Prolactin	
Group (reference – healthy controls)				
FEP	25.6 (8.13 – 43.0)	0.004*	22.1 (1.95 – 42.2)	0.032
CHR-P	4.86 (-12.7 – 22.4)	0.586	8.06 (-11.5 – 27.6)	0.418
age			1.49 (0.14 – 2.85)	0.031*
BMI			0.56 (-0.78 – 1.92)	0.409
Ethnicity (reference – White)				
Asian			0.57 (-20.5 – 21.7)	0.957
Black			-0.98 (-25.9 – 23.9)	0.938
Mixed			32.14 (-20.1 – 84.4)	0.226
Other			0.17 (-26.0 – 26.4)	0.990

Using log-transformed values, there was no correlation between prolactin and oestradiol in the whole sample. Similarly, when stratifying by group status, no correlations were significant, see Table 22. FEP participants were grouped by antipsychotic status into prolactin-raising or prolactin-sparing medications, using the same classification as the previous Chapter. A summary of hormone levels between medications groups is shown in Table 23. As expected, there was a significant difference in prolactin levels between groups (p=0.00025). There were no differences between groups in terms of oestradiol, testosterone, or LH. The prolactin-raising group had higher levels of FSH (p= 0.0072).

Table 22.Correlations of log prolactin with log oestradiol in PSYSCAN. Calculated using Pearson's correlations. FEP – first episode psychosis, CHR-P – clinical high risk for psychosis, CI – Confidence Interval

Group	Correlation (95% CI)	p value
Whole sample	-0.015 (-0.169 – 0.140	0.850
FEP	-0.209 (-0.436 – 0.043)	0.103
CHR-P	0.182 (-0.069 – 0.411)	0.153
Control	-0.063 (-0.383 – 0.272)	0.717

*Table 23. Comparison of hormone levels between FEP PSYSCAN participants prescribed prolactin-sparing and prolactin-raising antipsychotic medication. Differences between groups were tested using t-tests on log transformed variables. * Indicates statistical significance at the 5% level.*

Hormone	Prolactin-sparing (n=53)	Prolactin-raising (n=26)	p value
Oestradiol, pmol/L, median (IQR)	215.7 (106.9 – 410.3)	146 (101.5 – 260.5)	p=0.312
Testosterone, nmol/L, median, (IQR)	0.92 (0.72 – 1.25)	1.19 (0.91 – 1.38)	p=0.165
FSH, IU/L, median (IQR)	32.9 (20.4 – 42.4)	42.8 (33.1 – 51.3)	p= 0.0072*
LH, IU/L, median (IQR)	25.2 (16.9 – 40.3)	33.7 (27.9 – 42.7)	p=0.249
Prolactin, ng/mL, median (IQR)	12.4 (4.50 – 19.9)	61.6 (18.8 – 125.3)	p=0.0003*

5.4.3 Association with symptomatology

In the FEP group, there were no significant correlations between log oestradiol and PANSS subscales, as shown in Table 24. There was a significant correlation between log prolactin and the PANSS negative subscale (β=0.26, 95% CI: 0.007 – 0.476, p=0.044). In a linear regression model adjusted for chlorpromazine-equivalents (Table 25), the association of prolactin was no longer statistically significant. Antipsychotic dose itself was not significantly associated with negative symptoms. In the CHR-P group, there was no correlation of either log oestradiol or log prolactin with either CAARMS subscale, as shown in Table 26.

*Table 24. Correlations of log prolactin and log oestradiol with PANSS subscales in the FEP group (n=70) in PSYSCAN. Calculated using Pearson's correlations. PANSS – Positive and Negative Syndrome Scale, P – positive, N – negative, G – general, FEP – first episode psychosis, CI – Confidence Interval. * Indicates statistical significance at the 5% level.*

	Log oestradiol		Log prolactin	
Domain	Correlation (95% CI)	p value	Correlation (95% CI)	p value
PANSS-P	-0.095 (-0.323 – 0.143)	0.433	0.008 (-0.242 – 0.257)	0.950
PANSS-N	-0.15 (-0.371 – 0.089)	0.217	0.256 (0.007 – 0.476)	0.044*
PANSS-G	-0.014 (-0.249 – 0.221)	0.906	0.069 (-0.184 – 0.313)	0.596

*Table 25. Linear regression of log prolactin on PANSS negative subscale in FEP group (n=70) in PSYSCAN. Results presented for unadjusted model and adjusting for CPZ equivalents. PANSS – Positive and Negative Syndrome Scale, FEP – first episode psychosis, CPZ – chlorpromazine equivalents, CI – Confidence Interval. * Indicates statistical significance at the 5% level.*

	Unadjusted		Adjusted	
	β coefficient (95% CI)	p value	β coefficient (95% CI)	p value
Log prolactin	1.32 (0.034 – 2.61)	0.044*	1.24 (-0.430 – 2.91)	0.141
CPZ			0.004 (-0.009 – 0.016)	0.536

Table 26. Correlations of log oestradiol and log prolactin with CAARMS subscales in the CHR-P group (n=67) in PSYSCAN. Calculated using Pearson's correlations. CAARMS – Comprehensive Assessment of At-Risk Mental States, P – positive, N – negative, CI – Confidence Interval.

	Log oestradiol		Log prolactin	
Domain	Correlation (95% CI)	p value	Correlation (95% CI)	p value
CAARMS-P	0.143 (-0.105 – 0.374)	0.256	-0.111 (-0.353 – 0.145)	0.395
CAARMS-N	0.090 (-0.173 – 0.340)	0.503	-0.056 (-0.319 – 0.215)	0.690

In the whole sample, there was a positive correlation between log oestradiol and depressive symptomatology measured by the HDRS, of borderline statistical significance (r=0.150, 95% CI: 0.000 – 0.294, p=0.050). The CHR-P group also showed a positive correlation (r=0.258, 95% CI: 0.01 – 0.475, p=0.042). There were no correlations between oestradiol and depressive symptoms in the FEP or healthy control group. There were no correlations between prolactin and depressive symptomatology in any participant group or in the whole sample.

*Table 27. Correlations of log oestradiol and log prolactin with HDRS in PSYSCAN. Calculated using Pearson's correlations. HDRS – Hamilton Depression Rating Scale, FEP – first episode psychosis, CHR-P – clinical high risk for psychosis, CI – Confidence Interval. * Indicates statistical significance at the 5% level.*

	Log oestradiol		Log prolactin	
Group	Correlation (95% CI)	p value	Correlation (95% CI)	p value
Whole sample (n=171)	0.150 (0.000 – 0.294)	0.050	0.046 (-0.111 – 0.201)	0.568
FEP (n=70)	0.041 (-0.196 – 0.273)	0.737	0.016 (-0.235 – 0.265)	0.901
CHR-P (n=63)	0.258 (0.01 – 0.475)	0.042*	0.094 (-0.166 – 0.342)	0.477
Control (n=38)	0.171 (-0.157 – 0.466)	0.303	-0.186 (-0.485 – 0.152)	0.277

5.4.4 Association with cognition

The relationship of hormone levels with cognition using the composite PsyCog score is shown in Table 28. In the whole sample, there was a negative correlation between log prolactin and PsyCog score, implying that higher prolactin was associated with worse cognitive performance.

*Table 28. Correlations of log oestradiol and log prolactin with PsyCog score in PSYSCAN. Calculated using Pearson's correlations. FEP – first episode psychosis, CHR-P – clinical high risk for psychosis, CI – Confidence Interval. * Indicates statistical significance at the 5% level.*

	Log oestradiol		Log prolactin	
Group	Correlation (95% CI)	p value	Correlation (95% CI)	p value
Whole sample (n=156)	-0.113 (-0.266 – 0.044)	0.158	-0.287 (-0.43 – -0.13)	0.0005*
FEP (n=61)	-0.129 (-0.369 – 0.127)	0.323	-0.262 (-0.495 – 0.006)	0.055
CHR-P (n=58)	-0.101 (-0.35 – 0.162)	0.452	-0.240 (-0.473 – 0.025)	0.075
Control (n=38)	-0.140 (-0.444 – 0.193)	0.408	0.157 (-0.186 – 0.466)	0.368

Given there are medium-large differences in cognitive performances between these groups[188] and the FEP group had higher prolactin, linear regression adjusting for group status was performed, see Table 29. Adjusting for group status attenuated the association of prolactin with PsyCog score, though this remained statistically significant (β =-0.101, 95% CI: -0.188 – -0.013, p=0.024). As expected, both membership of the FEP (β=-0.711, 95% CI: -0.972 – -0.451, p<0.0001) and CHR-P (β =-0.509, 95% CI: -0.757 -0.261, p=0.0001) groups had negative effects on cognitive performance, relative to controls.

*Table 29. Linear regression of log prolactin on PsyCog score in the whole female PSYSCAN sample (n=156). Results presented for unadjusted model and adjusting for group status. FEP – first episode psychosis, CHR-P – clinical high risk for psychosis, CI – Confidence Interval. * Indicates statistical significance at the 5% level.*

	Unadjusted		Adjusted	
Variable	β coefficient (95% CI)	p value	β coefficient (95% CI)	p value
Log prolactin	-0.163 (-0.253 – -0.073)	0.0005*	-0.101 (-0.188 – -0.013)	0.024*
FEP			-0.711 (-0.972 – -0.451)	<0.0001*
CHR-P			-0.509 (-0.757 – -0.261)	0.0001*

5.5 Discussion

In this younger sample of women in the early phase of psychosis there were no differences in oestradiol, testosterone, FSH or LH compared with healthy controls. The FEP group had significantly higher levels of prolactin, though this was driven by women who were prescribed

prolactin-raising antipsychotic medication. There was no correlation between oestradiol and psychosis symptomatology in either psychotic (PANSS), or attenuated psychotic (CAARMS) scales. Prolactin was associated with more severe negative symptoms in FEP, though this did not remain significant after adjusting for antipsychotic dose. In the whole sample, there was a negative correlation between prolactin and cognitive performance, though this was not significant when examined in each group (FEP, CHR-P, or healthy controls).

To date, this is the first analysis of oestradiol in the CHR-P population. The lack of correlation between oestradiol and attenuated psychotic symptoms, is at odds with a recent study which found higher oestradiol was associated with greater likelihood of psychotic experiences in female adolescents.[195] Oestradiol has also been shown to modulate 'hallucination-proneness' in healthy women using a white-noise paradigm.[196] The PSYSCAN sample did not replicate findings from the previous Chapter showing reduced oestradiol in schizophrenia compared with healthy controls in the UK Biobank. However, there are notable differences between samples which may account for this apparent disagreement. Firstly, participants with psychosis in the UK Biobank were significantly older (mean age 47 years) than those in PSYSCAN (mean age 26.4 years). Not only does this represent a different reproductive life stage, but it also represents an exposure to potentially confounding lifestyle factors associated with hypo-oestrogenism including smoking, alcohol and obesity. Indeed, when lifestyle factors were included as covariates in the UK Biobank sample, oestradiol was no longer significantly different between groups. Secondly the sample size of PSYSCAN (n=175) is an order of magnitude smaller than the UK Biobank sample, limiting the power to detect differences between groups. Thirdly, the measurement of hormones was not comparable between samples, with the UK Biobank using immunoassay for oestradiol and PSYSCAN using mass spectrometry, which is a more sensitive and specific measurement of oestradiol, particularly at lower levels.[197] Taken together, these two studies suggest that lower levels of oestrogen in psychotic disorders are likely due to secondary factors associated with chronic psychosis, rather than an inherent part of the disease process. Consistent with this, there was no correlation between oestradiol and psychopathology.

