Human Reproduction, Vol.35, No.4, pp. 958–967, 2020
Advance Access Publication on March 29, 2020 doi:10.1093/humrep/deaa016

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Postpartum psychiatric disorders and subsequent live birth: a population-based cohort study in Denmark

X. Liu[1,*], O. Plana-Ripoll[1], K.G. Ingstrup[1], E. Agerbo[1,2,3], R. Skjærven[4,5], and T. Munk-Olsen[1]

[1]The National Centre for Register-based Research, Aarhus University, Aarhus, Denmark [2]CIRRAU-Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark [3]Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark [4]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway [5]Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway

*Correspondence address. The National Centre for Register-based Research, Aarhus University, Fuglesangs Allé 26, 8210 Aarhus V, Denmark. Tel: +45 8716 6268; E-mail: lxq@econ.au.dk

Submitted on July 22, 2019; resubmitted on January 8, 2020; editorial decision on January 22, 2020

STUDY QUESTION: Are women with a history of first-onset postpartum psychiatric disorders after their first liveborn delivery less likely to have a subsequent live birth?

SUMMARY ANSWER: Women with incident postpartum psychiatric disorders are less likely to go on to have further children.

WHAT IS KNOWN ALREADY: Women are particularly vulnerable to psychiatric disorders in the postpartum period. The potential effects of postpartum psychiatric disorders on the mother's future chances of live birth are so far under-researched.

STUDY DESIGN, SIZE, DURATION: A population-based cohort study consisted of 414 571 women who had their first live birth during 1997–2015. We followed the women for a maximum of 19.5 years from the date of the first liveborn delivery until the next conception leading to a live birth, emigration, death, their 45th birthday or 30 June 2016, whichever occurred first.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Postpartum psychiatric disorders were defined as filling a prescription for psychotropic medications or hospital contact for psychiatric disorders for the first time within 6 months postpartum. The outcome of interest was time to the next conception leading to live birth after the first liveborn delivery. Records on the death of a child were obtained through the Danish Register of Causes of Death. Cox regression was used to estimate the hazard ratios (HRs), stratified by the survival status of the first child.

MAIN RESULTS AND THE ROLE OF CHANCE: Altogether, 4327 (1.0%) women experienced postpartum psychiatric disorders after their first liveborn delivery. The probability of having a subsequent live birth was 69.1% (95% CI: 67.4–70.7%) among women with, and 82.3% (95% CI: 82.1–82.4%) among those without, postpartum psychiatric disorders. Women with postpartum psychiatric disorders had a 33% reduction in the rate of having second live birth (HR = 0.67, 95% CI: 0.64–0.69), compared to women without postpartum psychiatric disorders. The association disappeared if the first child died (HR = 1.01, 95% CI: 0.85–1.20). If postpartum psychiatric disorders required hospitalisations, this was associated with a more pronounced reduction in live birth rate, irrespective of the survival status of the first child (HR = 0.54, 95% CI: 0.47–0.61 if the first child survived, and HR = 0.49, 95% CI: 0.23–1.04 if the first child died).

LIMITATIONS, REASONS FOR CAUTION: The use of population-based registers allows for the inclusion of a representative cohort with almost complete follow-up. The large sample size enables us to perform detailed analyses, accounting for the survival status of the child. However, we did not have accurate information on stillbirths and miscarriages, and only pregnancies that led to live birth were included.

WIDE IMPLICATIONS OF THE FINDINGS: Our study is the first study to investigate subsequent live birth after postpartum psychiatric disorders in a large representative population. The current study indicates that postpartum psychiatric disorders have a significant impact on subsequent live birth, as women experiencing these disorders have a decreased likelihood of having more children. However, the variations in subsequent live birth rate are influenced by both the severity of the disorders and the survival status of the first-born child, indicating that both personal choices and decreased fertility may have a role in the reduced subsequent live birth rate among women with postpartum psychiatric disorders.

STUDY FUNDING/COMPETING INTEREST(S): This work was supported by the Danish Council for Independent Research (DFF-5053-00156B), the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No. 837180, AUFF NOVA (AUFF-E 2016-9-25), iPSYCH, the Lundbeck Foundation Initiative for Integrative Psychiatric Research (R155-2014-1724), Niels Bohr Professorship Grant from the Danish National Research Foundation and the Stanley Medical Research Institute, the National Institute of Mental Health (NIMH) (R01MH104468) and Fabrikant Vilhelm Pedersen og Hustrus Legat. The authors do not declare any conflicts of interest.

TRIAL REGISTRATION NUMBER: N/A.

Key words: live birth / cohort study / postpartum / psychiatric disorders / register

Introduction

Moderate to severe psychiatric disorders are common in the postpartum period (Munk-Olsen *et al*., 2006). Postpartum psychiatric disorders include both relatively common episodes such as depression and anxiety and the rare but more severe psychosis, e.g. mania, mixed episodes and schizophrenia (Meltzer-Brody *et al*., 2018). Overall, 3% of women develop incident psychiatric disorders during the first 3 months after childbirth, in contrast to less than 1% during pregnancy (Munk-Olsen *et al*., 2016). The focus of research regarding the impacts of postpartum psychiatric disorders has largely centred on the physical and mental well-being of the mother and child (Field, 2010), whereas the potential effects on the mother's future reproduction are so far under-researched.

There is some evidence that postpartum psychiatric disorders may be implicated in the reduction of future reproduction possibly through the impact on personal choices, social circumstances and fertility (Howard *et al*., 2002; Symon *et al*., 2002; Dolman *et al*., 2016; Shorey *et al*., 2018). It is suggested that women with a negative childbirth experience may decide to delay or not to have a subsequent child (Shorey *et al*., 2018). Women with postpartum psychiatric disorders may perceive pregnancy and childbirth as highly stressful and may also avoid subsequent pregnancies due to fears of having another postpartum episode (Dolman *et al*., 2016). Moreover, some women may continue to have symptoms such as depression beyond the first year postpartum (Goodman, 2004), and this may make them directly susceptible to subfertility (Howard *et al*., 2002).

There is a paucity of studies examining the association between postpartum psychiatric disorders and subsequent reproduction. Only a single study has been published (Myers *et al*., 2016), in which a reduced subsequent live birth was reported among women with postpartum depression. However, postpartum depression does not represent all psychiatric disorders observed postpartum (Munk-Olsen *et al*., 2006). Furthermore, this study was based on a selected population, a relatively small sample size and reliance on self-reported retrospectively collected data, which is vulnerable to recall bias.

