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Risk of miscarriage in women with psychiatric disorders

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Background

Some psychiatric disorders have been associated with increased risk of miscarriage. However, there is a lack of studies considering a broader spectrum of psychiatric disorders to clarify the role of common as opposed to independent mechanisms.

Aims

To examine the risk of miscarriage among women diagnosed with psychiatric conditions.

Method

We studied registered pregnancies in Norway between 2010 and 2016 ($n = 593\,009$). The birth registry captures pregnancies ending in gestational week 12 or later, and the patient and general practitioner databases were used to identify miscarriages and induced abortions before 12 gestational weeks. Odds ratios of miscarriage according to 12 psychiatric diagnoses were calculated by logistic regression.

Miscarriage risk was increased among women with bipolar disorders (adjusted odds ratio 1.35, 95% CI 1.26–1.44), personality disorders (adjusted odds ratio 1.32, 95% CI 1.12–1.55), attention-deficit hyperactivity disorder (adjusted odds ratio 1.27, 95% CI 1.21–1.33), conduct disorders (1.21, 95% CI 1.01, 1.46), anxiety disorders (adjusted odds ratio 1.25, 95% CI 1.23–1.28), depressive disorders (adjusted odds ratio 1.25, 95% CI 1.23–1.27), somatoform disorders (adjusted odds ratio 1.18, 95% CI 1.07–1.31) and eating disorders (adjusted odds ratio 1.14, 95% CI 1.08–1.22). The miscarriage risk was further increased among women with more than one psychiatric diagnosis. Our findings were robust to adjustment for other psychiatric diagnoses, chronic somatic disorders and substance use disorders. After mutual adjustment for co-occurring psychiatric disorders, we also observed a modest increased risk among women with schizophrenia spectrum disorders (adjusted odds ratio 1.22, 95% CI 1.03–1.44).

Conclusions

A wide range of psychiatric disorders were associated with increased risk of miscarriage. The heightened risk of miscarriage among women diagnosed with psychiatric disorders highlights the need for awareness and surveillance of this risk group in antenatal care.

Keywords

Miscarriage; anxiety disorders; depressive disorders; attention-deficit hyperactivity disorders; schizophrenia.

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Miscarriage risk is strongly associated with advanced maternal age and aneuploidy arising during fertilisation or development.[1,2] Despite decades of research, little is known about other factors that contribute to the risk of miscarriage. Stress and psychiatric disorders plausibly play a role, although evidence is limited. An increased risk of miscarriage has been reported among women with a history of eating disorders,[3] anxiety or depression.[4,5] The majority of studies of anxiety or depression have looked at these psychiatric disorders after a miscarriage, to better understand how experiencing miscarriages might affect a woman's mental health. They are, therefore, not looking at the relationship between pre-existing anxiety or depression in relation to the risk of miscarriage. A few studies also indicate that medications for bipolar disorders[6,7] or attention-deficit hyperactivity disorder (ADHD)[8] during pregnancy may increase the risk of miscarriage, although none of these studies examined the diagnosis themselves in detail.

Most of these existing studies are small and focused on specific outcomes. They also largely relied on retrospective recall of the psychiatric diagnosis after the end of pregnancy. Understanding whether miscarriage risk is increased for these particular psychiatric conditions is important because the findings have implications for awareness and surveillance of women at risk in antenatal care. It also highlights the need to understand the potential role of common (as opposed to independent) underlying biological mechanisms reflected in the risk of miscarriage.

The Norwegian health registries provide an opportunity to assess the relationship between psychiatric disorders and risk of miscarriage. Using prospective data on all pregnancies resulting in contact with the healthcare system during a 7-year period, we examined the risk of miscarriage across a broad range of psychiatric diagnoses.