Elevated prolactin in the FEP group was driven by participants who were prescribed antipsychotic medication known to be associated with hyperprolactinaemia. While increased prolactin was associated with more severe negative symptoms, this was not significant when adjusting for antipsychotic dose. Notably, prolactin was not correlated with oestradiol, even in the FEP group, suggesting that prolactin elevation in this group was not high enough to suppress endogenous oestradiol. In the whole sample, there was a negative correlation between

prolactin and cognitive performance which was attenuated by group status (FEP, CHR-P, or healthy controls). Within each group, there was no significant correlation between prolactin and cognitive performance, which may be partly explained by limited statistical power due to smaller sample sizes.

Neither participants with FEP prescribed prolactin-sparing antipsychotics nor CHR-P participants (who by definition should not be prescribed antipsychotics) showed differences in prolactin compared with the control groups, suggesting that elevated prolactin in psychosis is secondary to D2-blocking medication rather than an inherent part of psychotic illness. This contradicts a recent meta-analysis of prolactin in antipsychotic naïve participants with FEP[182] which showed elevated prolactin, with a medium-large effect size. However, all studies contributing to that meta-analysis had sample sizes with less than 40 female participants with psychosis, apart from Delgado-Alvarado et al.[198] which included 137 female psychosis participants and showed significant elevated prolactin compared with controls. A systematic review of CHR-P did not identify any study comparing prolactin levels with healthy control subjects.[199]

Overall, this Chapter suggests that hyperprolactinaemia in early psychosis is a consequence of antipsychotic medication. Both participants treated with prolactin-sparing antipsychotics and those at CHR-P did not have alterations in prolactin compared with healthy controls. Furthermore, there were no associations between prolactin levels and psychopathology, after controlling for antipsychotic-dose.

5.5.1 Strengths and limitations

The sample reported in this Chapter has several advantages compared with Chapter 4, being younger, at an earlier stage of illness and including a group at risk for psychosis. These factors mitigate against the long-term confounders associated with chronic severe mental illness that might also influence hormone levels. Indeed, there were no differences in oestradiol between groups, further suggesting that differences in Chapter 4 could be attributable to lifestyle factors. A further strength is measurement of steroid hormones using mass spectrometry, which is superior to immunoassay. While the sample size of the present study was larger than almost all previous studies of prolactin in FEP, it was markedly less than the UK Biobank sample. This will have limited the statistical power to detect smaller differences in hormone levels between groups and associations with psychopathology. As PSYSCAN was not designed to examine hormones specifically, samples were not timed to a particular time of day or phase of the menstrual cycle. Due to variability in blood sample procedures between sites, it was not

possible to classify samples based on cycle phase, as in the previous Chapter. Similarly, the gold-standard procedure of measuring serum prolactin in the morning, due to diurnal variation, was not possible. Large samples with measurement of hormone levels standardised to menstrual cycle phase and time of day are required to rule-out differences between groups in the early phase of psychosis.

5.5.2 Conclusion

There were no demonstrable differences in oestradiol between patients in the early phase of psychosis and healthy controls. While participants with FEP had raised prolactin, this was driven by those prescribed medication known to raise prolactin through D2 receptor blockage. There was similarly little evidence of association between hormone levels and psychopathology. Thus, hypo-oestrogenism associated with chronic schizophrenia may be due to secondary lifestyle factors rather than the disease process of psychosis.

6 Discussion

6.1 Summary

This thesis collated evidence for menstrual psychosis and examined the role of the menstrual cycle in patients with psychosis more generally. Psychotic episodes associated with the menstrual cycle have a distinctive clinical phenotype suggesting a hormonal vulnerability to psychosis. However, within patients already diagnosed with a psychotic disorder, there was little evidence of menstrual dysfunction or correlation of oestradiol with symptomatology or cognition. This Chapter will discuss possible reasons as to why certain cases of psychosis appear to be triggered by the hormonal fluctuations of the menstrual cycle, yet menstrual cycle dysfunction does not seem to be an inherent part of psychotic disorders, beyond the effects of chronic mental illness. I propose that within the psychosis spectrum, there exists a subgroup of women who are more vulnerability to ovarian hormone fluctuations. The clinical significance of identifying this 'hormone-sensitive' subgroup, how it could influence the treatment of psychotic disorders and how it should be incorporated within the oestrogen hypothesis will be tackled next.

6.1.1 Is menstrual psychosis a distinct disorder?

Menstrual psychosis is not a diagnostic entity in DSM[200] or ICD[113] classification systems. While descriptions of cases have been published throughout the history of psychiatry, there has been little empirical research or wider recognition of the disorder. This thesis provided the most comprehensive summary of menstrual psychosis case reports (Chapter 2), a synthesis of clinical characteristics and symptomatology across individual cases (Chapter 2), identification of unpublished cases from electronic health records (Chapter 3) and a comparison with episodes of psychosis not related to the menstrual cycle (Chapter 3).

Using the definition of menstrual psychosis taken from Brockington of acute brief psychotic episodes in synchrony with the menstrual cycle with full recovery between episodes, 455 unique cases were identified: 417 from case reports (Chapter 2) and 38 from electronic health records (Chapter 3). By synthesising characteristics of these cases aspects of the menstrual psychosis phenotype have been confirmed. Firstly, the onset of cases is usually in the premenstrual or menstrual phase of the cycle (Chapters 2 and 3). This is the time when both oestradiol and progesterone decline to their lowest levels and is consistently a time of vulnerability to psychotic disorders,[57] other mental disorders,[89] and physical disorders.[94] Secondly, menstrual psychosis is a disorder of adolescence, with peak age of onset at 14 years, considerably younger than the typical age of onset of other psychotic disorders (Chapters 2 and

3).[49] Thirdly, menstrual psychosis can be considered as being on the bipolar spectrum, with disturbances of affect being the most common type of symptom (Chapters 2 and 3) and bipolar disorder being the most common clinical diagnosis attributed to cases (Chapter 3). Finally, the symptomatology of menstrual psychosis is distinct from psychosis not related to menstruation, with more frequent symptoms of incoherence, clouded consciousness and lability, while displaying less suspiciousness, self-harm, suicidal behaviour and depressed mood (Chapter 3). Identifying unpublished cases from electronic health records of a single mental health services (a greater number than any previously published case series) strongly suggests that published case-reports under-recognise the prevalence of this condition (Chapter 3). Notably, cases from electronic records had an identical age of onset as published cases and similar symptomatology, suggesting that case reports are broadly representative of the underlying patient population.

Approximately three quarters of cases had at least a partial response to hormonal treatment when this was trialled (Chapters 2 and 3), with the combined oral contraceptive being the most common formulation. This suggests that an adjunctive hormonal treatment should be considered alongside conventional antipsychotic medication and, in a proportion, hormonal treatment alone may be sufficient to prevent relapse. While hormonal approaches are novel in psychosis, they have an increasing evidence base,[87] are a logical treatment for hormone-mediated disorders and are recommended for other premenstrual mental disorders.[122] That patients with menstrual psychosis could avoid long-term maintenance antipsychotic medication with its associated side-effects[1] is another reason for clinicians to better recognise this condition.

Considering whether menstrual psychosis should be categorised as a distinct psychiatric disorder, comparisons can be made with another reproductive disorder, postpartum psychosis. Both these conditions are thought to be triggered by hormone fluctuations, based on temporal association with childbirth or menstrual cycle phase. Postpartum psychosis is another condition conceptualised within the bipolar spectrum[100] and has comparable symptomatology of affective disturbance and confusion.[64] It is similarly uncommon, with an incidence of 1-2 per thousand births.[58] Even though each disorder is rare, I identified 70 individuals (15% of all menstrual psychosis cases) who had episodes of both menstrual and postpartum psychosis (Chapters 2 and 3). Despite postpartum psychosis being much more widely accepted within both the clinical and research community, like menstrual psychosis, it is not yet classified as a distinct disorder by either DSM or ICD. A recent consensus statement argues that it should be

included as a category within bipolar disorder, to aid detection, improve early treatment and to facilitate further research.[100]

What stops postpartum psychosis (and by implication menstrual psychosis) from being seen as a distinct disorder? One reason is that episodes are not usually confined to the postpartum period; more than half of cases go on to have non-postpartum episodes.[62] Another is that postpartum psychosis is treated similarly to non-hormonally related bipolar disorder, with lithium being a mainstay of treatment alongside antipsychotics, benzodiazepines and in some cases electro-convulsive therapy.[68] Unlike menstrual psychosis, hormone-based treatments are not currently advocated as a management option for postpartum psychosis.

I propose that the menstrual cycle (like childbirth) can be a trigger of acute affective psychotic episodes in susceptible individuals. As such, both these conditions can be conceptualised as the manifestation in an underlying hormone-sensitive bipolar spectrum disorder. In keeping with only a subset of female patients with psychosis being sensitive to these hormone fluctuations, the population of psychosis patients as a whole does not display clear menstrual dysfunction, in terms of irregular menstruation or hypo-oestrogenism, and does not show an association between hormone levels and psychotic symptoms.

6.1.2 Partial support for the oestrogen hypothesis

The identification of a subgroup of patients who experience psychotic episodes coinciding with phases of the menstrual cycle in which oestradiol is low or declining is consistent with the oestrogen hypothesis (Chapters 2 and 3). Further support is that more than half of those treated with a combination of oestrogen and progestogen showed at least a partial response (Chapters 2 and 3), while slightly less than half treated with oestrogen alone showed at least a partial response (Chapter 2). However, the identification of a menstrual psychosis phenotype is not specific to oestrogen. In the perimenstrual phase there is also declining levels of progesterone, which has metabolites like allopregnanolone with effects on the GABAergic system.[28] Furthermore, more than half of patients who received progestogen monotherapy had at least a partial response, suggesting that oestrogen is not necessarily required for response.

There was less evidence to support the oestrogen hypothesis in samples with chronic psychotic disorders (Chapter 4) or in the early phase of psychosis (Chapter 5). UK Biobank participants with schizophrenia did not have higher rates of menstrual irregularity than participants without psychiatric disorders (Chapter 4). Participants with schizophrenia did have an earlier age of menopause and later age of menarche than healthy participants (Chapter 4), which may be viewed as a marker of overall health. There were lower oestradiol levels in participants with

schizophrenia, though this was attenuated when adjusting for lifestyle factors such as smoking, social deprivation and BMI (Chapter 4). In those with schizophrenia, there was no significant relationship between cognitive performance and oestradiol (Chapter 4). In younger patients at an earlier stage of illness, there is less evidence of hypo-oestrogenism. There were no significant differences in oestradiol levels between groups of FEP, CHR-P and healthy controls (Chapter 5). Furthermore, there was no relationship between oestradiol and cognitive performance or psychotic symptomatology (Chapter 5). This is consistent with hypo-oestrogenism reported in schizophrenia being a result of chronic mental illness and lifestyle factors, rather than being an inherent part of psychotic illness, present at the time of onset. It should be noted that the PSYSCAN sample had a sample size that was approximately an order of magnitude smaller than the UK Biobank sample. While the PSYSCAN sample was large enough to detect the well-replicated finding of increased prolactin in patients with psychosis,[43] was among the largest studies of sex hormones in psychosis,[47] and represents the largest sample to examine sex hormones in FEP to date, it was still underpowered to detect small-medium effect sizes. Given blood samples were not timed to menstrual cycle phase, further variability was introduced. In the UK Biobank sample, hormone levels were standardised using time since last menstrual period as an approximation of menstrual cycle phase. This was not possible in the PSYSCAN sample, as time since last menstrual period was not systematically recorded. It is therefore plausible that the failure to replicate the UK Biobank findings was due to insufficient power of the smaller PSYSCAN sample and greater variability in the data due to a lack of standardisation by menstrual cycle phase.