The present study aimed to investigate subsequent live birth as a function of incident psychiatric disorders with an onset during the postpartum period, using longitudinal data in Denmark across several decades. We considered the postpartum period to be 0 to 6 months after live birth since our previous work has indicated increased vulnerability for psychiatric episodes up to 6 months after live birth (Munk-Olsen *et al*., 2006). Increased reproduction has been observed in women who have lost a child (Skjærven *et al*., 1988; Skjærven and Melve, 2007; Plana-Ripoll *et al*., 2018; Pirnat *et al*., 2019), and we further aimed to explore whether a possible association between incident postpartum psychiatric disorders and subsequent live birth was modified by the survival status of the first child. More specifically, we hypothesised that women with postpartum psychiatric disorders have a decreased subsequent live birth rate and that the reduced live birth rate would be mitigated if the first child died.

Materials and methods

Study population

We conducted a population-based cohort study utilising data from nationwide registers in Denmark. All residents in Denmark are assigned a unique Civil Registration number (CPR number) recorded in the Danish Civil Registration System (Pedersen, 2011), which was introduced in 1968 and holds information on the date of birth, emigration, death and identity of parents. This unique CPR number allows for cross-linkage of all national registers at the individual level. We first identified women who had their first live birth (births) during 1997–2015 ($N = 515\,073$) from the Danish Medical Birth Registry (Bliddal *et al*., 2018), which contains high quality and valid information on the date of birth, parity, gestational age and birthweight. Pregnancies of women aged less than 15 years are rare and highly selected, and the age of 45+ years would have precluded most of the women from having another child (Plana-Ripoll *et al*., 2018). We, therefore, excluded women if they were aged <15 or ≥ 45 years at the time of first live birth ($n = 315$) and women who emigrated before the index delivery ($n = 39$). To capture women who developed postpartum episodes as the first manifestation of psychiatric disorders, we excluded women who, before delivery, had hospital contact for psychiatric disorders (primary or secondary diagnosis, the International Classification of Diseases, 8th Revision (ICD-8) codes 290–315; and 10th Revision (ICD-10) codes F00–F99) or had redeemed prescriptions for psychotropic medications (the International Anatomical Therapeutic Chemical (ATC) classification codes N05 and N06) ($n = 100\,148$). Information on hospital contacts for psychiatric disorders was derived from the Danish Psychiatric Central Research Register (Mors *et al*., 2011), which contains information on inpatient contacts at psychiatric hospitals and wards during 1969–1994 and outpatient contacts since 1995. The ICD-8 codes were used until 1993, and ICD-10 codes were used from 1994 and onwards. Information on psychotropic medication prescription was extracted from the Danish National Prescription Registry (Pottegard *et al*., 2017). The register contains individual-level data on prescriptions dispensed at community pharmacies in Denmark since 1995. The data recorded include details of the dispensing date, drug name and ATC code. To ensure the exclusion of women who redeemed psychotropic prescriptions before delivery among those

who gave birth in earlier years, we introduced a washout period of a minimum of 2 years, from the start of 1995 to the end of 1996.

Definition of incident postpartum psychiatric disorders

Postpartum psychiatric disorders were defined as within 6 months after the liveborn delivery filling a prescription for psychotropic medications (ATC codes N05 and N06) or in- or out-patient treatment for psychiatric disorders (primary diagnosis) regardless of recorded subsequent treatment, excluding mental retardation and substance use disorders (F00–F99 excluding F10–F19 and F70–F79 in ICD-10 codes) (World Health Organization, 1993).

Subsequent live birth(s)

Information on subsequent live birth was retrieved from the Danish Medical Birth Registry. The estimated date of conception was calculated by subtracting gestational age from the date of birth. Gestational age was primarily based on the first or second trimester ultrasound scan during the study period (Jorgensen, 1999; Bliddal *et al*., 2018). When there were no ultrasound examinations available, the first day of the mother's last menstrual period was used to indicate the start of pregnancy (World Health Organization, 2004). Approximately 2.4% of the gestational age data in the second deliveries was missing; in these cases, the median pregnancy durations were used, i.e. 280 days for singletons and 263 days for twins.

Statistical analysis

All analyses were performed using Stata, version 15.0 (StataCorp, College Station, TX, USA). We followed the women from the date of first liveborn delivery until the next conception of live birth, emigration, death, 30 June 2016 or their 45th birthday, whichever came first. The outcome of interest was time to the next conception leading to a live birth after the first liveborn delivery. We first looked at the interpregnancy interval in women with and without postpartum psychiatric disorders among those who had subsequent live birth. We constructed Kaplan–Meier curves to illustrate the probability of having subsequent live birth within 5 years after the first live birth. Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) of having subsequent live birth among women with postpartum psychiatric disorders, in comparison to women with no postpartum psychiatric disorders. Proportionality was verified by visually inspecting 'log–log' plots. In those instances where hazards are not proportional over time, the Cox proportional hazards model estimates can be interpreted as an average HR over the entire follow-up period (Xu and O'Quigley, 2000). In the present study, if the HRs are lower than 1, the rate of having subsequent live birth is lower among women with postpartum psychiatric disorders than women without postpartum psychiatric disorders, and vice versa. We stratified all the analyses on the survival status of the first child, as loss of a child has been linked to an increased likelihood of subsequent childbirth (Plana-Ripoll *et al*., 2018). We evaluated the significance of effect modification by the survival status of the first child on the multiplicative scale by including an interaction term between postpartum psychiatric disorders and the survival status of the first child in the models. Records on the death of the child were obtained through the Danish Register of Causes of Death (Helweg-Larsen, 2011), which contains information on the date of death and causes of death coded in ICD-10 codes during the study period. The death of the first child was treated as a time-dependent variable. All the women were included in the group whose first child survived until they lost one child from her first live birth; from then, they would be included in the group of women whose first child died.