Method

We identified all registered pregnancies in Norway with an estimated date of conception between 1 January 2010 and 31 December 2016, using three national health registries: the Medical Birth Registry of Norway, the Norwegian Patient Registry and the general practice database.[9] The patient registry comprises visits to medical specialists and hospitals, with diagnoses coded according to the ICD-10[10] . Visits to general practitioners are coded according to the International Classification of Primary Care, Version 2 (ICPC-2)[11] . The birth registry includes information on pregnancies ending after 12 gestational weeks (live births, stillbirths, late miscarriages and late induced abortions). The patient registry and the general practice database provides information on all women in contact with healthcare services during pregnancy, including contacts during the first trimester. We linked information from the three health registries (birth registry, specialist care and the general practice database), using unique personal identification numbers.

Pregnancy outcomes and identification of unique pregnancies

We identified live births, induced abortions and foetal deaths after 12 gestational weeks from the birth registry. A foetal death at 20

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gestational weeks or later, or with a birth weight of ≥500 g, was considered a stillbirth, and a foetal death before 20 gestational weeks, with a birth weight <500 g, was considered a miscarriage. This distinction of stillbirth is in accordance with the American National Stillbirth Society and the National Institutes of Health. We included the following ICD-10 codes to capture miscarriages in the patient registry: hydatidiform mole (O01); blighted ovum and non-hydatidiform mole (O02.0); missed abortion (O02.1); other specified abnormal products of conception (O02.8); abnormal product of conception, unspecified (O02.9); spontaneous abortion (O03) and threatened abortion (O02.0). Induced abortion was defined by the following ICD-10 codes in the patient registry: medical abortion (O04), other abortion (O05) and unspecified abortion (O06).

We have expanded our definition of miscarriage used in a previous study to include events reported in the general practitioner database.[2] Bleeding in pregnancy (ICPC-2 code W03) and spontaneous abortion (ICPC-2 code W82) were defined as first trimester miscarriages if they were not followed by a registration in the birth registry or the patient registry.

Pregnancies in the patient registry and general practitioner database are not registered with unique pregnancy identifiers, which could lead to inadvertent counting of the same pregnancy multiple times. We minimised this error by requiring a minimum of 6 weeks (42 days) between two successive records in the patient registry, and a minimum of 3 months (90 days) between two successive records in the general practitioner database. These cut-offs were chosen by inspecting the distribution of times between registrations in the two registers. We used a longer interval in the general practitioner database because women have more follow-up visits with their general practitioners after a miscarriage. We also required that a record of a miscarriage or induced abortion in the patient registry or general practitioner database be at least 6 weeks (patient registry) or 3 months (general practitioner database) after a registered delivery to the woman in the birth registry. Finally, we excluded any miscarriage or induced abortion that occurred within the gestational period of a registered pregnancy to the same woman in the birth registry.

In the case of multiple foetuses, the outcome was regarded as a live birth if all deliveries resulted in live births, as a miscarriage if there was at least one miscarriage but no stillbirth, and as a stillbirth if at least one of the deliveries resulted in a stillbirth but none resulted in a miscarriage. A multiple birth could result in both a miscarriage and a stillbirth if there was a discrepancy in the birth weight between the foetuses.

Psychiatric disorders

We identified diagnostic codes for 12 psychiatric disorder groups, using information available in the patient registry and general practice database. The 12 diagnostic groups were schizophrenia spectrum disorders, bipolar spectrum disorders, depressive disorders, anxiety disorders, somatoform disorders, eating disorders, intellectual disability, autism spectrum disorders, ADHD, conduct disorder, personality disorders and unspecified psychiatric disorders. The diagnostic codes used to classify the various conditions are shown in Supplementary Table 1 available at https://doi.org/10.1192/bjp.2020.259.

We required a minimum of two registrations of the administrative code(s) used to define the particular psychiatric diagnosis to classify women as diagnosed with the psychiatric disorder, to avoid coding errors. To ensure that woman had been diagnosed with the condition before pregnancy, we required that at least one registration should be before the estimated date of the last menstrual period, defined as the date of delivery minus the gestational age in days. For miscarriages and induced abortions identified in the patient registry and general practice database (in which gestational week was not available), we assigned a gestational age of 12 weeks to ensure that the condition would have been diagnosed before pregnancy, assuming that the pregnancy would have been registered in the birth registry if the gestational age was >12 weeks.

