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Original article

The association between postpartum depression and perimenopausal depression: A nationwide register-based cohort study

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ABSTRACT

Objectives: The purpose of the study was to investigate whether postpartum depression is associated with a risk of depression during perimenopause.
Study design: This is a Danish nationwide register-based cohort study of 270,613 individuals who were born in 1960–1968, who gave birth to a liveborn child recorded in the Medical Birth Register before the age of 40, and who lived in Denmark when turning 47 years old. The association between postpartum depression and depression during perimenopause was analyzed using a Cox Proportional Hazards model adjusted for education level, marital status, and age at first delivery.
Main outcome measures: Depression during perimenopause was identified by a diagnosis of depression during nine years of follow-up registered in the Danish National Patient Registry.
Results: A total of 7694 (2.9 %) study participants were diagnosed with depression during perimenopause. Postpartum depression was associated with 12.82 [95 % confidence interval (CI): 8.93;18.41] times higher hazard of depression during perimenopause, while depression prior to study baseline was associated with 11.91 [95 % CI: 11.14;12.73] times higher hazard compared with individuals with no history of depression. There was no difference in the association between postpartum depression and depression prior to study baseline for depression during perimenopause.
Conclusion: Prior depression, no matter the timing, is associated with markedly higher risk of depression during perimenopause. Thus, individuals who have experienced postpartum depression do not experience a greater risk of depression during perimenopause compared with individuals who have experienced depression unrelated to periods of hormonal changes during their fertile life.

1. Introduction

Depression is a major burden for the individual and the society causing significant personal, societal and economic consequences [1]. The World Health Organization ranked major depression as the third cause of burden of disease worldwide in 2008, and projected that it would rank first in 2030 [2]. The prevalence of depression is reported to be twice as high in women compared to men, especially when women are in their reproductive years [3]. The sex gap in the prevalence of depression is thought to be linked to biological and psychological sex differences in susceptibility and in environmental factors [2].

Depressive episodes during reproductive events cover premenstrual dysphoric disorder, postpartum- and perimenopausal depression, also known as reproductive subtypes of depression. Postpartum depression is considered to be one of the most common medical complication of pregnancy [4], and according to a Danish cohort study (2005) of 5252 individuals who attended the antenatal clinic during pregnancy, 5.5% suffered from postpartum depression four months after giving birth [5]. A systematic review of eight studies also found that 28–29 % of individuals in the menopausal transition reported depressed mood symptoms [6], while an American cohort study (2006) found that 26 % of 231 individuals going through the menopausal transition met the diagnostic criteria for major depressive disorder [7]. One pathogenic hypothesis to explain depression during reproductive events is a biological vulnerability to the normal fluctuations in sex hormone levels during these events, caused by an interaction between estrogens and the serotonergic system [8], which triggers depressive symptoms [3,8,9], in contrast to the absolute levels of reproductive hormones [3,8,10].

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Another hypothesis is that individuals with reproductive depression have abnormalities within the gonadal steroid system [8].

Only four previous studies with small sample sizes (n = 72–302) from Mexico and America have investigated the association between postpartum depression and perimenopausal depression [10–13]. A better understanding of the link between depression and reproductive events, would heighten our understanding of the link between fluctuations in sex hormones and depression in relation to the identified sex differences in depression. The current study aims to investigate the association between postpartum depression and depression during perimenopause in a large nationwide register-based cohort study, based on a hypothesis that a history of postpartum depression is associated with an increased risk of depression during perimenopause. A confirmation of this hypothesis could potentially aid the detection and prevention of perimenopausal depression.

2. Materials and methods

2.1. Data sources

The cohort study was conducted using data on the entire Danish population from nationwide registers. The study population was identified through the Danish Civil Registration System [14] using a unique personal identification number, which enabled accurate linkage of individual-level recorded information in all registers: the Danish National Patient Registry [15], the Danish Psychiatric Central Research Registry [16], the Danish Medical Birth Register [17], and the Population's Education Register [18]. An overview of the included registers and their coverage as well as an overview of the birth cohorts and follow-up period for the present study is provided in Fig. 1.

2.1.1. Study population

The study population consisted of 270,613 individuals born between 1960 and 1968, who turned 47 years old in 2007–2015 while living in Denmark, and who gave birth to a live born child recorded in the Medical Birth Register before the age of 40. Thus, 2834 individuals were excluded because they gave birth to their first child at the age of 40 years or older. Cohort members who had been diagnosed with depression in the six months prior to their 47th birthday (n = 285) were excluded.