We selected a priori covariates to adjust for based on causal diagrams using directed acyclic graphs: maternal age at first live birth (<25, 25–34 or ≥35 years), cohabitant status at first live birth (married or cohabiting or single, divorced or widowed), highest educational attainment at first live birth (elementary school or above elementary school), fertility treatment before the first live birth (yes or no), smoking during pregnancy (yes or no), preeclampsia/eclampsia (ICD-10 codes O14 and O15; yes or no), diabetes mellitus during pregnancy (ICD-10 codes O24; yes, or no), caesarean section (ICD-10 codes O82; yes, or no), postpartum haemorrhage (ICD-10 codes O72; yes, or no), preterm birth of the first child (gestational age < 37 weeks; yes or no), birthweight of the first child (<2500 g, 2500–3999 g or ≥4000 g), major congenital malformations of the first child (ICD-10 codes Q00–Q99, excluding minor malformations according to the EUROCAT Guide 1.4 (EUROCAT); yes or no), number of first live birth (singleton or multiple births), family history of psychiatric disorders at first live birth (yes or no) and calendar year of birth (1997–2000, 2001–2005, 2006–2010 or 2011–2015). We defined fertility treatment as redeemed prescriptions for fertility drugs for induced ovulation or intrauterine insemination (follicle-stimulating hormone, clomiphene citrate, human chorionic gonadotrophin and gonadotropin-releasing hormone) before the first live birth. Information on fertility drugs (ATC codes G03GA01–09, G03GA30, G03GB02, G03DA04, H01CC01–02 and L02AE01) was retrieved from the Danish National Prescription Registry. Cohabitant status and education level were obtained from Statistics Denmark's registers on socioeconomic status (Petersson *et al*., 2011). Information on preeclampsia, gestational diabetes, postpartum haemorrhage and malformation was retrieved from the Danish National Patient Registry (Schmidt *et al*., 2015). The remaining covariates were defined by using national registers mentioned above. About 11.1% of the values were missing for any of the covariates, mainly among women aged less than 25 years and related to the calendar year at birth. We applied 20 imputations using the Markov Chain Monte Carlo technique for imputing missing values (Royston and White, 2011).

To study the possible influence of time of onset of the postpartum psychiatric disorders, in the second set of analyses, we categorised the timing of onset by the first occurrence of date of hospital contact for psychiatric disorders or filling a prescription of psychotropic medications into 0–90 and 91–183 days after the delivery. To explore the impact of severity of postpartum psychiatric disorders on subsequent live birth, we further subdivided postpartum psychiatric disorders into three hierarchical groups according to the treatment settings: (i) inpatient treatment, (ii) outpatient treatment and (iii) pharmaceutical treatment with psychotropic medications. We further categorised pharmaceutical treatment into four mutually exclusive groups in a hierarchical manner: typical and atypical antipsychotics (ATC code N05A excluding N05AN01) or mood stabilisers (ATC codes N03AF01, N03AF02, N03AG01, N03AX09, N03AX11, N03AX12 and N05AN01), anxiolytics (ATC codes N03AE01, N05BA, N05BE01 and N05CF), antidepressants (ATC code N06A) and other psychotropic medication (ATC code N05 and N06 excluding

ATC codes above). Furthermore, in a subgroup of women with hospital diagnosis of psychiatric disorders during the postpartum period, we also examined the rate of subsequent live birth across five different hierarchical diagnostic categories: schizophrenia or related disorders (ICD-10 codes F20–F29), bipolar affective disorders (ICD-10 codes F30–F31), single and recurrent depressive disorders (ICD-10 codes F32–F33), neurotic stress-related and somatoform disorders (ICD-10 codes F40–F48) and other diagnoses (remaining diagnoses).

Additional analyses

To test the robustness of our results, we performed four additional analyses. First, women who have singleton or multiple births may have different subsequent live birth rate, we, therefore, repeated our analyses in women who gave birth to a liveborn singleton at the first live birth ($n = 405\,081$). Second, to further account for that women at an advanced age may have different reproductive behaviour or preference, we restricted our analyses to women who gave their first live birth before age 35 years. Third, to explore whether the associations were affected by the timing of our applied definition of postpartum psychiatric disorders, we redefined this to 0–12 months after the first live birth. Fourth, to verify if our findings still hold in further deliveries, we investigated whether one or more postpartum psychiatric disorders influenced subsequent live birth. Specifically, we calculated the HRs for the progressing from having Child 2 to Child 3 as a function of postpartum psychiatric disorders following the first and second liveborn delivery: no postpartum psychiatric disorders or with postpartum psychiatric disorders following the first live birth only, following the second live birth only or following both liveborn deliveries.

Ethical approval

The study was approved by the Danish Data Protection Agency. By Danish law, no informed consent is required for a register-based study relied exclusively on de-identified data.

Results

Of 414 571 women in the study cohort, 4327 (1.0%) experienced postpartum psychiatric disorders within 6 months after the first live birth. Table I shows the characteristics of women with and without postpartum psychiatric disorders following the first live birth. Compared to women with no postpartum psychiatric disorders, women with postpartum psychiatric disorders tended to be younger, single at the time of live birth, less likely to have continued education beyond elementary school and more likely to receive fertility treatment, to smoke during pregnancy, to have a caesarean section, to have a preterm delivery, to have a child with low birthweight or major congenital malformations and to have family psychiatric history. Among 338 754 women who were married or cohabiting at the time of delivery, 6.4% of women with and 2.8% without postpartum psychiatric disorders became single, divorced or widowed 1 year after.

The women were followed a maximum of 19.5 years and contributed 1.5×10^6 person-years at risk. The median follow-up time for women with and without postpartum psychiatric disorders was 3.2 years (interquartile range: 1.8–6.9 years) and 2.3 years (interquartile range: 1.5–4.2 years), respectively. During follow-up, 2571 women with and 294 736 women without postpartum psychiatric disorders had a second live birth. Among those who had second live birth, the median time to next conception was 2.3 years (interquartile range: 1.5–3.7 years) for women with postpartum psychiatric disorders, which was longer than 2.0 years (interquartile range: 1.4–3.0 years) among women without postpartum psychiatric disorders. The probability of having a subsequent live birth was 69.1% (95% CI: 67.4–70.7%) among those with and 82.3% (95% CI: 82.1–82.4%) among those without postpartum psychiatric disorders.