Covariates

We had information on maternal age at the time of conception, gravidity, year of conception, substance use disorders and diagnoses of somatic conditions. Diagnoses of substance use disorders and somatic diseases were obtained from the patient and general practitioner databases. We included autoimmune diseases (systemic lupus erythematosus, type 1 diabetes, celiac disease, multiple sclerosis, rheumatoid arthritis/ankylosing spondylitis, ulcerative colitis, psoriasis, Addison disease, Crohn's disease, haemolytic anaemia), endocrinological diseases (Cushing syndrome, hypothyroidism, hyperthyroidism, hyperaldosteronism, hyperparathyroidism), cardiometabolic diseases (atherosclerosis, hypertensive disorders, type 2 diabetes), allergic diseases (asthma, allergic rhinitis, atopic dermatitis), neurological diseases (epilepsy, migraine) and reproductive diseases (polycystic ovary syndrome and endometriosis). The various ICD-10 codes (specialist healthcare services) and ICPC-2 codes (primary healthcare services) used to capture these disorders are listed in Supplementary Table 2.

Statistical analysis

We used logistic regression to calculate odds ratios of miscarriage, according to psychiatric disorders. We attempted to estimate relative risks by using log-binomial regression; however, the model failed to converge for several of the psychiatric diagnoses. We therefore present results obtained with logistic regression for all disorders for consistency. We also estimated risk differences as an absolute measure of the difference in the risk of miscarriage, using linear regression. Because some women experienced more than one pregnancy during the time period, we used cluster variance estimation to calculate 95% confidence intervals. We have previously shown that miscarriage risk increases in a non-linear fashion with maternal age,[2] so we adjusted for age at the start of pregnancy by including age as both a linear and squared term. We adjusted for the competing risk of induced abortion by adding 20% of induced abortions to the comparison group in the analysis, together with all live and stillbirths. Our basis for this adjustment is described in detail in Supplementary Appendix 1, methods (SA1).

We conducted stratified analyses according to whether the woman had previously been pregnant, and whether the miscarriage was registered in the specialist healthcare services or only in primary healthcare services. We also conducted sensitivity analyses further adjusting for year of conception, restricting to psychiatric disorders registered in the specialist healthcare services, excluding hydatidiform mole from the definition of miscarriage, and further adjusting for underlying chronic somatic conditions. To examine the independent relationship of the various diagnoses with miscarriage risk, we included all 12 psychiatric diagnoses simultaneously in the model. As an indicator of psychiatric multimorbidity, we also examined the risk of miscarriage according to the total number of different psychiatric diagnoses a woman had been diagnosed with before pregnancy, categorised as none (reference), one, two and three or more diagnoses. This did not include additional registrations of administrative codes used to define the same diagnosis. All analyses were conducted with Stata version 15 for Windows (StataCorp).

Ethics of research

The study was approved by the Committee for Medical and Health Research Ethics of South/East Norway (ref 2014/404). The use of the