Both the UK Biobank (Chapter 4) and PSYSCAN (Chapter 5) highlight the limitations of cross-sectional hormone measurement which is not timed to a specific menstrual cycle phase. Ovarian hormones display marked fluctuation across a single menstrual cycle and show substantial variability both within and between individuals. While cross-sectional hormone measures did show robust differences between groups in the UK Biobank sample, there was no association between oestradiol and cognitive functioning, despite menstrual cycle phase being associated with cognitive performance in these participants. This discrepancy highlights that a single measurement of oestradiol gives no information as to whether this hormone is rising (as in the follicular phase or early luteal phase), peaking (prior to ovulation and in the mid-luteal phase) or falling (in the late luteal phase). Since a one-off measurement of oestradiol cannot determine menstrual cycle phase, it is impossible to know the other hormonal dynamics at that timepoint. An oestradiol level taken in the follicular phase is accompanied by low progesterone, whereas oestradiol in the luteal phase may be in the context of rising or falling progesterone. In

keeping with this, oestradiol was not associated with cognitive performance or symptomatology in the PSYSCAN sample, despite menstrual cycle phase previously being associated with exacerbation of psychotic disorders.[57]

The limitations described here are inherent to secondary analysis of data from studies (UK Biobank and PSYSCAN) that was not designed for the purpose of examining female sex hormones. A better study design would be to anchor measurement of hormones to menstrual cycle phase (mid-follicular, periovulatory, mid-luteal and perimenstrual) and to combine blood-samples with measures of cognitive performance and symptomatology.[133] This approach in adequately powered samples is needed to determine whether oestradiol levels are reduced in early and chronic psychotic disorders and whether endogenous oestradiol levels are associated with the cognitive dysfunction[141] and symptomatology[136] which characterises psychosis.

Overall, while this thesis presents limited evidence for menstrual dysfunction as a central feature of psychosis, it suggests there is a hormone-sensitive subgroup who may have distinct clinical features and a response to hormone-based treatment. How to identify this putative subgroup will be addressed next.

6.2 Future directions

6.2.1 Mapping psychotic symptoms across the menstrual cycle

While there are some individuals who experience distinct episodes of psychosis linked to the menstrual cycle, it is not known what proportion of female patients with psychosis might experience menstrual exacerbation of psychotic symptoms. Research to date has typically compared symptom scores at two or three timepoints in the cycle,[79,80,84,201] which lacks the temporal precision to determine cyclical fluctuations. To account for the large between-person variability in menstrual cycle phases and allow individual-level interpretation, daily symptom measurement is the gold-standard diagnostic method for premenstrual disorders.[202] The importance of prospective rating is emphasised by a lack of agreement between retrospective and prospectively diagnosed premenstrual mood disorders, with retrospective reporting of symptoms leading to false positives.[138,203,204] The ubiquity of smartphones ownership, including in patients with psychosis, has made it possible to send daily electronic questionnaires to research participants, which is a convenient and ecologically valid alternative to clinician rated symptom scales.[205]

To examine menstrual exacerbation of psychotic symptoms at the individual level, I have set-up the study *MAPS: Mapping Psychotic Symptoms Across the Menstrual Cycle Through Daily*

Remote Symptom Monitoring. This uses a commercially available research platform ExpiWell[206] to send daily symptom questionnaires using an app on each participant's personal device.

6.2.1.1 Methodology

The design is a longitudinal naturalistic observational study. Participants have a screening assessment and then complete daily smartphone questionnaires for three months (throughout their menstrual cycle). Questionnaires were designed to include all items of a validated tool for diagnosing PMDD (the Daily Record of Severity of Problems[207]), as well as the most frequently reported symptoms found in menstrual psychosis (identified in Chapters 2 and 3), and onset of menstrual bleeding. The full questionnaire items are provided in Appendices. Participants must either meet criteria for FEP, clinical high risk for psychosis or bipolar disorder, or healthy controls as per the inclusion criteria below.

For all participants:

- Female, aged 18 – 40 years
- Self-report of natural menstrual cycles between 21 – 35 days
- Not currently prescribed any form of hormonal medication or contraception
- No diagnosis of a gynaecological disorder that affects the menstrual cycle, for example, polycystic ovarian syndrome, endometriosis, uterine fibroids
- Not currently pregnant or breast feeding

For patients with FEP:

- First episode of psychosis as defined by a DSM-5 diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar affective disorder with psychotic symptoms, based on the Mini International Neuropsychiatric Interview DSM-5
- Onset of psychosis within the past 24 months, with onset of psychosis defined as the first contact with a healthcare professional during which the diagnosis is made

For patients at clinical high risk for psychosis or bipolar disorder:

- CHR-P criteria according to CAARMS

OR

- Bipolar At-Risk criteria according to the Semi-structured Interview of At-Risk Bipolar States

For healthy controls:

- No previous diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder
- No previous diagnosis of 'at risk mental state' for psychosis or bipolar disorder

Participants with FEP are recruited from Oxford Early Intervention Service and Bucks Early Intervention Service. Clinical high-risk participants are recruited from Oxford Prevention and Early Detection Service. Healthy controls are recruited by local advertisement.

At baseline assessment, participants undergo a diagnostic interview (the Mini International Neuropsychiatric Interview[208]) and Reproductive Status Questionnaire[133] to ensure they meet inclusion criteria. Clinical high risk participants complete the CAARMS[190] and the Semi-structured Interview of At Risk Bipolar States.[209] Participants complete rating scales including the Premenstrual Symptoms Screening Tool,[210] Calgary Depression Scale for Schizophrenia,[211] Social and Occupational Functioning Assessment Scale,[212] Sheehan Disability Scale,[213] Brief Negative Symptom Scale,[214] and Sleep Condition Indicator.[215] The FEP group additionally complete the PANSS,[136] Young Mania Rating Scale,[216] Global Assessment of Functioning,[217] and Clinical Global Impression.[218] All participants complete the Subjective Scale to Investigate Cognition in Schizophrenia[219] and the Screen for Cognitive Impairment in Psychiatry.[220] Participants are shown how to install the ExpiWell app and to complete daily symptom measures. Each subject takes part in the study for three months, during which ExpiWell will send one notification per day requiring completion of a brief assessment.

6.2.1.2 Analysis plan

Multilevel modelling will be used for the primary analysis. It is ideally suited to a nested data structure, where datapoints are longitudinal repeated measurements nested within individuals, who are themselves nested within larger groups (FEP, clinical high risk, healthy controls). This can account for missing data, different numbers of measurements between individuals and autocorrelation of measurements due to proximity in time.

6.2.1.3 Study progress

The study received all approvals including from Health Research Authority and local Oxford Health Research and Development by January 2025. Recruitment commenced in March 2025 and since then has enrolled 31 participants: 15 with FEP and 16 healthy controls. Of these, 15 have successfully completed three months of data collection using ExpiWell. The target sample size is 25 participants per group.

6.2.2 Towards a hormone-sensitive psychosis subgroup

Postulating that there is a subgroup of female patients who are particularly vulnerable to ovarian hormone fluctuation produces several testable hypotheses. Differences are expected between female patients who experience menstrual exacerbation of their illness and those who do not. These two groups could be compared in terms of other reproductive life events. For example, a hormone-sensitive subgroup would be expected to have higher rates of postpartum relapse and perimenopausal deterioration. This has been shown for other hormone-sensitive groups, such as PMS being associated with increased risk for postpartum depression.[221] They would be expected to have a differential response to suppression of the ovarian axis, analogous to symptoms of PMDD remitting on suppression of ovarian hormones and recurring when exogenous oestradiol or progesterone are reintroduced.[222] They would be expected to show a better respond to hormonal treatments such as the combined oral contraceptive and transdermal oestradiol. More fundamentally, whether hormone-sensitivity is associated with a distinct neurotransmitter receptor profile[223] or genetic vulernability[224] across mental disorders is an intriguing possibility. These questions are tractable and could improve our understanding of mental disorders more broadly, as well as offering individualised treatment for individuals affected.

Another strategy is to identify patients who already have evidence for a hormonal trigger to their illness. The most established hormone-mediated psychotic disorder in this context is postpartum psychosis. By recruiting women who have experienced postpartum psychotic episodes, particularly those with episodes within the first days-weeks following birth, the clinical effect of exogenous hormones can be examined. Given that more than half of women who develop postpartum psychosis will go on to experience further episodes outside the postpartum period,[60] this group is an ideal population to trial hormonal interventions. Determining whether this group has elevated risk of relapse at other times of hormonal transition (such as the perimenopause[78]) and whether they particularly benefit from hormonal stabilisation in the form of HRT is a testable hypothesis. One approach is to recruit perimenopausal participants with a history of postpartum psychosis to a randomised, placebo-controlled trial of transdermal oestradiol. The outcome of psychosis relapse could be utilised to determine whether this approach prevents recurrence of illness during the perimenopause, similar to a previous trial for the prevention of menopausal depression.[85] Not only would this validate the concept of a hormone-sensitive subgroup of psychosis, it would also provide a preventative clinical intervention to reduce the risk of relapse in this patient population.

Ultimately, the approach of identifying individuals whose illness is susceptible to hormonal fluctuations could represent the opportunity for personalised, hormone-informed care. For psychotic disorders, this would represent a new paradigm of treatment, distinct from dopamine-blocking medication which is currently the only effective pharmacological treatment for these disorders. It is now widely accepted that times of hormonal transition can impact susceptible individuals, triggering new-onset or relapse of psychotic disorders. The next step is to utilise this knowledge for novel therapeutic approaches that build on hormonal treatments already used in other medical contexts.

6.3 Conclusions

Throughout the history of psychiatry, the role of menstrual cycle in psychosis has been a topic of speculation but little research beyond clinical description has been produced. This thesis has synthesised the clinical phenotype of menstrual psychosis while also examining the menstrual cycle in female patients throughout the psychosis illness course. I have shown that menstrual psychosis is a disorder of adolescence, with a symptom profile and illness course which can be conceptualised within the bipolar spectrum. I have shown that there is limited evidence for menstrual cycle dysfunction at the early stages of psychotic illness and that hypo-oestrogenism seen in chronic schizophrenia is largely explained by lifestyle factors. This provides partial support for the oestrogen hypothesis. Finally, I have speculated that there is a hormone-sensitive subgroup within the psychosis patient population who may be particularly vulnerable to reproductive life events and may show a differential response to hormone-based treatments.