Overall, 2075 women lost their first child during the follow-up. Among these women, 1525 (73.5%) lost their child within 1 month after delivery, 330 (15.9%) from 1 month to 1 year and 220 (10.6%) after 1 year, and the probability of having subsequent live birth was 86.0% (95% CI: 81.0–90.2%), 89.1% (95% CI: 84.3–92.9%) and 90.6% (95% CI: 85.3–94.6%) among these women, respectively. The main causes of death were conditions originating in the perinatal period (45.9%) and congenital malformations (20.2%). The corresponding probability of having subsequent live birth among women who lost their first child due to these two main causes of death was 88.0 (95% CI: 80.0–93.9%) and 90.0 (95% CI: 86.5–92.4%). The Kaplan–Meier curve (Fig. 1) illustrates the probability of having subsequent live birth within 5 years after the first live birth by postpartum psychiatric disorders and the survival of the first child.

After adjustment for all the covariates, women with postpartum psychiatric disorders had a 33% reduction in the rate of having second live birth (HR = 0.67, 95% CI: 0.64–0.69), compared to women with no postpartum psychiatric disorders. The association was modified by the survival status of the first child (HR = 0.65, 95% CI: 0.63–0.68 if the first child survived; HR = 1.01, 95% CI: 0.85–1.20 if the first child died). The death of the first child was associated with an increased rate of having second live birth: the HR was 3.87 (95% CI: 3.20–4.68) and 2.81 (95% CI: 2.67–2.97) for women with and without postpartum psychiatric disorders, respectively. The interaction of postpartum psychiatric disorders and the survival status of the first child was statistically significant ($P < 0.001$).

When exploring the impact of severity of disorders, we found that the reduced live birth rate was more pronounced among women who were admitted for psychiatric disorders, a proxy for most severe episodes, in the postpartum period in comparison to women with no postpartum psychiatric disorders, with a 47% reduction in the rate (HR = 0.53, 95% CI: 0.46–0.61); the HR was 0.54 (95% CI: 0.47–0.61) if the first child survived and 0.49 (95% CI: 0.23–1.04) if the first child died. The reduced live birth risk did not differ by the type of psychotropic drug treatment. The associations between postpartum psychiatric disorders and subsequent live birth did not differ by subcategories of diagnosis (Table II).

Additional analyses

The main result remained unchanged in the analysis restricted to women who gave birth to singletons at the first live birth (HR = 0.66, 95% CI: 0.64–0.69). A similar result was obtained when we repeated our analysis in 379 757 women who gave birth to their first live birth before age 35 years; the HR was 0.67 (95% CI: 0.64–0.69). When redefining the postpartum psychiatric disorders as incident

Table I Characteristics of study subjects by postpartum psychiatric disorders.

Characteristic	Women with postpartum psychiatric disorders ($N = 4327$)	Women with no postpartum psychiatric disorders ($N = 410\,244$)
Age at first live birth (years)		
15–25	1206 (27.9)	90 047 (21.9)
25–34	2718 (62.8)	285 786 (69.7)
35–45	403 (9.3)	34 411 (8.4)
Marital status at live birth		
Married or cohabiting	3423 (79.1)	335 331 (81.7)
Single, divorced or widow	785 (18.1)	63 617 (15.5)
Missing	119 (2.8)	11 296 (2.8)
Highest educational attainment		
Elementary school	1071 (24.8)	63 910 (15.6)
Above elementary school	2996 (69.2)	317 472 (77.4)
Missing	260 (6.0)	28 862 (7.0)
Fertility treatment before first live birth	578 (13.4)	46 477 (11.3)
Smoking during the first pregnancy		
Yes	945 (21.8)	59 981 (14.6)
No	3186 (73.6)	333 682 (81.3)
Missing	196 (4.5)	16 581 (4.0)
Preeclampsia/eclampsia	196 (4.5)	15 289 (3.7)
Gestational diabetes	108 (2.5)	7834 (1.9)
Caesarean section	942 (21.8)	75 285 (18.4)
Postpartum haemorrhage	813 (18.8)	84 940 (20.7)
Preterm birth (gestational age < 37 weeks)		
Yes	413 (9.5)	28 260 (6.9)
No	3822 (88.3)	372 463 (90.8)
Missing	92 (2.1)	9521 (2.3)
Birthweight		
Low birthweight (<2500 g)	370 (8.6)	23 153 (5.6)
Normal birthweight (2500–3999 g)	3312 (76.5)	323 125 (78.8)
High birthweight (≥4000 g)	549 (12.7)	56 093 (13.7)
Missing	96 (2.2)	7873 (1.9)
Major congenital malformations	434 (10.0)	30 265 (7.4)
Number of first live birth		
Singleton	4198 (97.0)	400 883 (97.7)
Multiple births	129 (3.0)	9361 (2.3)
Family psychiatric history before first live birth	718 (16.6)	48 122 (11.7)
Calendar year of the first live birth		
1997–2000	951 (22.0)	101 171 (24.7)
2001–2005	1159 (26.8)	112 855 (27.5)
2006–2010	1335 (30.9)	104 363 (25.4)
2011–2015	882 (20.4)	91 855 (22.4)

Figures are numbers (%).

psychiatric disorders with an onset during 0–12 months after the first live birth, 8156 women were categorised as having postpartum psychiatric disorders. Postpartum psychiatric disorders were associated with a 35% decrease in the rate of having second live birth (HR = 0.65, 95% CI: 0.63–0.67). Altogether, 78 405 women had a third live birth. Continuation to a third pregnancy was related to the most recent postpartum psychiatric disorder (Fig. 2). Women with a history of postpartum psychiatric disorders both after first and second live birth