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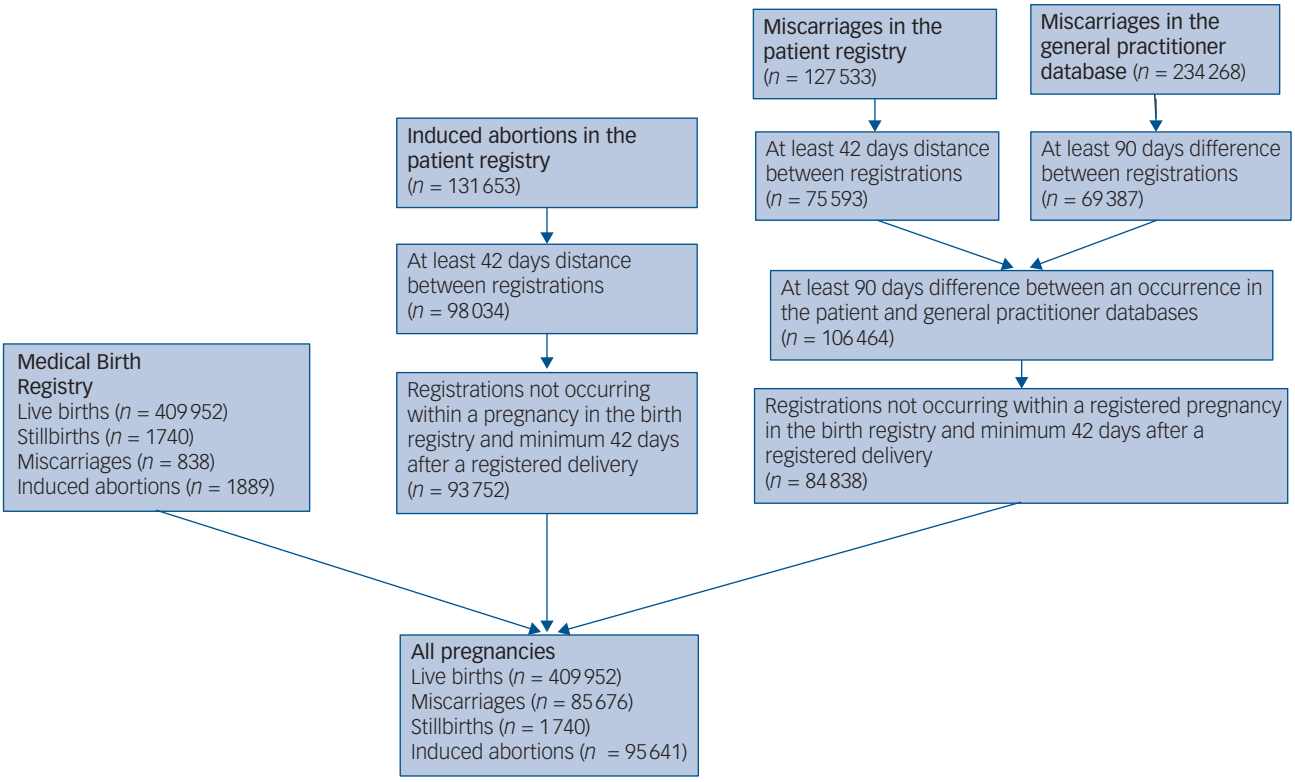

Fig. 1 Illustration of identification of unique pregnancies across health registries.

national health registries for health-related research does not require consent, according to Norwegian legislation.

Results

We identified a total of 593 009 pregnancies with last menstrual period between 1 January 2010 and 31 December 2016 (Fig. 1). Of these pregnancies, 409 952 (69.1%) ended in a live birth, 1740 (0.3%) ended in a stillbirth, 95 641 (16.1%) ended in an induced abortion and 85 676 (14.4%) ended in miscarriage. Miscarriage risk estimated as a proportion of miscarriages plus live and stillbirths was 17.2%, which was reduced to 16.6% after adjustment for the competing risk of induced abortions.

A total of 22% of women had a diagnosis of one or more psychiatric conditions, with depressive disorders (12.1%) and anxiety disorders (8.3%) being the most common by far (Table 1). The proportion of pregnant women diagnosed with other psychiatric disorders ranged from 0.02% for autism spectrum disorders to 1.5% for ADHD (Table 1).

Table 1 Distribution of psychiatric conditions in 593 009 pregnancies in Norway, 2010–2016

Psychiatric disorders	Frequency	Percentage
Schizophrenia spectrum disorders	631	0.11
Bipolar disorder	3554	0.6
Depressive disorders	71 551	12.1
Anxiety disorders	49 472	8.3
Somatoform disorders	1644	0.3
Eating disorders	5131	0.9
Intellectual disability	548	0.1
Autism spectrum disorders	142	0.02
Attention-deficit hyperactivity disorders	8796	1.5
Personality disorders	687	0.1
Conduct disorder	608	0.1
Unspecified mental disorder	6496	1.1
Any psychiatric disorder	131 151	22.1