2.1.2. Variables

2.1.2.1. Prior depression (exposure). Depression prior to baseline (age 47 years) was the main exposure and categorized as no depression (reference), postpartum depression including additional depressive episodes at any other time, and depression prior to study baseline exclusive of postpartum depression. Postpartum depression was defined as a depression diagnosis within the first year of giving birth.

Information of depression diagnoses was based on the International Classification of Disease diagnostic codes version eight and ten (ICD-8 and ICD-10) from the Danish National Patient Registry and the Psychiatric Central Research Registry, using ICD-8 codes until 1993 and ICD-10 from 1994 [16]. Prior to 1995, only diagnoses based on in-patient visits were included, whereas from 1995 and forward both in- and out-patient visits were included. Depression was classified as 296 and 300.4 in ICD-8, and F32 and F33 in ICD-10 [19]. The subcategories of the ICD codes can be found in the supplementary Table S1 in the Appendix.

2.1.2.2. Depression during perimenopause (outcome). Depression during perimenopause was recorded during the follow-up period, between the participants 47th and 56th birthday i.e., during the period where menopause often occurs, using data from the Danish National Patient Registry and the Psychiatric Central Research Registry based on the following ICD10 codes: F32 and F33.

2.1.3. Covariates

Educational level, age at first delivery, and marital status were identified as potential confounders of the association between postpartum depression and depression during perimenopause, based on reviews of the literature [1,3,20–25].

Data on marital status and education was collected at first delivery, however data on education was not available until 1981, therefore it was collected at this point for participants who had given birth before 1981. Marital status was recorded in the Civil Registration System, and it was divided into three groups: married/in a registered partnership (reference), divorced/revoked partnership/widowed, or unmarried. Data on education was included from the Danish Education Registers and categorized into four categories: high (bachelor's degree or higher) (reference), medium (high school), low (primary school) or undisclosed. Age at first delivery was registered in the Danish National Patient Registry and birth cohort was obtained through the Civil Registration System, both were included in the study as continuous variables.

2.1.4. Statistics

Descriptive statistics were conducted using means with standard deviation for continuous variables and frequencies with percentages for categorical variables. Furthermore, the incidence rates of being diagnosed with depression during the follow-up period were calculated.

Cox Proportional Hazard regression analyses were performed to estimate the hazard ratio of the association between postpartum depression and depression during perimenopause stratified by birth cohort and with the participants age as timescale. The 270,613 individuals in the study population were followed from their 47th birthday until a

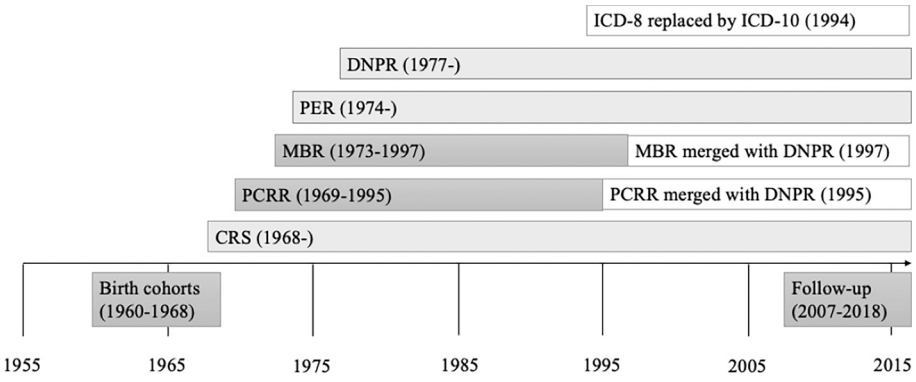

Fig. 1. Timeline of registers, cohorts, and follow-up.
Abbreviations: DNPR: Danish National Patient Registry, PER: Population's Education Register, MBR: Medical Birth Register, PCRR: Psychiatric Central Research Registry, CRS: Danish Civil Registration System.

diagnosis of depression, emigration, death, or end of follow-up (age 56 years or December 31st, 2018), whichever came first. Two analyses were conducted: 1) unadjusted- and 2) adjusted for potential confounders: educational level, age at first delivery, and marital status. Additional analyses with change of reference category of the main exposure to compare postpartum depression and depression prior to study baseline were also performed. The Cox Proportional Hazard model's assumption was tested by graphing Log-Log plots for each categorical variable and Schoenfeld residuals for continuous variables. The proportional hazard assumption was not violated. All statistical analyses were carried out in the program Stata and tested with 95 % confidence intervals and a significance level of 5 %.