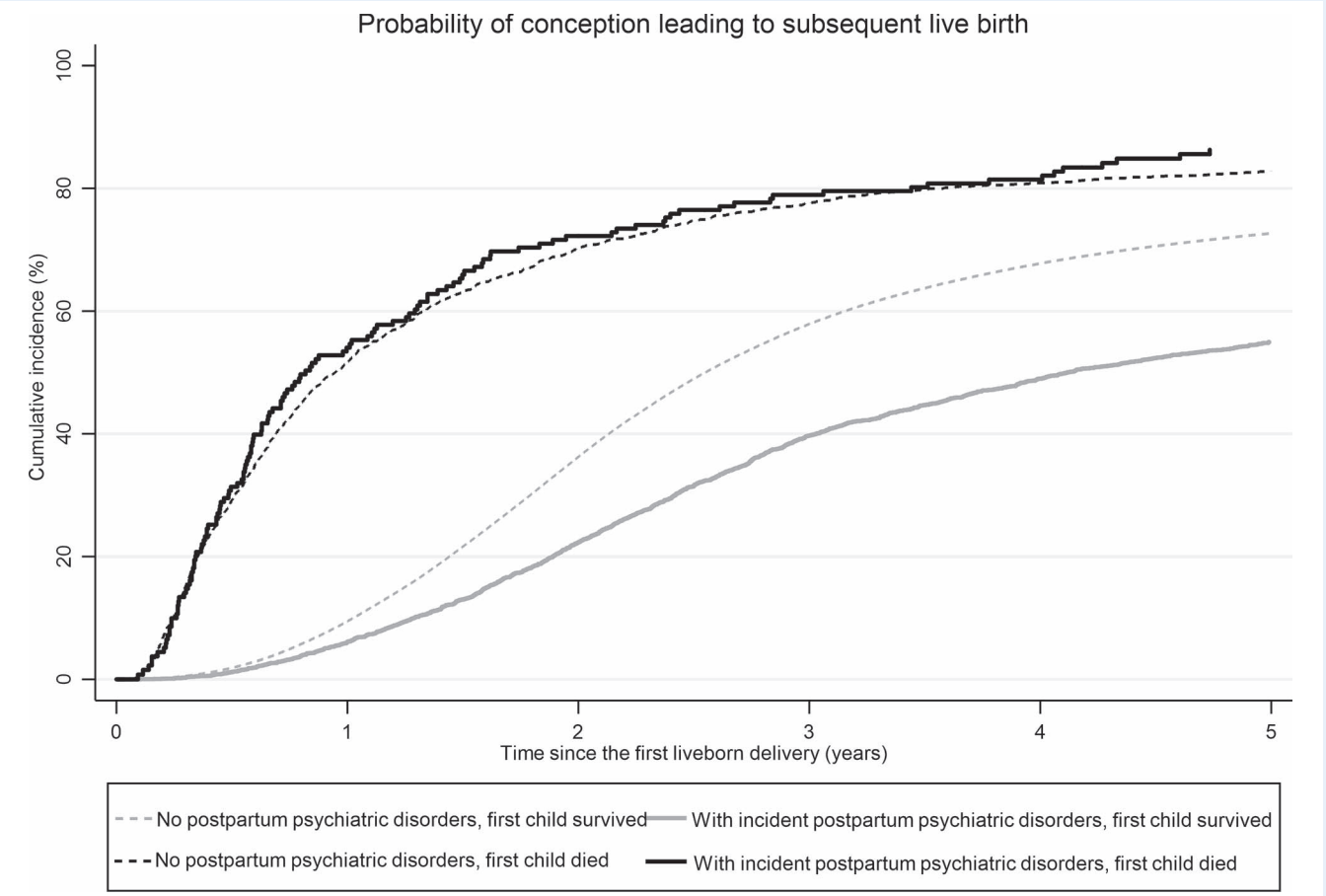

Figure 1 Kaplan–Meier estimates of the probability of conception leading to subsequent live birth within 5 years by postpartum psychiatric disorders after the first liveborn delivery and survival of the first child, unadjusted.

had a significantly lower rate of having a third live birth (HR = 0.53, 95% CI: 0.44–0.64).

Discussion

In this population-based cohort study, we found that women with incident postpartum psychiatric disorders were less likely to go on to have further children, in comparison to women with no postpartum psychiatric disorders, but this association depended on the severity of disorders and was modified by the survival status of the first child.

Factors influencing the observed subsequent live birth

In cases where the first child died, we did not observe a reduced subsequent live birth in women with postpartum psychiatric disorders. Among women with postpartum psychiatric disorders, women whose first child died were 3.87 times as likely to have subsequent live birth as women whose first child survived. Jointly, these findings suggest the overall reduced subsequent live birth in this population is at least in part voluntary. Specifically, given the recurrence risks of postpartum psychiatric disorders are substantial (Wesseloo *et al*., 2016; Munk-Olsen *et al*., 2019), women who had postpartum psychiatric disorders may choose not to have subsequent pregnancies to avoid risks of another postpartum psychiatric episode (Dolman *et al*., 2016). However, in the case of the loss of the first child, this concern may not influence women's motivation and wishes to have another pregnancy, irrespective of the substantial recurrence risk.

We also found a more pronounced reduced live birth rate among women with severe postpartum psychiatric disorders requiring hospitalisation irrespective of the survival status of the first child, suggesting that the severity of maternal psychiatric disorders also directly or indirectly influences reproductive choices. Other than personal choices, postpartum psychiatric disorders may also render women less able to conceive through inhibition of the hypothalamic–pituitary–ovarian axis (Young *et al*., 2000; Harlow *et al*., 2003). Studies have found that women with psychiatric disorders have an increased risk of irregular menstrual cycles or earlier perimenopause (Harlow *et al*., 2003; Nillni *et al*., 2018). Moreover, women with postpartum psychiatric disorders may have a worse relationship with partners or other family members (Symon *et al*., 2002). We found that 6.4% of women with postpartum psychiatric disorders became single, divorced or widow 1 year after the index delivery, in contrast to 2.8% of women with no postpartum psychiatric disorders. The reason why women with postpartum psychiatric disorders choose to have fewer children needs to be explored further.

Table II The hazard ratio of subsequent live birth according to postpartum psychiatric disorders by the survival of the first child[a].