Women with psychiatric disorders had an increased risk of miscarriage (Fig. 2). The absolute increase in miscarriage risk ranged from 2% to 5% on a baseline rate of nearly 17% (Supplementary Fig. 1). Odds ratios for specific diagnostic groups were 1.35 for bipolar disorders (95% CI 1.26–1.44), 1.32 for personality disorders (95% CI 1.12–1.55), 1.27 for ADHD (95% CI 1.21–1.33), 1.25 for anxiety disorders (95% CI 1.23–1.28), 1,21 for conduct disorders (95% CI 1.01–1.46), 1.25 for depressive disorders (95% CI 1.23–1.27), 1.18 for somatoform disorders (95% CI 1.07–1.31) and 1.14 for eating disorders (95% CI 1.08–1.22) (Fig. 2). Women's age was an important confounder, as shown by the stronger associations in unadjusted analysis (Supplementary Fig. 2). Further adjustment for year of conception, to account for the amount of follow-up information available, did not change the associations (Supplementary Fig. 3).

A total of 5% of all pregnancies were to women with more than one psychiatric diagnosis. The most common combination was anxiety and depression diagnoses (2% of all pregnancies). When we adjusted the risk of miscarriage for each diagnosis for the co-occurrence of other psychiatric diagnoses, the risks of miscarriage were slightly attenuated (Fig. 3). The only exception was schizophrenia spectrum disorders, where we observed a strengthening of the association, with an adjusted odds ratio of 1.22 (95% CI 1.03–1.44). We also looked at the risk of miscarriage according to the number of psychiatric diagnoses, as an indicator of psychiatric multimorbidity. The adjusted odds ratio was 1.27 (95% CI 1.25–1.30) for miscarriage and one psychiatric diagnosis; 1.45 (95% CI 1.40–1.51) for miscarriage and two psychiatric diagnoses, and 1.51 (95% CI 1.31–1.73) for miscarriage and three or more diagnoses.

A past miscarriage might contribute to psychiatric conditions, so we conducted a sensitivity analysis restricting to first pregnancies

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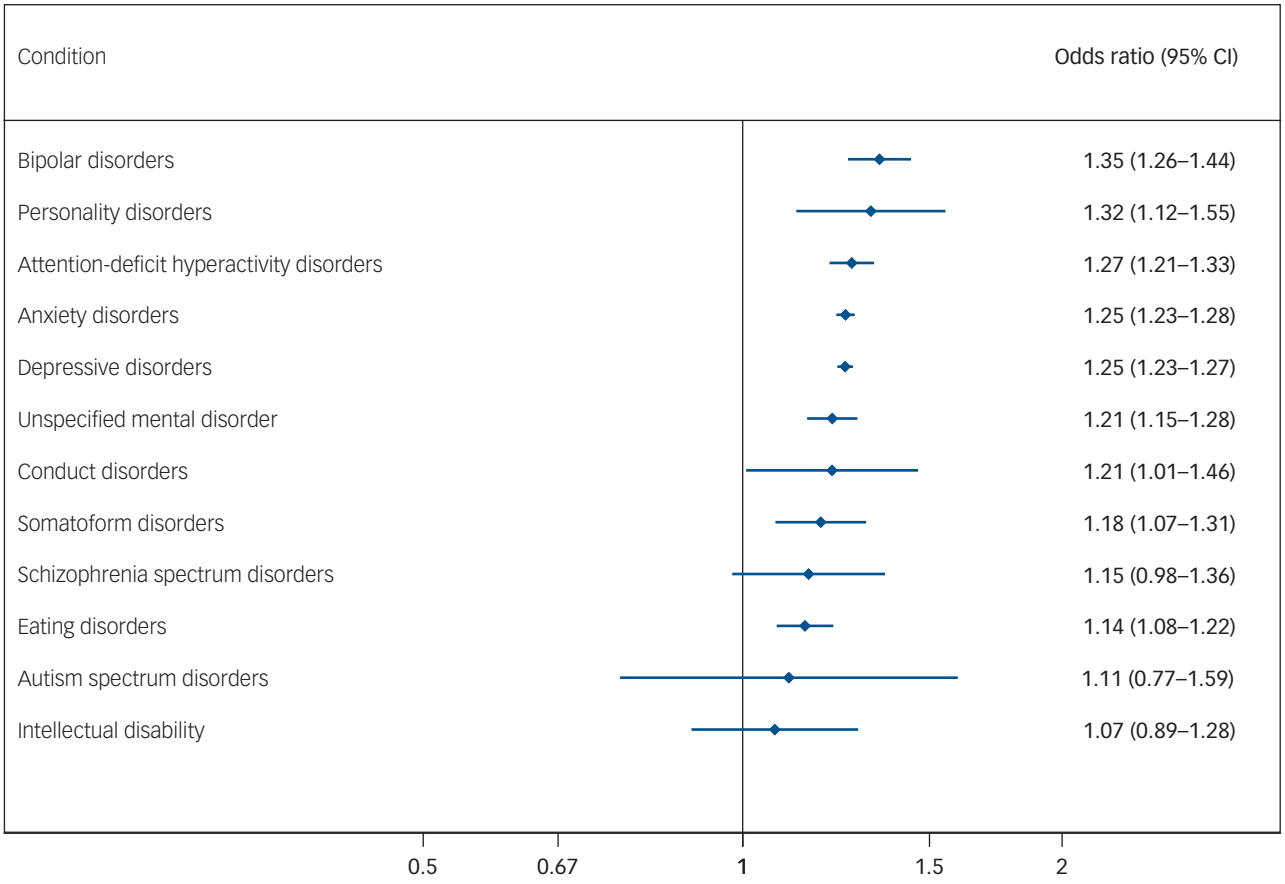