3. Results

3.1. Descriptive statistics

The characteristics of the 270,613 participants included in this study are shown in Table 1. At baseline 7486 (2.8 %) individuals had been diagnosed with depression at some point in their lives excluding the first year after giving birth, whereas 208 (0.1 %) individuals were diagnosed with postpartum depression including additional episodes of depression.

During the 10-years of follow-up, 4883 individuals were diagnosed with depression (Table S2 in the Appendix). The incidence rate per 1000 person years is 1.85 [95 % confidence interval (CI): 1.79;1.91] for participants with no depression, 23.11 [95 % CI: 16.16;33.05] for participants with postpartum depression, and 24.69 [95 % CI: 23.32;26.13] for participants with depression prior to study baseline.

Table 1
Baseline characteristics of study population (270,613 individuals) by prior depression.

		No depression	Postpartum depression	Depression prior to study baseline
		Number (%)		
All participants		262,919 (100 %)	208 (100 %)	7486 (100 %)
Education at first delivery	Low education	79,812 (30.4 %)	35 (16.8 %)	3338 (44.6 %)
	Medium education	128,068 (48.7 %)	108 (51.9 %)	2956 (39.5 %)
	High education (ref.)	46,913 (17.8 %)	55 (26.4 %)	834 (11.1 %)
	Undisclosed	8126 (3.1 %)	10 (4.8 %)	358 (4.8 %)
Age at first delivery	<24 years	97,577 (37.1 %)	14 (6.7 %)	3568 (47.7 %)
	25–29 years	100,851 (38.4 %)	46 (22.1 %)	2384 (31.9 %)
	30–34 years	47,491 (18.1 %)	93 (44.7 %)	1085 (14.5 %)
	>35 years	17,000 (6.5 %)	55 (26.4 %)	449 (6.0 %)
	Mean age (SD)	26.4 (±SD. 4.8)	31.8 (±SD. 4.5)	25.4 (±SD. 5.1)
Marital status at first delivery	Unmarried	153,043 (58.2 %)	93 (44.7 %)	4529 (60.1 %)
	Divorced/ revoked partnership/ widowed	4197 (1.6 %)	9 (4.3 %)	166 (2.2 %)
	Married/ registered partnership (ref.)	105,679 (40.2 %)	106 (51.0 %)	2791 (37.3 %)
Birth cohort	1960–1964	159,273 (60,6 %)	100 (48.1 %)	4056 (54.2 %)
	1965–1969	103,646 (39.4 %)	108 (51.9 %)	3430 (45.8 %)

Abbreviations: SD: standard deviation.

3.2. Association between postpartum depression and depression during perimenopause

The hazard ratios (HR) of the unadjusted and adjusted Cox Proportional Hazard regression of the association between postpartum depression and depression during perimenopause, with no depression as the reference group, are shown in Fig. 2. In the unadjusted model, participants with a history of postpartum depression are associated with 12.44 [95 % CI: 8.68;17.82] times higher risk of depression during perimenopause compared to participants with no history of depression. A history of depression prior to study baseline was associated with a 13.26 [95 % CI: 12.41;14.16] times higher risk of depression during perimenopause compared to participants with no depression.

When adjusting for confounders, the HR of perimenopausal depression for participants with postpartum depression remains almost unchanged (HR: 12.82 [95 % CI: 8.93;18.41]), whereas the HR for participants with a history of depression prior to study baseline decreases slightly (HR: 11.91 [95 % CI: 11.14;12.73]).

To examine the difference in the risk of perimenopausal depression between individuals with a history of postpartum depression and depression prior to study baseline, a supplementary analysis was performed with the reference category being depression prior to study baseline (Table 2). The analyses showed no statistically significant difference between participants with a history of postpartum depression and participants with a history of depression prior to study baseline in the unadjusted (HR: 0.94 [95 % CI: 0.65;1.35]) and the adjusted analyses (HR: 1.08 [95 % CI: 0.75;1.55]).

The findings of this analysis do not support our hypothesis that a history of postpartum depression is associated with depression during perimenopause.