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8 Appendices

8.1 AMDP symptoms

Symptom	Domain	Definition
Lowered vigilance	Disorders of consciousness	Disturbances of vigilance
Clouded consciousness	Disorders of consciousness	Qualitative impairment in clarity of consciousness. Impaired ability to understand aspects relating to one's own person and the environment, to make meaningful connections between them, and to communicate and act sensibly
Narrowed consciousness	Disorders of consciousness	Diminished experience and restricted behaviour with accompanying diminished responsiveness to external stimuli.
Expanded consciousness	Disorders of consciousness	This is a qualitative dimension of consciousness disturbances, where patients report instances of heightened or intensified awareness of inner and outer events
Disorientation time	Disturbances of orientation	Current date (day, month, year), day of the week or season/time of year are not or only partially known
Disorientation place	Disturbances of orientation	The patient is unable to identify their present location, or the answers produced in this respect are extremely inaccurate
Disorientation situation	Disturbances of orientation	The patient displays only partial or no awareness of current surroundings and proceedings and their significance or purpose
Disorientation person	Disturbances of orientation	The patient is not or only partially aware of their identity and/or personal history
Disturbed appreception	Disturbances of attention and memory	A patient's impaired ability to understand the meaning and significance of verbal utterances and written texts and to establish meaningful connections between their contents and the context in which they were made or written. The patient's degree of ability to cognitively process received information is being assessed here.
Disturbed concentration	Disturbances of attention and memory	Reduced ability to keep one's attention and remained focused on an activity or topic for a prolonged period
Disturbed short-term memory	Disturbances of attention and memory	Partial or total inability to retain fresh information and subsequent recall over a time span of around 10 minutes
Disturbed long-term memory	Disturbances of attention and memory	Reduction in or loss of ability to store information in the memory for longer than 10 minutes or recall previously studied material from memory
Confabulation	Disturbances of attention and memory	The filling of memory gaps with spontaneously occurring and changing contents
Paramnesias	Disturbances of attention and memory	Distorted or deceptive memories involuntary upcoming memories heightened memory recall

Inhibited thinking	Formal thought disorders	The thinking process us subjectively experienced by the patient as being slowed down or blocked (as by an inner wall of resistance)
Retarded thinking	Formal thought disorders	The flow of thought processes is slowed down and sluggish
Circumstantial thinking	Formal thought disorders	An inability to separate the essential from the unessential during a conversation without, however, rendering the conversation incoherent
Restricted thinking	Formal thought disorders	Limited range of thought content, fixation on one particular topic or a small number of topics only. Fixation on a small number of objectives only. Stereotyped pattern of thinking
Perseverative thinking	Formal thought disorders	Persistent repetition of previously used words, phrases, or details to the point where they become meaningless in the context of the current stage of the interview
Rumination	Formal thought disorders	Endless mental preoccupation with, or excessive concern over, mostly unpleasant thoughts
Pressured thinking	Formal thought disorders	The patient feels helplessly exposed to the pressures of floods of different ideas or thoughts
Flight of ideas	Formal thought disorders	An increasing multitude of thoughts and ideas which, however, are no longer firmly guided by clear goal-directed thinking. As a result of diverse associations, thinking goals change frequently or become lost.
Tangential thinking	Formal thought disorders	The patient appears to understand the contents of the question addressed to them but provides answers which are completely out of context ("vorbeireden" or "talking past the point")
Thought blocking / disruption of thought	Formal thought disorders	Sudden disruption of an otherwise normal flow of thought or speech for no obvious reason
Incoherence derailment	Formal thought disorders	The interviewer is unable to establish sensible connections between the patient's thinking and verbal output, which is sometimes also called derailment. In extreme cases, what remains is a seemingly arbitrary tumble of fragmented sentences, phrases, and thoughts
Neologisms	Formal thought disorders	The formation of new words, or usage of words, which disregard normal conventions and are generally not easily understandable
Suspiciousness	Worries and compulsions	The behaviour of others is viewed with anxiety, mistrust or hostility and perceived as directed at one's own person
Hypochondriasis	Worries and compulsions	Anxious, fearful perception of one's own body whereby, eg physical sensations of discomfort are felt, accompanied by an objectively unfounded fear of falling ill or being ill, or of being or becoming physically disfigured. Normal bodily functions are attributed disproportionately large significance
Phobias	Worries and compulsions	An overwhelming fear/anxiety of particular situations or objects, generally resulting in active avoidance of the stimulus or stimuli in question

Obsessive thoughts	Worries and compulsions	Persistent, recurring self-generated thoughts that are experienced as unreasonable or exaggerated, and which the patient tries to resist or dismiss
Compulsive impulses	Worries and compulsions	Persistently recurring impulses to perform certain actions (which may be physical or mental), which are experienced as senseless or exaggerated, and which reduce the anxiety generated by obsessions
Compulsive actions	Worries and compulsions	Persistently and repeatedly carried out actions which are experienced as futile or exaggerated, and which may reduce the anxiety generated by obsessions
Delusional mood	Delusions	Delusional mood indicates an unusual, often confused, and tense emotional state of mind preceding manifestation of the delusion. The mood consists of attributing significance to, and making connections between, unsubstantiated guesses, suppositions, and expectations, which, to the healthy person, have no meaning or relevance
Delusional perception	Delusions	Abnormal significance/meaning, usually related to one's self, is attributed to a real perception. This happens without the presence of rationally or emotionally understandable underlying reasons. This symptom represents a delusional misinterpretation of an accurate perception of an external stimulus.
Sudden delusional ideas	Delusions	Purely mentally conceived, newly emerged delusional ideas and convictions
Delusional ideas	Delusions	Persistent or enduring delusional thoughts and convictions
Systematized delusions	Delusions	"Degree of interconnectedness" (logical or paralogical) among individual delusional symptoms and other delusional phenomena, hallucinations, ego-disorders, or also nonpathological, changed observations or experiences
Delusional dynamics	Delusions	The extent or intensity of affects emerging from the delusions
Delusions of reference	Delusions	The delusional conviction that environmental events or objects are intended to be of special significance to the patient. Delusional attribution of events to one's self.
Delusions of persecution	Delusions	The patient experiences themselves as the target of hostilities or monitoring. They have delusions that they are threatened, offended, insulted, mocked, under surveillance or derided by others who are after their money and belongings or out to destroy their health or even their life
Delusions of jealousy	Delusions	Delusional conviction of being deceived or betrayed by their partner, that their pattern is unfaithful
Delusions of guilt	Delusions	Delusional conviction of having failed in one's duty, committed a crime or sin, or having wronged others
Delusions of impoverishment	Delusions	Delusional conviction of not having enough financial means to live on and make ends meet

Hypochondrial delusions	Delusions	Delusional conviction of having fallen ill with a serious illness
Delusions of grandiosity	Delusions	Delusional exaggerated self-esteem or self-aggrandizement, or the belief of having special powers or skills
Other delusions	Delusions	Delusions that do not fit in any of the above categories
Illusions	Disorders of perception	Misjudgements or misperceptions of real objects, noises, or persons
Hearing voices	Disorders of perception	Perception of voices (phonemes) without someone speaking
Other auditory hallucinations	Disorders of perception	Perception of nonverbal hallucinatory sounds or noises (acouasm)
Visual hallucinations	Disorders of perception	Visual perceptions without corresponding external stimuli
Bodily hallucinations	Disorders of perception	Tactile perception without corresponding stimuli, or altered bodily perceptions (coenesthesia)
Olfactory and gustatory hallucinations	Disorders of perception	Perceptions of particular tastes and smells without the presence of corresponding external stimuli
Derealization	Ego (boundary) disturbances	The patient experiences surroundings or time as if they are unreal and changed; all feelings of familiarity with and trust in the environment are lost
Depersonalization	Ego (boundary) disturbances	The patient perceives themselves as alien, unreal, changed, or as a stranger
Thought broadcasting	Ego (boundary) disturbances	The patient's personal thoughts are experienced as no longer belonging to the patient alone but accessible by others who will know what the patient is thinking (mind reading). This can be a passive experience with the patient believing their thoughts as accessible to others, without someone else actively attempting to read their mind
Thought withdrawal	Ego (boundary) disturbances	The patient's thoughts are being removed or "stripped from them"
Thought insertion	Ego (boundary) disturbances	Patients experience their thoughts and ideas as being externally influenced, made externally, controlled, directed, entered/ or externally imposed
Other feelings of alien influence	Ego (boundary) disturbances	Feelings, intentions, behaviour, or bodily functions are experienced as externally controlled or made by others (passivity phenomena.
Perplexity	Disturbances of affect	The patient appears in the state of mind of someone who is totally lost and no longer capable of properly assessing their situation, surroundings, or future. The patient can no longer understand what is happening to them and appears stunned and perplexed (bewildered, helpless).

Feeling of loss of feeling	Disturbances of affect	The patient reports a reduction in or loss of affective experience and a subjectively felt emotional emptiness. The patient experiences themself as deprived of feelings, inwardly empty and numb, both in terms of positive feelings such as joy and happiness, but also negative emotional states such as sadness and despair
Blunted affect	Disturbances of affect	The number (spectrum) of affective states displayed is diminished
Felt loss of vitality	Disturbances of affect	A reduction in the overall strength, energy and vitality
Depressed mood	Disturbances of affect	Negatively tinged affective state characterised by low mood, sadness and dejection
Hopelessness	Disturbances of affect	Diminished hopes, pessimistic frame of mind, lack of future perspective. Little or no belief/trust in a positive future (a fatalistic attitude of impending doom and gloom)
Anxiety	Disturbances of affect	The patient reports feeling anxious and fearful, sometimes without being able to indicate why, or of what
Euphoria	Disturbances of affect	Experiencing a state of excessive well-being, of comfort and contentment, of cheerfulness, confidence and enhanced levels of vitality
Dysphoria	Disturbances of affect	Discontented ill-humouredness. The patient is in a dissatisfied mood displaying a sullen, crabby, discordant, unhappy, angry attitude
Irritability	Disturbances of affect	The patient reacts in an inappropriately swift or fierce manner with anger and/or aggression
Inner restlessness	Disturbances of affect	The patient senses inner excitability/agitation, tension or nervousness
Complaintiveness	Disturbances of affect	Pain, grief and anxiety are explicitly communicated through words, facial expressions and physical gestures (wailing/lamenting)
Feelings of inadequacy	Disturbances of affect	Trust and confidence in one's own achievement potential or one's self-worth is diminished or lost
Exaggerated self-esteem	Disturbances of affect	A positively experienced feeling of heightened self-esteem, strength or potential for achievement
Feelings of guilt	Disturbances of affect	The patient feels guilty because of their actions, thoughts or desires. They are under the impression of having done wrong and acted in contravention of a given set of norms
Feelings of impoverishment	Disturbances of affect	The patient worries about not having the necessary financial means to meet the cost of living and make ends meet and believes they are impoverished
Ambivalence	Disturbances of affect	The co-existence of contradictory feelings or impulses (ambitendency in a patient, which they perceive as simultaneously present and distressing)
Parathymia / incongruent affect	Disturbances of affect	Nonverbal expressions of feelings and the contents of reported experiences do not correspond
Affective lability	Disturbances of affect	A rapid change of affects/emotions that occurs spontaneously or as a result of external stimuli (emotional instability)

Affective incontinence	Disturbances of affect	Affective reactions/expressions may become overbearing at the slightest impulse, remain beyond the control of the patient and at times assume an exaggerated level of intensity (lack of affective self-control)
Affective rigidity	Disturbances of affect	Reduction or loss of emotional modulation with reduced range of levels of affective expressiveness (amplitude)
Lack of drive	Disorders of drive and psychomotor activity	Lack of energy, initiative and interest
Inhibition of drive	Disorders of drive and psychomotor activity	The patient experiences levels of energy and personal initiative as stalled or blocked
Increased drive	Disorders of drive and psychomotor activity	Increased levels of energy, initiative and interest
Motor restlessness	Disorders of drive and psychomotor activity	Increased levels of undirected motor activity
Parakinesia	Disorders of drive and psychomotor activity	Parakinesia includes several psychopathological symptoms. - Parakinesias are qualitatively abnormal, mostly complex physical movements, which often involve gestural and facial expressions, and also speech. - Stereotypy involves a patient's tendency to repeat speech or motor expressions persistently in identical form over a longer period of time. In contrast to 19. Perseverative thinking, there is no recognisable connection or relevance to words or gestures used earlier in the conversation. Stereotypy also includes verbigerations (word stereotypy), echolalia (echo-like repeating of words and phrases), echopraxia (automaton- like imitating), catalepsy (postural stereotypy), and flexibilitas cerea (waxy flexibility). Mechanical laughter may also be recorded here. - Command automatism involves the patient mechanically performing actions in response to corresponding external stimuli. - Negativism involves a patient's failure to perform in precisely those areas where it is expected or asked of them to do so (passive negativism), or they engage in exactly the Opposite (active negativism). Negativistic patients can in certain cases be brought to perform according to expectations by prohibiting them to do so in respect of the desired action, or by asking them to do the opposite of what is required (command negativism).
Mannerisms	Disorders of drive and psychomotor activity	Everyday movements and actions (also physical gestures, facial expressions and speech) appear to the outside observer as eccentric, cranky, showy and forced; they are sometimes performed in a distinctive/exaggeratedly playful manner
Histrionics	Disorders of drive and psychomotor activity	Patients give the impression of play-acting themselves
Mutism	Disorders of drive and psychomotor activity	The patient is taciturn or does not speak at all (falling silent)