Postpartum psychiatric disorders	The survival of the first child				The death of the first child				P for postpartum psychiatric disorders × survival of first child
	No. of subsequent delivery/ total no.	Person-years	Crude HR	Adjusted HR (95% CI)[c]	No. of subsequent delivery/ total no.	Person-years	Crude HR	Adjusted HR (95% CI)[c]	
No postpartum psychiatric disorders	293 292/410244	1 504 467	1	1 (ref)	1444/1888	4661	1	1 (ref)	<0.001
Any postpartum psychiatric disorders	2420/4327	20 582	0.63	0.65 (0.63–0.68)	151/187	439	1.01	1.01 (0.85–1.20)	
Onset of postpartum psychiatric disorders									
Within 90 days postpartum	1210/2256	10 348	0.62	0.64 (0.61–0.68)	122/152	334	1.04	1.04 (0.86–1.25)	<0.001
90–183 days postpartum	1210/2071	10 234	0.64	0.67 (0.63–0.71)	29/35	105	0.89	0.91 (0.63–1.32)	0.229
Severity of postpartum psychiatric disorders									
Inpatient treatment	210/391	2257	0.53	0.54 (0.47–0.61)	7/12	42	0.50	0.49 (0.23–1.04)	0.224
Outpatient treatment	711/1233	5840	0.64	0.66 (0.61–0.71)	15/20	66	0.88	0.93 (0.56–1.55)	0.397
Psychotropic drug treatment	1499/2703	12 485	0.64	0.67 (0.64–0.70)	129/155	331	1.08	1.08 (0.90–1.30)	<0.001
Antipsychotics or mood stabilizers	44/74	386	0.68	0.70 (0.53–0.94)	NA	NA	NA	NA	NA
Anxiolytics	596/1153	5417	0.62	0.74 (0.69–0.80)	109/128	272	1.12	1.06 (0.88–1.29)	<0.001
Antidepressants	807/1377	6251	0.65	0.69 (0.64–0.74)	14/16	25	1.09	1.16 (0.68–1.98)	0.024
Other psychotropic medication	52/99	431	0.68	0.75 (0.57–0.97)	NA	NA	NA	NA	NA
Subcategories of postpartum psychiatric disorders[b]									
Schizophrenia or related disorders	43/83	406	0.55	0.55 (0.41–0.74)	NA	NA	NA	NA	NA
Bipolar affective disorders	12/28	154	0.45	0.46 (0.26–0.82)	NA	NA	NA	NA	NA
Depressive disorders	312/546	2699	0.62	0.61 (0.54–0.68)	NA	NA	NA	NA	NA
Neurotic disorders	438/764	3711	0.63	0.67 (0.61–0.74)	NA	NA	NA	NA	NA
Other psychiatric disorders	116/203	1126	0.59	0.61 (0.51–0.74)	NA	NA	NA	NA	NA

[a]Please note that all women contributed to the analyses on women who had their first child survived and then some of them contributed to the analysis on women who had their first child died from the time they lost their first child. [b]Not all women with postpartum diagnosis received a clinical diagnosis since 2703 of them were identified from prescription registry. [c]Adjusted for maternal age at first live birth, cohabitant status, highest educational attainment, fertility treatment before the first live birth, smoking during pregnancy, preeclampsia/eclampsia, diabetes mellitus during pregnancy, caesarean section, postpartum haemorrhage, preterm birth, birthweight, major congenital malformations of the first child, number of first live birth, family history of psychiatric disorders and calendar year of birth. NA, the numbers are too small to make accurate estimations.

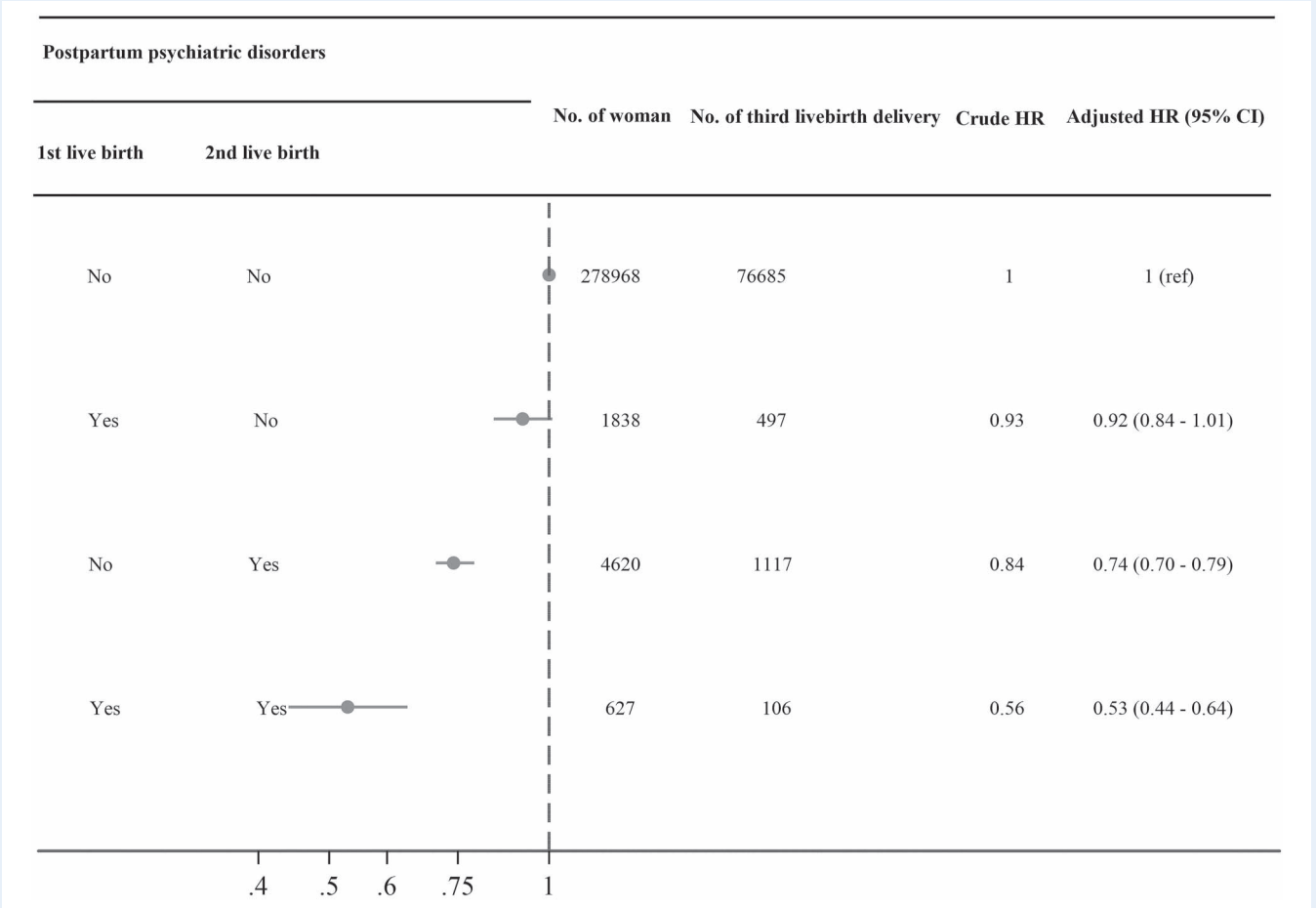

Figure 2 The adjusted hazard ratio of third live birth according to postpartum psychiatric disorders following the first two liveborn deliveries ($n = 286\,053$).* The crude HR and adjusted HR were calculated by stratifying on the survival status of the first child. In the adjusted models, we controlled for maternal age at first live birth, cohabitant status, highest education, fertility treatment before the first live birth, smoking during pregnancy, preeclampsia/eclampsia, diabetes mellitus during pregnancy, caesarian section, postpartum hemorrhage, preterm birth, birth weight, major congenital malformations of the first child, number of first live birth, family history of psychiatric disorders, and calendar year of birth.
*Of 297 307 women who gave birth to a second child, 11 254 gave birth after the end of follow-up and thus were excluded from this analysis.