Fig. 2 Odds ratios for miscarriage, adjusted by pre-existing psychiatric disorders. Adjusted for age at the start of pregnancy as a linear and squared term.

(Supplementary Fig. 4). The main associations persisted. Excluding hydatidiform mole from the definition of miscarriage did not change results.

About 25% of miscarriages were identified in the general practitioner database, with no subsequent record in the patient registry or the birth registry. When we analysed the general practitioner and specialist healthcare sources of data separately, results were similar overall, although risks were more consistently elevated among women whose miscarriage was referred to specialist healthcare services (Supplementary Fig. 5). Associations were slightly stronger when restricting the evaluation to psychiatric disorders diagnosed in specialist care services (Supplementary Fig. 6).

We also conducted an evaluation of the role of somatic chronic conditions. The proportion of women with the different chronic somatic conditions is shown in Supplementary Table 3. Further adjustment for substance use disorders and all somatic conditions did not explain the increased risk of miscarriage seen among women with psychiatric disorders in the main analysis (Supplementary Fig. 7).

Discussion

In this large registry-based study, women with a broad range of psychiatric disorders had an increased risk of miscarriage. Risks were most prominently elevated with bipolar disorders, personality disorders, conduct disorders, ADHD, anxiety disorders, depressive disorders and somatoform disorders. We also observed weak evidence for an increased risk of miscarriage among women with schizophrenia, which was strengthened after mutual adjustment for co-occurring psychiatric disorders. The risk of miscarriage increased with multiple psychiatric diagnoses.

Our results confirm specific associations with risk of miscarriage reported in previous studies of women with eating disorders,[3] bipolar disorder[6,7,12] and anxiety or depression.[4,5] A systematic review found evidence for increased miscarriage risk specifically among women with anorexia nervosa,[3] and a few small-scale studies support an increased risk with anxiety or depression.[4,5] Some previous studies obtained information on pre-existing psychiatric disorders retrospectively, after the end of pregnancy, which enables the possibility of recall bias following a miscarriage. Women with schizophrenia also have an increased risk of certain pregnancy complications.[13,14] The modest increased risk of miscarriage among women with schizophrenia spectrum disorders identified in this study is novel and should be further explored.