Logorrhoea	Disorders of drive and psychomotor activity	Increased loquacity (talkativeness)
Worse in the morning	Circadian disturbances	Regular worsening of symptoms in the morning
Worse in the evening	Circadian disturbances	Regular worsening of symptoms in the evening
Better in the evening	Circadian disturbances	Regular improvement of the symptoms in the evening
Social withdrawal	Other disturbances	Withdrawal from other people's company
Excessive social contact	Other disturbances	Increased social activity
Aggressiveness	Other disturbances	Hostile, offensive and attacking behaviour
Suicidal behaviour	Other disturbances	Thoughts, plans and concrete action taken in preparation of fulfilling a wish to die or of committing suicide
Self-harm	Other disturbances	Self-harming without suicidal intent
Lack of feeling ill	Other disturbances	The patient feels considerably less ill than they actually are, or not ill at all
Lack of insight into illness	Other disturbances	The patient fails to perceive their complaints as manifestations of their psychopathological condition
Uncooperativeness	Other disturbances	The patient refuses treatment or resists attempts to be treated
Need for care	Other disturbances	A patient is reliant on others for the performance of activities relating to everyday functioning
Attacks of anxiety	Additional psychopathological items	Attacks of anxiety (panic attacks) are sudden, temporally discrete, clearly definable episodes of intense fear, frequently linked to physical symptoms. They can appear out of the blue or can be triggered by particular situations
Acceleration of thinking	Additional psychopathological items	Subjective perception of experiencing accelerated thought processes
Ideas of reference	Additional psychopathological items	Feeling that coincidental events are of particular and unusual significance for the patient
Disorganisation	Additional psychopathological items	In the context of everyday activities, difficulties are experienced with the organisation and meaningful sequencing of a series of small steps of action into a coherent whole in order to achieve completion of a specific task
Obtrusive behaviour	Additional psychopathological items	Physical positioning of improper/inappropriate physical proximity and overstepping socioculturally accepted boundaries of interpersonal distance

Hearing ones own thoughts	Additional psychopathological items	Hearing one's own thoughts in a clearly auditory, fully verbalised form ("gerdankenlautwerden").
Impulsive	Additional psychopathological items	Sudden rash and hasty action that is triggered by external stimuli or inner impulse
Disturbance of body image	Additional psychopathological items	Excessively negative or distorted aesthetic perception of one's own body or parts of it
Feelings of shame	Additional psychopathological items	Excessive levels of self-consciousness, shyness and personal embarrassment on account of perceived personal exposure when being noticed, observed and/or critically appraised by others
Overvalued ideas	Additional psychopathological items	Ideas that are of particularly significant importance to the patient themselves but barely or not at all comprehensible to others
Anomic aphasia	Additional psychopathological items	Common items of vocabulary previously used by the patient on a general everyday basis persistently elude them during the interview
Difficulty falling asleep	Disturbances of sleep and vigilance	Prolonged periods of inability to fall asleep
Interrupted sleep	Disturbances of sleep and vigilance	No continuous period of sustained sleep is experienced after falling asleep. The patient possibly experiences several instances of waking up and consciously registers these disruptions, but generally manages to fall back asleep
Shortened sleep	Disturbances of sleep and vigilance	Reduction in overall period of uninterrupted sleep experienced at night
Early morning wakening	Disturbances of sleep and vigilance	Distinctly earlier than usual wake-up time with accompanying inability to fall back to sleep
Tiredness	Disturbances of sleep and vigilance	Feeling of reduced alertness and an accompanying decrease in mental alacrity, in some cases resulting in a tendency to fall asleep
Decreased appetite	Appetitive disturbances	A reduction in the perceived need for nourishment accompanied by a reduced ability to take enjoyment from consuming food and/or drink
Excessive appetite	Appetitive disturbances	Excessive craving for nourishment
Excessive thirst	Appetitive disturbances	A patient perceives an excessive need to drink fluids
Decreased libido	Appetitive disturbances	Decreased sexual desire

Hypersalivation	Gastrointestinal disturbances	Excessive salivation
Dry mouth	Gastrointestinal disturbances	A feeling of dryness of mouth; reduced salivation
Nausea	Gastrointestinal disturbances	The patient suffers from nausea or a feeling of an impending need to be sick (retching)
Vomiting	Gastrointestinal disturbances	Spontaneous and/or induced vomiting
Gastric discomfort	Gastrointestinal disturbances	Localised discomfort in abdominal region
Constipation	Gastrointestinal disturbances	Uncomfortable bowel movements or constipation
Diarrhoea	Gastrointestinal disturbances	More frequent bowel movements and softer or runny stools
Breathing difficulties	Cardiac-respiratory disturbances	Having difficulties breathing
Dizziness	Cardiac-respiratory disturbances	Every form of dizziness is included here, as well as orthostatic complaints
Palpitations	Cardiac-respiratory disturbances	The patient complains about a more noticeable accelerated or irregular heartbeat
Cardiac pain	Cardiac-respiratory disturbances	Oppressively worrying hear complaints, possibly experienced in the form of a piercing feeling or feelings of tightness and as external or internal pressure on the heart
Blurred vision	Other autonomic disturbances	Loss of the ability to visually focus clearly on fixed objects; seeing things fuzzy or blurred
Increased perspiration	Other autonomic disturbances	A tendency to increased sweating or breaking out in a sweat
Seborrhoea	Other autonomic disturbances	Excessively active sebaceous glands
Micturition difficulties	Other autonomic disturbances	Various disturbances related to emptying of the bladder (eg impaired micturition, pollakiuria, enuresis)
Menstrual disturbances	Other autonomic disturbances	Instances of irregularities in the menstrual cycle or unusual complaints experienced in connection with menstruation
Head pressure	Other somatic disturbances	This symptom comprises complaints ranging from feelings of pressure in the head to dull headaches to intense, throbbing pain in the head, etc
Backache	Other somatic disturbances	Various forms of backache are included: feelings of pain, tension and pressure of either a clearly defined or diffuse nature, and present on a constant or only intermittent basis

Heaviness in the legs	Other somatic disturbances	The patient reports their legs feeling heavier than usual
Hot flashes	Other somatic disturbances	Various forms of feelings of heat in the body are included here: hot flashes, hot flush phenomena, feelings of rising inner body heat, etc. Despite the absence of comparatively high indoor or outdoor temperatures or an illness-related body temperature, the patient feels subjectively warmer or hotter than normal
Chills	Other somatic disturbances	Despite the absence of an illness-related raised body temperature, the patient feels cold and chilly
Conversion symptoms	Other somatic disturbances	Conversion symptoms appear to be neurological symptoms, but have no clear-cut neurological or somatic basis. They are either directly observable during examination or plausibly reported by the patient to have occurred during the assessment period. They often develop shortly after a traumatising experience, unresolved or insufferable conflicts or troubled relationships. Conversion symptoms can also be known as dissociative disorders.
Rigor	Neurological disturbances	Rigor refers to increased muscle tone presenting in the context of an extrapyramidal motor disorder, which becomes noticeable throughout an entire passive movement
Muscle hypotonia	Neurological disturbances	Reduced muscle tone is evident from decreased resistance to attempts at flexing or stretching of musculature in a naturally relaxed state
Tremor	Neurological disturbances	Involuntary shaking. Successive rhythmic contractions of seemingly antagonistic muscles
Acute dyskinesia	Neurological disturbances	Motor dysfunction of extrapyramidal motor disorders
Hypokinesia	Neurological disturbances	Poverty and slowness of physiological associated movements, voluntary and spontaneous movements, mostly related to problems in the extrapyramidal system
Ataxia	Neurological disturbances	Disturbed coordination between groups of muscles when attempting to perform targeted movements or assume particular physical postures
Nystagmus	Neurological disturbances	Involuntary, rhythmic eye movements, consisting of two consecutive phases: with jerk nystagmus, eye movement in one direction is rapid while slowed down in the opposite direction; with pendular nystagmus, both phases are of identical length.
Paraesthesia	Neurological disturbances	All forms of abnormal physical sensation are documented here, not only paraesthesia (i.e., sensitive irritations that are not associated with particular physical discomfort), but also dysesthesias (which are experienced as distinctly disagreeable irritations)
Parasomnia	Additional somatic items	Unusual experience or instances of behaviour that present alongside sleep, particular phases of sleep, or during transition from sleep to wakefulness
Increased libido	Additional somatic items	Increased sexual desire and /or sexual activity compared with the patient's usual levels of sexual interest and functioning

8.2 Menstrual psychosis case reports

Case	Year	First author	Reference
1	1816	Esquirol	Panckonike, C.L.F. *Dictionaire Des Sciences Médicales*. Vol 60. 1822. p191-192
2	1817	Fodéré	Fodéré F.E. *Traité Du Délire Appliqué à La Médecine, à La Morale et à La Législation*. Vol 2. 1817. p191-193
3	1819	Louyer-Villermay	Panckonike, C.L.F. *Dictionaire Des Sciences Médicales*. Vol 60. 1822. p563
4	1822	Pritchard	Pritchard, J.C. *A Treatise on Diseases of the Nervous System: Part the First, Comprising Convulsive and Maniacal Affections*. 1822.
5	1830	Strecker	Wunsch zu Heiligenstadt. Gutachten über eine mania transitoria einer Wöchnerin. *Ztschr Staatsarznk*. 1830;10:115-135.
6	1848	Sauvet	Sauvet, J.J. Réflexions sur l'emploi des évacuations sanguines dans le traitement des maladies mentales. *Annales médico-psychologiques*. 1848;12:157-191.
7	1849	Barbier	Barbier, M.V. *De l'influence de La Menstruation Sur Les Maladies Mentales*. Paris; 1848.
8	1851	Brière de Boismont	Brière de Boismont, A. Recherches bibliographiques et cliniques sur la folie puerpérale, precedées d'un aperçu sur les rapports de la menstruation et de l'aliénation mentale. *Annales Medico-psychologiques*. 1851;3:574-610.
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13	1856	Marcé	Marcé LV. Manie hystérique intermittente à la suite de sèvrage. *Gazette des Hopitaux*. 1856;29:526.
14	1858	Azam	Azam, Étienne Eugène. *De La Folie Sympathique Provoquée Ou Entretenue Par Les Lésions Organiques de l'utérus*.; 1858.
15	1857	Marcé	Marcé LV. De la grossesse et de l'accouchement sur la guérison de l'aliénation mentale. *Annales Médico-Psychologiques*. 1857;3:337-339.
16	1858	Schlager	Schlager, L. Die Bedeutung des Menstrualprocesses und seiner Anomalieen für die Entwicklung und den Verlauf der psychischen Störungen. *Zeitschrift für Psychiatrie*. 1858;15:459-498.
17	1864	Delasiauve	Delasiauve, Antoine Laurent Jules. Folie occasionnée par la menstruation. *Journal de Médecine Mentale*. 1864;4:241-248.
18	1865	Zepuder	Zepuder, F. Fall von Mania menstrualis. *Wiener medizinische Presse*. 1865;6:928-929.
19	1866	Dauby	Dauby, Édouard. *Quelques Considérations Sur La Menstruation Dans Ses Rapports Avec La Folie*. Paris; 1866.