Live birth in women with postpartum psychiatric disorders: clinical implications

Reproductive decisions made by women with postpartum psychiatric disorders are individual, personal and influenced by multiple factors, and fear of relapse may be one of them. Almost 30% of women with a history of postpartum psychosis experience a severe postpartum episode after subsequent pregnancy (recurrence risk = 29%, 95% CI: 20–41%) (Wesseloo *et al*., 2016). The particularly high recurrence risk will understandably raise concerns in women with a history of postpartum psychosis and is confirmed to influence reproductive decisions in interviews (Dolman *et al*., 2016). In clinical care, it is undoubtedly a challenge guiding women at high risk, e.g. psychosis in the postpartum (Bergink *et al*., 2016). However, an important clinical message to women with a history of severe postpartum psychiatric disorders, including postpartum psychosis, is that prevention of relapse is possible (Bergink *et al*., 2012), and clinical guidelines are available for the prevention and treatment of postpartum psychiatric disorders (Bergink *et al*., 2016). More specifically, plans for relapse prevention exist and can be individualised and adapted to fit personal needs (Bergink *et al*., 2016), all aimed at reducing the risk of relapse and possibly also indirectly influencing reproduction in women with postpartum psychiatric disorders. Women with previous psychiatric disorders are, therefore, recommended to have pre-pregnancy counselling when they consider or plan to have another child to evaluate the risk of relapse, to plan prevention strategies and to have their well-being and symptoms closely monitored and treated.

Strengths and limitations

The present study has a number of strengths. Our study was based on a population-representative cohort with longitudinal data on the entire Danish female population, and the nature of these data sources provides unique opportunities to study live birth. The large sample size enabled us to investigate the associations, accounting for the survival status of the child, which has not been considered in the previous study (Myers *et al*., 2016). We were able to explore the influence of mild to severe postpartum psychiatric disorders, defined by

hospital contact for psychiatric disorders and filling prescriptions of psychotropic medications. Data obtained from the registers are considered to be of high quality (Jensen and Rasmussen, 2011; Petersson et al., 2011; Schmidt et al., 2015; Pottegard et al., 2017; Bliddal et al., 2018), and information on postpartum psychiatric disorders and live birth was independently collected in a prospective manner and thus not vulnerable to recall bias as other designs relying on self-reports might be.

Our study also has limitations. First, we defined postpartum psychiatric disorders as filling a prescription for psychotropic medications or in- or out-patient treatment for psychiatric disorders. However, some women may receive psychotropic medications for symptoms other than psychiatric disorders, and we will consequently misclassify them as cases. Similarly, not all postpartum psychiatric disorder cases received medical treatment and thus would have been classified as non-cases. These misclassifications will make the postpartum psychiatric disorder group and comparison group similar and bias our findings toward the null. Second, we do not have accurate information on stillbirths and miscarriages before and after the first live birth. There is evidence that women with mental disorders have a higher risk of obstetric and pregnancy complications (Boden et al., 2012), and therefore, they may also have an increased risk of miscarriage. Moreover, women with severe postpartum psychiatric disorders may require pharmaceutical treatment with antipsychotics, which has been linked to an elevated risk of miscarriage (Coughlin et al., 2015; Sorensen et al., 2015; Kimmel et al., 2016). If women with postpartum psychiatric disorders are more likely to have pregnancies leading to stillbirths and miscarriages, they will keep trying until they have one or more successful pregnancies, i.e. increased childbirth rate (Skjærven, 2015). This may lead to an underestimation of the impact of postpartum psychiatric disorders on subsequent live birth. Third, although our study provides clues regarding the possible explanations for reduced childbirth among women with postpartum psychiatric disorders, we are not able to examine pregnancy intention, choice or interest directly. Fourth, although we adjusted for a wide range of covariates, as in other observational studies, we cannot rule out residual confounding by other important confounders such as the obesity status of the women. Fifth, even though our study has a large sample size, we have insufficient statistical power to examine the association between subcategories of postpartum psychiatric disorders and subsequent live birth. Finally, our findings are based on Danish women, while the associations could be essentially cultural and contextual. Therefore, this finding may not be generalisable to other study populations.

Conclusion

Reproductive decisions are personal, and postpartum psychiatric disorders have a significant impact on subsequent live birth, as women experiencing these disorders have a decreased likelihood of having more children. However, variations in live birth are influenced directly by both the severity of the postpartum psychiatric disorders and the survival status of the first-born child.

Authors' roles

X.L. and T.M. conceived and designed the study. X.L. analysed the data and drafted the manuscript. X.L., O.P., K.I., E.A., R.S. and T.M. interpreted the data and revised the manuscript critically. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding

Danish Council for Independent Research (DFF-5053-00156B); European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant (agreement no. 837180); AUFF NOVA (AUFF-E 2016-9-25); iPSYCH; the Lundbeck Foundation Initiative for Integrative Psychiatric Research (R155-2014-1724); Niels Bohr Professorship Grant from the Danish National Research Foundation and the Stanley Medical Research Institute; the National Institute of Mental Health (NIMH) (R01MH104468); Fabrikant Vilhelm Pedersen og Hustrus Legat.

Conflict of interest

None declared.

References

Bergink V, Bouvy PF, Vervoort JS, Koorengevel KM, Steegers EA, Kushner SA. Prevention of postpartum psychosis and mania in women at high risk. *Am J Psychiatry* 2012;**169**:609–615.

Bergink V, Rasgon N, Postpartum Psychosis WKL. Madness, mania, and melancholia in motherhood. *Am J Psychiatry* 2016;**173**:1179–1188.