It is well documented that women who experience miscarriage (especially recurrent miscarriage) have an increased risk of psychiatric disorders.[15,16] We therefore conducted a sensitivity analysis restricted to women who were pregnant for the first time, to address the possibility of reverse causation. The results were overall very similar to our main findings including all pregnancies. Although it is plausible that miscarriage can increase the risk of psychiatric illness, this sensitivity analysis shows that such an effect does not contribute to the associations we observe.

A direct effect of psychiatric illness on miscarriage risk is plausible. One potential biological mechanisms is the link between peptides and proteins synthesised in the brain and placental

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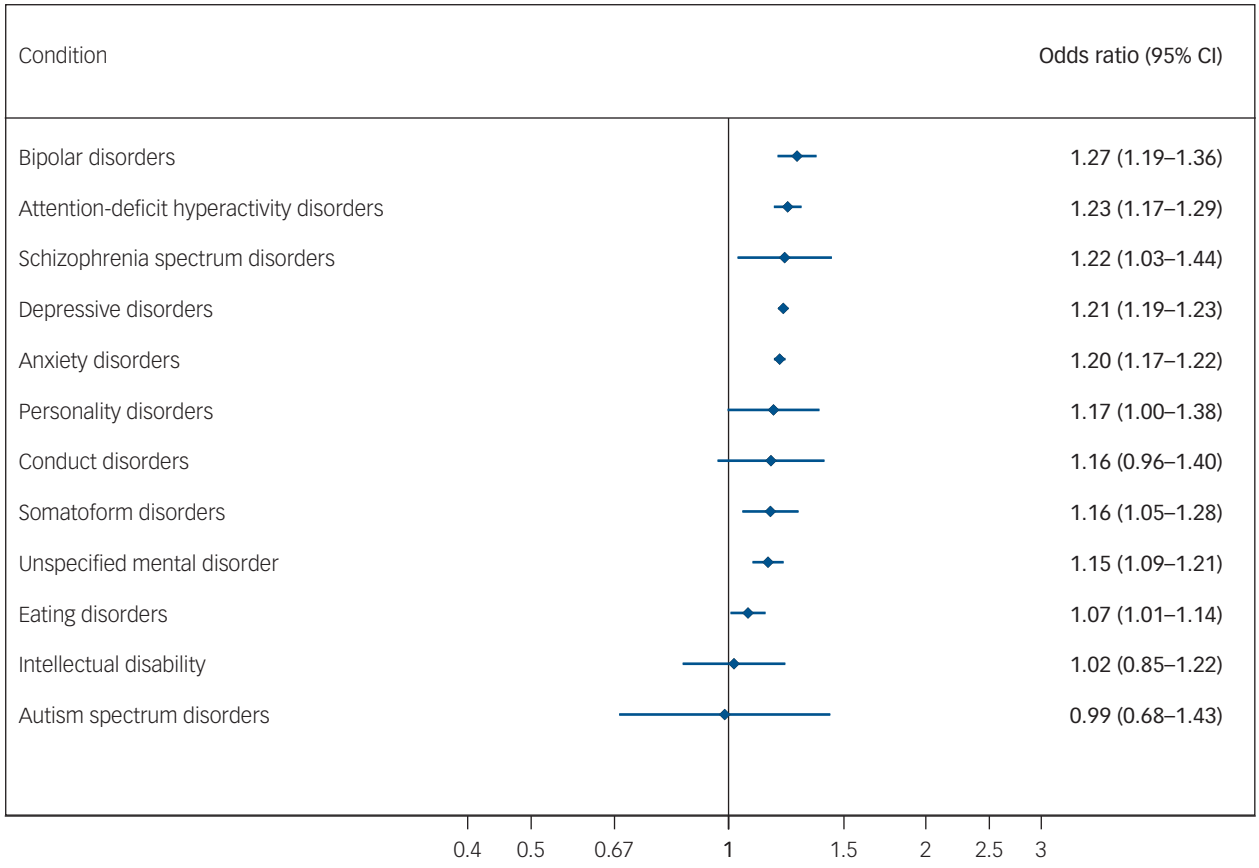