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21	1869	Van Holbeck	Icard, Séverin. *Contribution à l'Etude de Létat Psychique de La Femme Pendant La Période Menstruelle, Considéré plus Spécialement Dans Ses Rapports Avec Le Morale et La Médécine Légale,*. Paris; 1889.
22	1872	Martini	Martini. Zwei Fälle von Menstruationsstörungen und plötzliche Herstellung der Menses durch psychischen Einfluss. *Allgemeine Zeitschrift für Psychiatrie*. 1872;28:657-659.
23	1872	Winge	Winge. Beziehungen zwischen Menstruation und Geisteskrankheit. *Norsk Magasin for Lagevidrnskap*. 1873;3(6):99-102.
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28	1874	Schröter	Schröter, R. Die Menstruation in ihrer Beziehungen zu den Psychosen. *Allgemeine Zeitschrift für Psychiatrie*. 1874;30:551-572.
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33	1878	von Krafft-Ebing	von Krafft-Ebing, Richard. Untersuchungen über Irresein zur Zeit der Menstruation. *Archiv für Psychiatrie*. 1878;8:65-107.
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216	1988	Kimura	Kimura, T., Tomonari, H., Waseda, Y. A case of atypical psychosis responding favourably to bromocriptine. *Japanese Journal of Clinical Psychiatry*. 1988;17:249-256.
217	1988	Leetz	Leetz KL, Rodenhauser P, Wheelock J. Medroxyprogesterone in the treatment of periodic menstrual psychosis. *J Clin Psychiatry*. 1988;49(9):372-373.
218	1990	Lischka	Lischka E. Motility psychoses in childhood and adolescence? *Acta Paedopsychiatr*. 1990;53(4):308-310.
219	1991	Koshikawa	Koshikawa, N. Neuroendocrinological studies on puerperal psychiatry problems: a possible etiology based on the longitudinal examinations of H-P-G axis in postpartum mental disorders. *Seishin Shinkeigaku Zasshi*. 1991;92:20-58.
220	1991	Labbate	Labbate LA, Shearer G, Waldrep DA. A case of recurrent premenstrual psychosis. *Am J Psychiatry*. 1991;148(1):147.
221	1992	Koyama	Matsunaga H, Sarai M, Taniguchi N, Kagomoto T, Inui M, Kameda H. [Gonadal function in young female affective illness associated with the menstrual cycle--in relation to the polycystic ovary syndrome]. *Seishin Shinkeigaku Zasshi*. 1992;94(8):738-758.
222	1992	Lovestone	Lovestone S. Periodic psychosis associated with the menstrual cycle and increased blink rate. *Br J Psychiatry*. 1992;161:402-404.
223	1992	Martinius	Martinius J. [Periodic psychosis in adolescence]. *Z Kinder Jugendpsychiatr*. 1992;20(2):121-125.
224	1992	Schenck	Schenck CH, Mandell M, Lewis GM. A case of monthly unipolar psychotic depression with suicide attempt by self-burning: selective response to bupropion treatment. *Compr Psychiatry*. 1992;33(5):353-356.
225	1993	Birmingham	Birmingham MK, Solyom L, Vecsei P. Cortisol/18-OH-DOC in menstrual cycle. *Biol Psychiatry*. 1993;33(1):58-60.
226	1993	Constant	Constant M, Abrams CA, Chasalow FI. Gonadotropin-associated psychosis in perimenstrual behavior disorder. *Horm Res*. 1993;40(4):141-144.
227	1993	Constant	Constant M, Abrams CA, Chasalow FI. Gonadotropin-associated psychosis in perimenstrual behavior disorder. *Horm Res*. 1993;40(4):141-144.

228	1993	Matsunaga	Matsunaga H, Sarai M. Elevated serum LH and androgens in affective disorder related to the menstrual cycle: with reference to polycystic ovary syndrome. *Jpn J Psychiatry Neurol*. 1993;47(4):825-842.
229	1993	Severino	Severino SK, Yonkers KA. A literature review of psychotic symptoms associated with the premenstruum. *Psychosomatics*. 1993;34(4):299-306.
230	1993	Sothern	Sothern RB, Slover GP, Morris RW. Circannual and menstrual rhythm characteristics in manic episodes and body temperature. *Biol Psychiatry*. 1993;33(3):194-203
231	1993	Stein	Stein D, Hanukoglu A, Blank S, Elizur A. Cyclic psychosis associated with the menstrual cycle. *Br J Psychiatry*. 1993;163:824-828.
232	1993	Yamashita	Yamashita, I. *Periodic Psychosis of Adolescence*. Hokkaido University Press; 1993.
233	1994	Ambelas	Ambelas A. Cyclic psychosis, menstrual cycle and adolescence. *The British Journal of Psychiatry*. 1994;164(5):709-709.
234	1995	Abe	Abe K, Ohta M. Recurrent brief episodes with psychotic features in adolescence: periodic psychosis of puberty revisited. *Br J Psychiatry*. 1995;167(4):507-513.
235	1995	Korhonen	Korhonen S, Saarijärvi S, Aito M. Successful estradiol treatment of psychotic symptoms in the premenstrual phase: a case report. *Acta Psychiatr Scand*. 1995;92(3):237-238.
236	2001	Al-Dabbas	al-Dabbas, Muhammad H. Premenstrual mania. *The Arab Journal of Psychiatry*. 2001;12(1):45-49.
237	2003	Al-Habeeb	Al-Habeeb TA. Premenstrual Manic Disorder: Review of Literature, Case Report and the Efficacy of Trifluoperazine. *Arab Journal of Psychiatry*. 2003;14(1):57-62.
238	2001	Wakutani	Wakutani Y, Nakayasu H, Takeshima T, et al. [A case of late-onset carbamoyl phosphate synthetase I deficiency, presenting periodic psychotic episodes coinciding with menstrual periods]. *Rinsho Shinkeigaku*. 2001;41(11):780-785.
239	2003	Stein	Stein D, Blumensohn R, Witztum E. Perimenstrual psychosis among female adolescents: two case reports and an update of the literature. *Int J Psychiatry Med*. 2003;33(2):169-179.
240	2003	Stein	Stein D, Blumensohn R, Witztum E. Perimenstrual psychosis among female adolescents: two case reports and an update of the literature. *Int J Psychiatry Med*. 2003;33(2):169-179.
241	2003	Shah	Shah AB, Vahia VN, Yadav R, Sonavane SS. Menstrual psychosis : a case report. *Indian J Psychiatry*. 2003;45(2):61-62.
242	2004	Becker	Becker OV, Rasgon NL, Marsh WK, Glenn T, Ketter TA. Lamotrigine therapy in treatment-resistant menstrually-related rapid cycling bipolar disorder: a case report. *Bipolar Disord*. 2004;6(5):435-439.
243	2007	Hsiao	Hsiao MC, Liu CY. Unusual manifestations of premenstrual syndrome. *Psychiatry Clin Neurosci*. 2007;61(1):120-123.
244	2007	Hsiao	Hsiao MC, Liu CY. Unusual manifestations of premenstrual syndrome. *Psychiatry Clin Neurosci*. 2007;61(1):120-123.
245	2007	Hsiao	Hsiao MC, Liu CY. Unusual manifestations of premenstrual syndrome. *Psychiatry Clin Neurosci*. 2007;61(1):120-123.
246	2007	Otsuka	Otsuka K, Sakai A, Okudera T, Shibata E, Matoh K, Kawamura S. Oral contraceptive administration prevents relapse of periodic psychosis with hyperprolactinemia. *Psychiatry Clin Neurosci*. 2007;61(1):127-128.

247	2007	Sheinfeld	Sheinfeld H, Gal M, Bunzel ME, Vishne T. The etiology of some menstrual disorders: a gynecological and psychiatric issue. *Health Care Women Int*. 2007;28(9):817-827.
248	2008	Andreou	Andreou C, Syngelakis M, Karavatos A. Metformine for psychosis associated with the menstrual cycle in a patient with polycystic ovary syndrome. *Arch Womens Ment Health*. 2008;11(5-6):387-388.
249	2008	Huang	Huang MC, Wang YB, Chan CH. Estrogen-progesterone combination for treatment-refractory post-partum mania. *Psychiatry Clin Neurosci*. 2008;62(1):126.
250	2009	Kobayashi	Kobayashi T, Kato S. Menstrual catatonia. *Psychiatry Clin Neurosci*. 2009;63(6):773-774.
251	2009	Coromina Sadurni	Coromina Sadurni M, Rodie JU, de Montagut LM, Sánchez Autet M. The use of oral contraceptives as a prevention of recurrent premenstrual psychosis. *Psychiatry Res*. 2009;170(2-3):290-291.
252	2010	Karatepe	Karatepe HT, Işık H, Sayar K, Yavuz F. Menstruation-related recurrent psychotic disorder: a case report. *Dusunen Adam*. Published online December 30, 2010:282-287.
253	2011	Aalouane	Aalouane R, Rammouz I, Elghazouani F, Aarab C, Blecha L. Hypomanic episodes during menstrual periods: bipolar II disorder? *Psychiatry Clin Neurosci*. 2011;65(1):112-113.
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255	2012	Lee	Lee YT, Chou YH. Lack of Efficacy of Antipsychotics on Premenstrual Psychosis: A Case Report. *Psychopharmacol Bull*. 2012;45(1):31-34.
256	2012	Pamfile	Pamfile D, Malassine T. P-1475 - Differential diagnosis of menstrual psychosis versus menstrual exacerbation of schizoaffective disorder in the context of acculturation difficulties: a case report. *European Psychiatry*. 2012;27:1.
257	2013	Ellison-Wright	Ellison-Wright, Z., O'Keane, V. Menstrual psychosis in an adolescent girl. *Progress in Neurology and Psychiatry*. Published online 2013:17-23.
258	2013	Ghosh	Ghosh S. Rapid cycling bipolar-II disorder presenting as hypomanic episodes associated with menstruation: a case report. *Sri Lanka Journal of Psychiatry*. 2013;4(2):47-48.
259	2013	Hu	Hu LY, Chen PM. Olanzapine treatment of premenstrual onset psychosis: a case report. *General Hospital Psychiatry*. 2013;35(4):452.e1-452.e3.
260	2013	López Arteaga	López Arteaga T, Loro López M. Cyclic psychosis and menstruation: Presentation of a case. *Rev Psiquiatr Salud Ment*. 2013;6(1):52-53.
261	2013	Puiu	Puiu MG, Manea M, Iordan AM, Manea M, Patrichi BE, Frunza AA. 1649 – Possible menstrual psychosis: a case report. *European Psychiatry*. 2013;28:1.
262	2013	Santos-Cubiñá	Santos-Cubiñá J, Castaing-Lespier PA, Sabaté N, Torres-Martin A, Quiñones-Fernandini VM. Menstrual psychosis: presenting symptom of bipolar disorder not otherwise specified in a 13-years-old Hispanic female. *Bol Asoc Med P R*. 2013;105(3):53-55.
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264	2014	Matsoaka	Matsuoka K, Yasuno F, Inoue M, et al. Microstructural changes of the nucleus accumbens due to increase of estradiol level during menstrual cycle contribute to recurrent manic episodes--a single case study. Psychiatry Res. 2014;221(2):149-154.
265	2014	Mendelevich	Mendelevich DM, Gatin FF, Mitrofanov IA. Case of 38-years favorable current of premenstrual psychosis. *Neurology Bulletin*. 2014;XLVI(4):97-105.
266	2014	Vijapura	Vijapura S, Schofield M, Maneta E, Coffey BJ. Mania in an adolescent with autism and premenstrual mood variation: a diagnostic and treatment dilemma. *J Child Adolesc Psychopharmacol*. 2014;24(3):161-164.
267	2015	Sönmez	Sönmez I, Kosger F. Menstrual Cycle in Schizophrenic Patients: Review with a Case. *Arch Neuropsychiatr*. 2015;52(4):417-419.
268	2015	Zanzonico	Zanzonico, Roberta, Vergne, Derick E. Menstrual Psychosis: A Forgotten Disorder? Medscape. Accessed November 28, 2025. https://www.medscape.com/viewarticle/851170
269	2016	Aktepe	Aktepe, E., Özen, E., Eroglu, Ö. Menstrual psikoz: oglu sunumu. *Anatolian Journal of Psychiatry*. 2016;7:88-90.
270	2016	Che	Che KI. Recurrent Psychotic Episodes with a Near-monthly Cycle. *East Asian Arch Psychiatry*. 2016;26(4):137-140.
271	2016	Tarazi	Tarazi MS, Fida-Al-Atrash, Dandona P, Kuhadiya ND. A Case of Menstruation Related Psychosis-A Rare Entity. *General Medicine (Los Angeles)*. 2016;4(2).
272	2017	Jalnapurkar	Jalnapurkar I, Findley JC. A case of repeated mixed mood episodes with psychotic symptoms associated with the premenstrual period in a patient with polycystic ovarian syndrome. *Gynecological Endocrinology*. 2018;34(6):467-469.
273	2017	Susser	Susser LC, Hermann AD. Protection against hormone-mediated mood symptoms. *Arch Womens Ment Health*. 2017;20(2):355-356.
274	2018	Fatica	Fatica JP, Jiwani S, Salman R, Majeed S. Premenstrual Psychosis in an Adolescent: A Case Report. *Clin Schizophr Relat Psychoses*.
275	2018	Kiel	Kiel W, Rhonda W, Geetanjali R. A Case of Menstrual Psychosis, an Under Recognized Diagnosis. *OJNBD*. 2018;2(2):1-3.
276	2018	Talukdar	Talukdar B, Deb K, Sengupta S. Menstruation-related psychosis. *Open Jour of Psych & Allied Scie*. 2019;10(1):82.
277	2018	Thippaiah	Thippaiah SM, Nagaraja S, Birur B, Cohen AW. An Interesting Presentation About Cyclical Menstrual Psychosis with an Updated Review of Literature. *Psychopharmacol Bull*. 2018;48(3):16-21.
278	2018	Vengadavaradan	Vengadavaradan A, Sathyanarayanan G, Kuppili PP, Bharadwaj B. Is menstrual Psychosis a Forgotten Entity? *Indian Journal of Psychological Medicine*. 2018;40(6):574-576
279	2018	Zwiebel	Zwiebel S, Villasante-Tejanos AG, de Leon J. Periodic Catatonia Marked by Hypercortisolemia and Exacerbated by the Menses: A Case Report and Literature Review. *Case Rep Psychiatry*. 2018;(1):4264763.
280	2019	Ahern	Ahern E, Cohen D, Prior C, Raji E. Menstrual psychosis. *Ir J Psychol Med*. 2022;39(1):103-105.
281	2019	Heinzman	Heinzman JT, Buckingham ET. Menstrual Psychosis and the Workup of New-Onset Psychosis in a Teenager. *JAACAP Connect*. 2019;6(2):36-39.