Bliddal M, Broe A, Pottegard A, Olsen J, Langhoff-Roos J. The Danish medical birth register. *Eur J Epidemiol* 2018;**33**:27–36.

Boden R, Lundgren M, Brandt L, Reutfors J, Andersen M, Kieler H. Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. *BMJ* 2012;**345**:e7085.

Coughlin CG, Blackwell KA, Bartley C, Hay M, Yonkers KA, Bloch MH. Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy. *Obstet Gynecol* 2015;**125**:1224–1235.

Dolman C, Jones IR, Howard LM. Women with bipolar disorder and pregnancy: factors influencing their decision-making. *BJPsych Open* 2016;**2**:294–300.

EUROCAT. Guide 1.4 and reference documents: instructions for the registration and surveillance of congenital anomalies. *European surveillance of Congenit Anom* 2013. Available from http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/guide1_4. (23 April 2019, date last accessed).

Field T. Postpartum depression effects on early interactions, parenting, and safety practices: a review. *Infant Behav Dev* 2010;**33**:1–6.

Goodman JH. Postpartum depression beyond the early postpartum period. *J Obstet Gynecol Neonatal Nurs* 2004;**33**:410–420.

Harlow BL, Wise LA, Otto MW, Soares CN, Cohen LS. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. *Arch Gen Psychiatry* 2003;**60**:29–36.

Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health* 2011;**39**:26–29.

Howard LM, Kumar C, Leese M, Thornicroft G. The general fertility rate in women with psychotic disorders. *Am J Psychiatry* 2002;**159**:991–997.

Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health* 2011;**39**:91–94.

Jorgensen FS. Epidemiological studies of obstetric ultrasound examinations in Denmark 1989-1990 versus 1994-1995. *Acta Obstet Gynecol Scand* 1999;**78**:305–309.

Kimmel MC, Ferguson EH, Zerwas S, Bulik CM, Meltzer-Brody S. Obstetric and gynecologic problems associated with eating disorders. *Int J Eat Disord* 2016;**49**:260–275.

Meltzer-Brody S, Howard LM, Bergink V, Vigod S, Jones I, Munk-Olsen T, Honikman S, Milgrom J. Postpartum psychiatric disorders. *Nat Rev Dis Primers* 2018;**4**:18022.

Mors O, Perto GP, Mortensen PB. The Danish psychiatric central research register. *Scand J Public Health* 2011;**39**:54–57.

Munk-Olsen T, Laursen TM, Pedersen CB, Mors O, Mortensen PB. New parents and mental disorders: a population-based register study. *JAMA* 2006;**296**:2582–2589.

Munk-Olsen T, Maegbaek ML, Johannsen BM, Liu X, Howard LM, di Florio A, Bergink V, Meltzer-Brody S. Perinatal psychiatric episodes: a population-based study on treatment incidence and prevalence. *Transl Psychiatry* 2016;**6**:e919.

Munk-Olsen T, Ingstrup KG, Johannsen BM, Liu X. Population-based assessment of the recurrence risk of postpartum mental disorders: will it happen again? *JAMA Psychiat* 2019. doi: 10.1001/jamapsychiatry.2019.3208.

Myers S, Burger O, Johns SE. Postnatal depression and reproductive success in modern, low-fertility contexts. *Evol Med Public Health* 2016;**2016**:71–84.

Nillni YI, Wesselink AK, Hatch EE, Mikkelsen EM, Gradus JL, Rothman KJ, Wise LA. Mental health, psychotropic medication use, and menstrual cycle characteristics. *Clin Epidemiol* 2018;**10**:1073–1082.

Pedersen CB. The Danish civil registration system. *Scand J Public Health* 2011;**39**:22–25.

Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health* 2011;**39**:95–98.

Pirnat A, DeRoo LA, Skjaerven R, Morken NH. Risk of having one lifetime pregnancy and modification by outcome of pregnancy and perinatal loss. *Acta Obstet Gynecol Scand* 2019;**98**:753–760.

Plana-Ripoll O, Basso O, Laszlo KD, Olsen J, Parner E, Cnattingius S, Obel C, Li J. Reproduction after the loss of a child: a population-based matched cohort study. *Hum Reprod* 2018;**33**:1557–1565.

Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol* 2017;**46**:798–798f.

Royston P, White IR. Multiple Imputation by Chained Equations (MICE): implementation in Stata. *J Stat Softw* 2011;**45**:1–20.

Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–490.

Shorey S, Yang YY, Ang E. The impact of negative childbirth experience on future reproductive decisions: a quantitative systematic review. *J Adv Nurs* 2018;**74**:1236–1244.

Skjærven R, Wilcox AJ, Lie RT, Irgens LM. Selective fertility and the distortion of perinatal mortality. *Am J Epidemiol* 1988;**128**:1352–1363.

Skjærven R, Melve KK. Selective fertility – the examples of perinatal death and preeclampsia. *Norsk Epidemiologi* 2007;**17**:175–180.

Skjærven R. Registry based perinatal epidemiology: the importance of sibling and generation data. *Norsk Epidemiologi* 2015;**25**:53–62.

Sorensen MJ, Kjaersgaard MI, Pedersen HS, Vestergaard M, Christensen J, Olsen J, Parner E, Pedersen LH, Bech BH. Risk of fetal death after treatment with antipsychotic medications during pregnancy. *PloS One* 2015;**10**:e0132280.

Symon A, MacDonald A, Ruta D. Postnatal quality of life assessment: introducing the mother-generated index. *Birth* 2002;**29**:40–46.

Wesseloo R, Kamperman AM, Munk-Olsen T, Pop VJ, Kushner SA, Bergink V. Risk of Postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis. *Am J Psychiatry* 2016;**173**:117–127.

World Health Organization. The ICD-10 classification of mental and behavioural disorders. In: Geneva, 1993.

World Health Organization. ICD-10: International statistical classification of diseases and related health problems, 10th revision. In: 2004 WHO, Geneva, 95.

Xu R, O'Quigley J. Estimating average regression effect under non-proportional hazards. *Biostatistics* 2000;**1**:423–439.

Young EA, Midgley AR, Carlson NE, Brown MB. Alteration in the hypothalamic-pituitary-ovarian axis in depressed women. *Arch Gen Psychiatry* 2000;**57**:1157–1162.