4. Discussion

4.1. Comparisons with previous studies

In total, five small studies (n = 72–302) on the association between postpartum depression and depression during perimenopause were identified through a systematic literature search. Most of the previous studies support the findings of this current study that previous episodes of depression in general are associated with higher risk of depression during perimenopause [10–13,26]. Studies by Flores-Ramos et al. [11] and Woods et al. [12] of 141 Mexican and 302 American participants respectively, as well as a literature review by Soares and Zitek [10] confirm our findings. Yet, these studies also report a considerably higher occurrence of postpartum depression, than we have found in this present study. Flores-Ramos et al. [11] reported a postpartum depression history of 11.3 % in their study population, and Soares and Zitek [10] cite studies with prevalence ranging from 4.4 to 18 %, compared to only 0.1 % in our study. The difference in prevalence may be due to the use of questionnaires and interviews based on the Center for Epidemiologic Studies Depression Scale (CES-D) to assess depression [10–12], compared to only using in-hospital diagnoses based on the ICD for postpartum depression in the present study. Only one study by Steinberg et al. of 116 American individuals contradicts our findings, and show that postpartum depression is not an antecedent of depression during the perimenopause [26]. This could express a need for further research to fully understand this association.

4.1.1. Possible mechanisms linking depression during reproductive events

Gordon and Sander [13] have investigated the association between estradiol fluctuations and reproductive depression. They imply an existence of four estradiol sensitivity profiles: decrease sensitive, increase sensitive, change sensitive or insensitive. Individuals with a decrease sensitive profile will experience negative mood with decreasing levels of estradiol, and vice versa for individuals with an increase sensitive profile. The change sensitive profile is characterized by negative mood

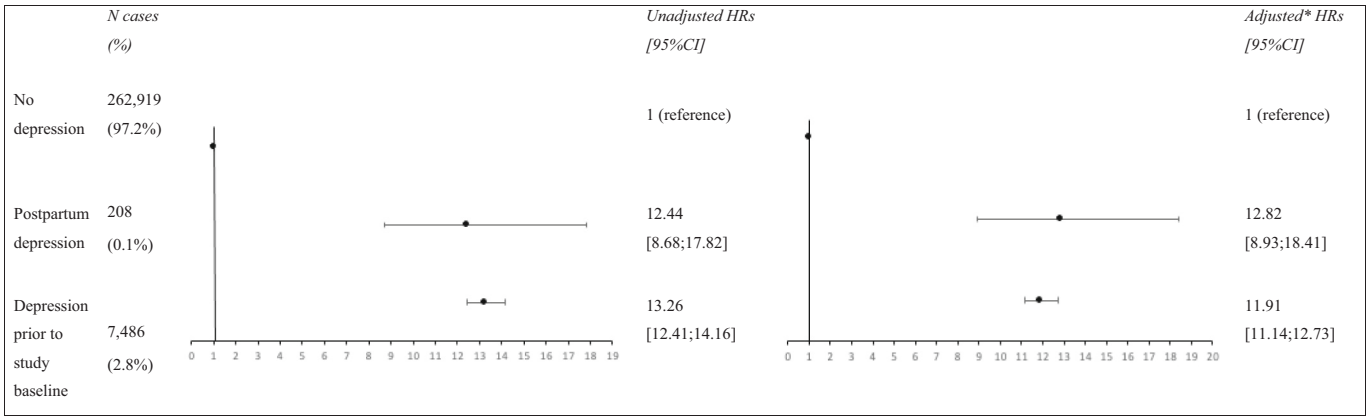

Fig. 2. Cox Proportional Hazard regression with unadjusted and adjusted hazard ratios (HRs) with 95 % confidence intervals (95 % CIs) for the association between depression and depression during perimenopause, stratified by birth cohort in 270,613 individuals.
*Adjusted for educational level, age at first delivery, and marital status.

Table 2
Cox Proportional Hazard regression with unadjusted and adjusted HRs with 95 % confidence intervals [95 % CI] for the association between depression and depression during perimenopause, stratified by birth cohort with depression prior to study baseline as the reference group.