282	2019	Langer	Langer S, Frankel J, Derish N, Poulsen R, Coffey BJ. Brief Psychosis in the Premenstrual Phase in an Adolescent Girl: Adolescent Menstrual Psychosis? *J Child Adolesc Psychopharmacol*. 2019;29(5):392-394.
283	2019	Öztürk	Öztürk, K., Güven, A.S., Kyrymas, M. [Menstruation-related recurrent psychosis: a case report]. *Pediatric Practice and Research*. Published online 2019:191-194.
284	2019	Ward	Ward HB, Greenberg JA, Almeida M. Perimenstrual psychiatric hospitalization: case report and literature review. *Arch Womens Ment Health*. 2020;23(2):141-147.
285	2020	Al-Sibani	Al-Sibani N, Al-Maqbali M, Mahadevan S, Al-Huseini S, Al-Muzeni M, Al-Adawi S. Psychiatric, cognitive functioning and socio-cultural views of menstrual psychosis in Oman: an idiographic approach. *BMC Womens Health*. 2020;20(1):215.
286	2020	Al-Sibani	Al-Sibani N, Al-Maqbali M, Mahadevan S, Al-Huseini S, Al-Muzeni M, Al-Adawi S. Psychiatric, cognitive functioning and socio-cultural views of menstrual psychosis in Oman: an idiographic approach. *BMC Womens Health*. 2020;20(1):215.
287	2020	Al-Sibani	Al-Sibani N, Al-Maqbali M, Mahadevan S, Al-Huseini S, Al-Muzeni M, Al-Adawi S. Psychiatric, cognitive functioning and socio-cultural views of menstrual psychosis in Oman: an idiographic approach. *BMC Womens Health*. 2020;20(1):215.
288	2020	Al-Sibani	Al-Sibani N, Al-Maqbali M, Mahadevan S, Al-Huseini S, Al-Muzeni M, Al-Adawi S. Psychiatric, cognitive functioning and socio-cultural views of menstrual psychosis in Oman: an idiographic approach. *BMC Womens Health*. 2020;20(1):215.
289	2020	Colak	Colak S, Suyabatmaz G, Hocaoglu C. A little known topic 'Menstrual Psychosis': A case report and a short review literature. *JGON*. 2020;17(4):629-631.
290	2020	Pang	Pang T, Lui YS, Chee TT. Premenstrual Psychosis In A Patient With Polycystic Ovary Syndrome: A Case Report. *Research Square*. 2020.
291	2020	Ray	Ray R, Paul I. Menstrual psychosis: A not so forgotten reality. *Indian J Psychiatry*. 2020;62(5):585-587.
292	2020	Ray	Ray R, Paul I. Menstrual psychosis: A not so forgotten reality. *Indian J Psychiatry*. 2020;62(5):585-587.
293	2020	Ray	Ray R, Paul I. Menstrual psychosis: A not so forgotten reality. *Indian J Psychiatry*. 2020;62(5):585-587.
294	2020	Takahashi	Takahashi Y, Mikami K, Akama F, Onishi Y, Yamamoto K, Matsumoto H. Reconsideration of Periodic Psychosis of Adolescence. *Tokai J Exp Clin Med*. 2020;45(1):1-4.
295	2021	Alalmaei Asiri	Alalmaei Asiri WM. Menstrual psychosis – From myth to reality: A case report of periodic psychotic symptoms associated with the menstrual cycle. *S Afr J Psychiatr*. 2021;27:1650.
296	2021	Rawal	Rawal M, Folsom LJ. Cyclical Premenstrual Psychosis - Sometimes It Is Your Hormones. *J Endocr Soc*. 2021;5(Supplement_1):A779.
297	2022	O'Mahony	O'Mahony B. A case of pre-menstrual psychosis with catatonic symptoms. *Psychiatry Research Case Reports*. 2022;1(2):100065.
298	N/A	Braunscharm	Unpublished case
299	N/A	Chou	Unpublished case
300	N/A	Okano	Unpublished case
301-399	N/A	Brockington	Unpublished cases

400	1929	Danby	Danby A, Sykes K. Chronic mental disease associated with ovarian dysfunction. *The Lancet*. 1929;213:129-129.
401	1950	Corrandini	Corrandini, E., Sagripanti, P. [Menstrual psychosis and hyperostosis frontalis interna]. *Riv Sper Freniatr Med Leg Alien Ment Sep*. 1950;74(3):359-380.
402	1954	Vidal	Vidal, Guillermo. Seven cases of periodic amentia. *Acta Psiquiatrica y Psicologica de America Latina*. 1954;50(1):85-96.
403	1954	Vidal	Vidal, Guillermo. Seven cases of periodic amentia. *Acta Psiquiatrica y Psicologica de America Latina*. 1954;50(1):85-96.
404	1954	Vidal	Vidal, Guillermo. Seven cases of periodic amentia. *Acta Psiquiatrica y Psicologica de America Latina*. 1954;50(1):85-96.
405	1966	Matusova	Matusova, S.I., Isaev, D.N. [On cases of manic-depressive psychosis against a background of oligophrenia]. *Zh Nevropatol Psikhiatr Im S S Korsakova*. 1966;66(4):620-624.
406	1978	Yamada	Yamada, M., Mizuki, A., Kawazawa, S., Sasaki, T. Periodic psychosis in adolescence. *Bulletin of the Yamaguchi Medical School*. 1978;25(1-2):87-93.
407	1980	Zhou	Zhou, K. [Periodic psychoses and its treatment of promoting blood circulation and relieving stasis (author's transl)]. *Chinese journal of neurology and psychiatry*. 1980;13(2):114.
408	1991	Mizuki	Mizuki Y, Kajimura N, Miyoshi A, Ushijima I, et al. Neuroendocrinological studies on patients with periodic psychosis of adolescence before and after menarche. *Integrative Psychiatry*. 1991;7(3-4):241-247.
409	1996	Meerdinkveldboom	Meerdinkveldboom JW, Berkestijn H van. A female adolescent with a periodic psychosis. *Tijdschrift voor Psychiatrie*. 1996;38(7):558.
410	1998	Ambelas	Ambelas A, Kat H. Periodic menstruation-linked psychosis of adolescence. *International Journal of Psychiatry in Clinical Practice*. 1998;2(1):61-63.
411	2000	Goldberg	Goldberg D, Floyd A, Lee-Jones R, Lewis S. Intensive Community Management of an Adolescent with Psychosis. *Clin Child Psychol Psychiatry*. 2000;5(1):85-95.
412	2010	Goyal	Goyal N, Bhattacharya A, Goswami K, Sinha VK. Rapid cycling associated with menstrual periods in an adolescent: electrophysiological underpinnings for bipolarity. *J Neuropsychiatry Clin Neurosci*. 2010;22(4):451-ll.e22-451.e24.
413	2016	Helton	Helton, E., Page, M., Getz, G., Swanson, G., Smith, C., Nickell, P. Blood brain barrier integrity and premenstrual psychosis: A case example. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2016;28(3):e47.
414	2018	Hegde	Hegde, HV, Kumar V. A case report of menstrual catatonia causing delayed emergence from anaesthesia: a diagnostic dilemma. *JACCOA*. 2018;10(5):159-160.
415	2022	Adão	Adão C, Donas-Boto I, Velosa A, Trindade P, Caetano R. Menstrual psychosis diagnosis: Does it still hold? *European Psychiatry*. 2022;65(S1):S195-S195.
416	2023	Gilmore	Gilmore A, Cottrell TJ, Chen SE. Challenges in diagnosis, treatment and coordination of care of menstrual psychosis. *BMJ Case Rep*. 2023;16(4):e251555.
417	1980	Zhou	Zhou, K. [Periodic psychoses and its treatment of promoting blood circulation and relieving stasis (author's transl)]. *Chinese journal of neurology and psychiatry*. 1980;13(2):114.