Fig. 3 Odds ratios for miscarriage, adjusted by pre-existing psychiatric disorders after mutual adjustment for other comorbid psychiatric disorders. Adjusted for age at the start of pregnancy as a linear and squared term.

development.[17] It has been hypothesized that women with psychiatric conditions such as depression, bipolar disorder and schizophrenia experience an increased risk of adverse obstetric outcomes through changes in these neurotrophic factors in the brain.[18,19] Another possibility is an effect of stress hormones, which can influence both placental development and the intrauterine environment, potentially increasing the risk of miscarriage.[5] These biological mechanisms may be shared across diverse psychiatric disorders. More specific mechanisms may be at work in conditions such as anorexia nervosa, in which nutritional deficiency may impair the woman's ability to sustain a pregnancy.[20] Prenatal depression has also been associated with placental barrier dysfunction.[5]

There can also be other direct or indirect explanations for the relationship between psychiatric disorders and risk of miscarriage. This can include both socioeconomic pathways and lifestyle factors. The risk of psychiatric disorders is strongly related to socioeconomic factors,[21,22] but the extent to which such factors might influence miscarriage risk is not well established. We used the E-value[23] to estimate that an unmeasured confounder would have to be associated with a 1.7-fold increased risk of both miscarriage and bipolar disorders (the strongest association in our analysis) to completely explain the relationship. Lifestyle characteristics that are strongly linked to psychiatric disorders (for example, smoking and higher body mass index)[24,25] may also contribute to explain an increased risk of miscarriage. Differences in lifestyle factors between women with and without psychiatric disorders could therefore be one explanatory pathway for an increased risk of miscarriage.

Our prospective data on diagnosis of both miscarriage and psychiatric conditions provide a strong basis for assessing associations free of self-reporting bias. Coverage across the whole population of Norway provides power and protects against selection bias that might arise within self-selected study populations.

Perhaps the most important limitation of our analysis is the lack of data on medications used for psychiatric conditions. We did not have this information available because of the strict regulations for linkage with the prescription registry. An increased risk of miscarriage has been reported with use of lithium for bipolar disorders,[6,7] various antidepressants and antianxiety medications,[26,27] and medications for ADHD.[8,28] However, if psychiatric illness has a causal effect on risk of miscarriage, it is also possible that treatment reduces the risk of miscarriage. A better understanding of underlying mechanisms would allow clinicians to properly weigh the potential risks of treatment against the risks of untreated disease.

We are likely to have underestimated the proportion of women with a psychiatric condition before pregnancy, as our databases capture diagnoses only among women who seek care from the healthcare system.[29,30] If this is the case, our estimates of miscarriage risk may be biased toward the null. Furthermore, we did not have information available on the age of diagnosis of the psychiatric disorder, and could therefore not account for the potential chronicity of the condition.

In conclusion, a wide range of psychiatric diagnoses were associated with increased risk of miscarriage. Although these associations are biologically plausible, we cannot assess the extent to which treatment for the illness might influence the observed risk. Nevertheless, the findings highlight the importance of identifying

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and adequately treating psychiatric disorders among women of reproductive age.

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Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1192/bjp.2020.259

Data availability

Data from the national health registries are available upon application though an online proposal system. Information regarding access can be found on the Directorate of e-Health website (https://helsedata.no/no/om-helsedata/).

Author contributions

M.C.M., A.J.W., N.-H.M., K.-A.W. and S.E.H. contributed to the design of the study. M.C.M., A.H., N.-H.M., K.-A.W., A.J.W. and S.E.H. contributed to the organisation and conduct of the study. S.E.H. was responsible for acquisition of data. M.C.M. analysed the data and drafted the initial version of the manuscript. All authors contributed to the interpretation of the data. All authors have read and approved the final version of the manuscript. M.C.M. will serve as guarantor for the contents of the paper.

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Declaration of interest

None.

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