8.3 Electronic health record search terms

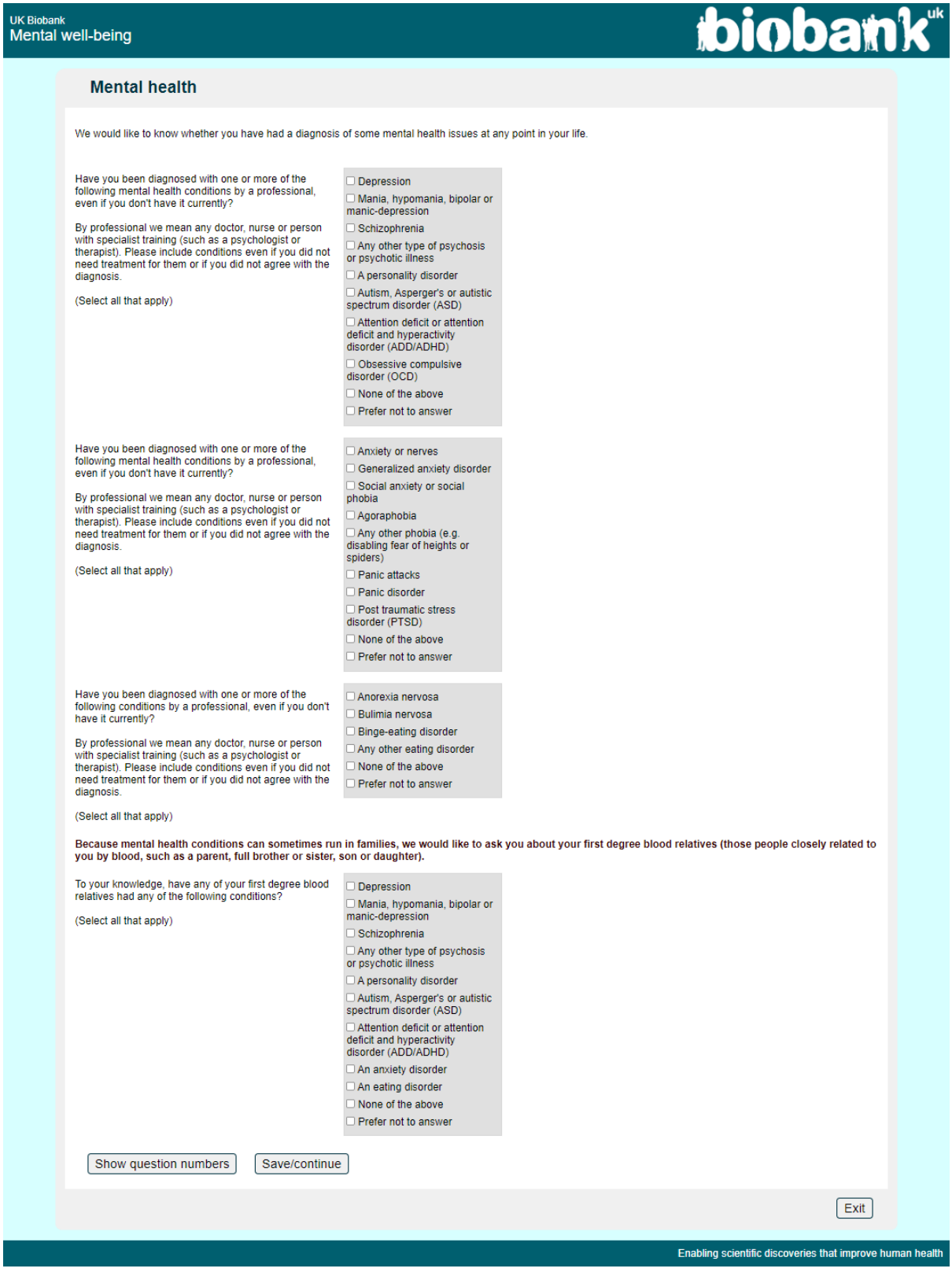
8.3.1 Free text search

Term 1	Term 2
catamenial	(psychosis OR psychotic OR mania OR manic OR bipolar OR schizophrenia OR schizoaffective)
menses	(psychosis OR psychotic OR mania OR manic OR bipolar OR schizophrenia OR schizoaffective)
menstrual	(psychosis OR psychotic OR mania OR manic OR bipolar OR schizophrenia OR schizoaffective)
menstrual	(episode* OR exacerbate* OR exacerbating* OR exacerbation* OR relapse* OR trigger*)
menstruation	(psychosis OR psychotic OR mania OR manic OR bipolar OR schizophrenia OR schizoaffective)
premenstrual	(psychosis OR psychotic OR mania OR manic OR bipolar OR schizophrenia OR schizoaffective)
premenstrual	(episode* OR exacerbate* OR exacerbating* OR exacerbation* OR relapse* OR trigger*)
pre-menstrual	(psychosis OR psychotic OR mania OR manic OR bipolar OR schizophrenia OR schizoaffective)
pre-menstrual	(episode* OR exacerbate* OR exacerbating* OR exacerbation* OR relapse* OR trigger*)

8.3.2 Diagnosis search

ICD-10 code	Term 2
F06* OR F1*.5 OR F2* OR F30* OR F31* OR F32.3* OR F33.3*	(episode OR link OR linked $X menstrual) OR (menstrual $X episode OR link OR linked)
F06* OR F1*.5 OR F2* OR F30* OR F31* OR F32.3* OR F33.3*	(menstrual AND cyclical)
F06* OR F1*.5 OR F2* OR F30* OR F31* OR F32.3* OR F33.3*	(menstrual phase OR perimenstrual phase OR peri-menstrual phase)
F06* OR F1*.5 OR F2* OR F30* OR F31* OR F32.3* OR F33.3*	(menstrual AND brief $ episode)
F06* OR F1*.5 OR F2* OR F30* OR F31* OR F32.3* OR F33.3*	(premenstrual phase OR pre-menstrual phase)
F06* OR F1*.5 OR F2* OR F30* OR F31* OR F32.3* OR F33.3*	(premenstrual AND (exacerbate OR exacerbating OR exacerbation OR worsen OR worsening OR relapse))
F06* OR F1*.5 OR F2* OR F30* OR F31* OR F32.3* OR F33.3*	(menstrual AND (exacerbate OR exacerbating OR exacerbation OR worsen OR worsening OR relapse))
F06* OR F1*.5 OR F2* OR F30* OR F31* OR F32.3* OR F33.3*	(pre-menstrual AND (exacerbate OR exacerbating OR exacerbation OR worsen OR worsening OR relapse))
F06* OR F1*.5 OR F2* OR F30* OR F31* OR F32.3* OR F33.3*	(menstrual AND brief episode)

8.4 UK Biobank self-report questions



UK Biobank
Mental well-being

biobank uk

Mental health

We would like to know whether you have had a diagnosis of some mental health issues at any point in your life.

Have you been diagnosed with one or more of the following mental health conditions by a professional, even if you don't have it currently?

By professional we mean any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include conditions even if you did not need treatment for them or if you did not agree with the diagnosis.

(Select all that apply)

- ☐ Depression
- ☐ Mania, hypomania, bipolar or manic-depression
- ☐ Schizophrenia
- ☐ Any other type of psychosis or psychotic illness
- ☐ A personality disorder
- ☐ Autism, Asperger's or autistic spectrum disorder (ASD)
- ☐ Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD)
- ☐ Obsessive compulsive disorder (OCD)
- ☐ None of the above
- ☐ Prefer not to answer

Have you been diagnosed with one or more of the following mental health conditions by a professional, even if you don't have it currently?

By professional we mean any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include conditions even if you did not need treatment for them or if you did not agree with the diagnosis.

(Select all that apply)

- ☐ Anxiety or nerves
- ☐ Generalized anxiety disorder
- ☐ Social anxiety or social phobia
- ☐ Agoraphobia
- ☐ Any other phobia (e.g. disabling fear of heights or spiders)
- ☐ Panic attacks
- ☐ Panic disorder
- ☐ Post traumatic stress disorder (PTSD)
- ☐ None of the above
- ☐ Prefer not to answer

Have you been diagnosed with one or more of the following conditions by a professional, even if you don't have it currently?

By professional we mean any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include conditions even if you did not need treatment for them or if you did not agree with the diagnosis.

(Select all that apply)

- ☐ Anorexia nervosa
- ☐ Bulimia nervosa
- ☐ Binge-eating disorder
- ☐ Any other eating disorder
- ☐ None of the above
- ☐ Prefer not to answer

Because mental health conditions can sometimes run in families, we would like to ask you about your first degree blood relatives (those people closely related to you by blood, such as a parent, full brother or sister, son or daughter).

To your knowledge, have any of your first degree blood relatives had any of the following conditions?

(Select all that apply)

- ☐ Depression
- ☐ Mania, hypomania, bipolar or manic-depression
- ☐ Schizophrenia
- ☐ Any other type of psychosis or psychotic illness
- ☐ A personality disorder
- ☐ Autism, Asperger's or autistic spectrum disorder (ASD)
- ☐ Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD)
- ☐ An anxiety disorder
- ☐ An eating disorder
- ☐ None of the above
- ☐ Prefer not to answer

Show question numbers | Save/continue

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Enabling scientific discoveries that improve human health

biobank uk **Thoughts *and feelings***

Diagnoses

A3 Have you been diagnosed with one or more of the following mental health problems by a professional, even if you don't have it currently? (tick all that apply):

By professional we mean: any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include disorders even if you did not need treatment for them or if you did not agree with the diagnosis.

- ☐ Depression
- ☐ Mania, hypomania, bipolar or manic-depression
- ☐ Anxiety, nerves or generalized anxiety disorder
- ☐ Social anxiety or social phobia
- ☐ Agoraphobia
- ☐ Any other phobia (eg disabling fear of heights or spiders)
- ☐ Panic attacks
- ☐ Obsessive compulsive disorder (OCD)
- ☐ None of the above
- ☐ Prefer not to answer

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PROGRESS:

Improving the health of future generations

biobank uk **Thoughts *and feelings***

Diagnoses

A4 Have you been diagnosed with one or more of the following mental health problems by a professional, even if you don't have it currently? (tick all that apply):

By professional we mean: any doctor, nurse or person with specialist training (such as a psychologist or therapist). Please include disorders even if you did not need treatment for them or if you did not agree with the diagnosis.

- ☐ Anorexia nervosa
- ☐ Bulimia nervosa
- ☐ Psychological over-eating or binge-eating
- ☐ Schizophrenia
- ☐ Any other type of psychosis or psychotic illness
- ☐ A personality disorder
- ☐ Autism, Asperger's or autistic spectrum disorder
- ☐ Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD)
- ☑ **None of the above**
- ☐ Prefer not to answer

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PROGRESS:

Improving the health of future generations

8.5 MAPS daily questionnaire

Question	Response	Source
I felt sad or depressed	Likert scale (1-7)	DRSP
I felt anxious	Likert scale (1-7)	DRSP
I had mood swings	Likert scale (1-7)	DRSP
I felt irritable or angry	Likert scale (1-7)	DRSP
I struggled to concentrate	Likert scale (1-7)	DRSP
I lacked energy	Likert scale (1-7)	DRSP
I had increased appetite or food cravings	Likert scale (1-7)	DRSP
I slept more than usual or napped during the day	Likert scale (1-7)	DRSP
I felt overwhelmed or unable to cope	Likert scale (1-7)	DRSP
I had breast tenderness or swelling	Likert scale (1-7)	DRSP
I had pain in my joints	Likert scale (1-7)	ICD-11
I had swelling of my legs/ankles/feet	Likert scale (1-7)	ICD-11
I was forgetful	Likert scale (1-7)	ICD-11
I felt elated (extremely happy)	Likert scale (1-7)	Chapter 2
I had lots of energy	Likert scale (1-7)	Chapter 2
I had a headache	Likert scale (1-7)	Chapter 2
I had difficulty falling asleep last night	Likert scale (1-7)	Chapter 2
I woke up frequently during the night	Likert scale (1-7)	Chapter 2
I heard things other people couldn’t hear like voices whispering or talking	Likert scale (1-7)	Chapter 2
I saw things that other people couldn't see	Likert scale (1-7)	Chapter 2
I felt that people were giving me a hard time for no reason	Likert scale (1-7)	Chapter 2
Did you experience menstrual bleeding or spotting today?	1. Yes 2. No	
Was today the start of your monthly menstrual period?	1. Yes. 2. No	