Exposure	N cases	Unadjusted HR [95 % CI]	Adjusted* HR [95 % CI]
Depression prior to study baseline	7486	1 (reference)	1 (reference)
No depression	262,919	0.08 [0.07;0.08]	0.08 [0.08;0.09]
Postpartum depression	208	0.94 [0.65;1.35]	1.08 [0.75;1.55]

*Adjusted for educational level, age at first delivery, and marital status.

when estradiol levels fluctuate in either direction, while the insensitive profile does not experience mood changes based on estradiol levels. Each sensitivity profile has a different history of depression and risk of when, during the menopausal transition, depression is most likely to occur. According to Gordon and Sander's findings, both estradiol-decrease sensitive individuals and estradiol-change sensitive individuals have a history of postpartum depression. Furthermore, the latter also have a history of premenstrual dysphoric disorder [13]. In the current study >14 % of the individuals with a history of postpartum depression developed depression during the perimenopause. In relation to the study of Gordon and Sander [13], this could imply that those 14 % are estradiol-decrease- or change sensitive. Furthermore, almost 16 % of the participants in our study with a history of depression prior to study baseline develop depression during perimenopause. Some of the cases of depression prior to study baseline could be caused by episodes of premenstrual dysphoric disorder. Gordon and Sander found that estradiol-increase sensitive individuals had a history of premenstrual dysphoric disorder but not postpartum depression [13], hence a part of the 16 % in our study could be estradiol-increase sensitive, but this is difficult to infer from our results as the exposure categories are very broad. Finally, most of our study population are not diagnosed with depression during perimenopause, which could imply that they are insensitive to estradiol fluctuations. Individuals with an estradiol insensitivity may have a history of mood disorders, but these are not tied to reproductive events, and they are of no increased risk of depression during menopause compared to premenopausal levels [13].

4.2. Strengths and limitations

A major strength in this study is the low risk of selection bias by including a large nationwide study population (n = 270,613) covering all Danish women who turned 47 years old in 2007–2015 with information from a high-quality nationwide register. A limitation in the study is using age as a proxy measure of perimenopause. Ideally, we would want specific information on the age of menopause on the individual level, but this information is not recorded in any registers. If the true association for perimenopausal depression is larger than for depression in general, the usage of age as a proxy measure may have led to random misclassification of some of the depression cases as being related to perimenopausal depression where in fact they are not. In this case, it would cause us to potentially underestimate the association. Another limitation is the small number of postpartum depression cases, yet, based on this number and the size of the study population, we found a 90 % least detectable HR of 1.23 in a power calculation. Thus, the study may only have been underpowered to detect smaller differences, which may especially be of concern for the analyses of the difference between postpartum depression and depression prior to study baseline. The low prevalence of postpartum depression may be caused by the definition criteria and the registers used, allowing only the most severe cases to be captured, which limits the generalizability of the study. Finally, it is a strength that we included adjustment for age and educational level as individuals diagnosed with postpartum depression had higher level of both, which may be explained by these individuals being more likely to receive the diagnosis due to their health seeking behavior. Unfortunately, we did not have information on other potential confounding factors such as genetic disposition or other mental health issues. The information on co-morbidity might not fully reflect the cohort members' symptom profile and function. Thus, we might have some unmeasured confounding in our study.

Information on depression is included from the Psychiatric Central Research Registry and the National Patient register that records information about admissions to psychiatric hospitals which limits the risk of information bias. The sensitivity and specificity of the use of ICD diagnostic codes, has been investigated in three Danish cross-sectional studies [27–29], concluding that the validity of diagnoses is moderate to high. However the diagnosis and treatment of many mild to moderate mental disorders are often administered by general practitioners and specialist in psychiatry working in private practice, which is not recorded in the register [16]. Furthermore, information on out-patient visits is only included from 1995 and onwards. This may have caused us to underestimate the associations because the category with no history of depression may include both milder cases of depression that are treated in primary care and out-patient facilities prior to 1995. We have stratified the analyses on birth cohort to ensure that we only compare individuals within periods with the same level of available information. It would have been valuable to include information on antidepressant prescriptions to define depression, as our findings only include major depression leading to hospital contact, yet the Danish National

Prescription Registry only include information from 1995 and onwards [30], which would not cover the period after giving birth for the majority of the study population.

4.3. Clinical implications and future studies

We identified no difference in the association between postpartum depression and depression prior to study baseline, in relation to the development of perimenopausal depression when limiting to depression diagnoses based on contact with the secondary health care system. This suggests that prevention of perimenopausal depression should be centered on all individuals with a history of depression. Further research is needed to fully understand the association between reproductive subtypes of depression, meaning premenstrual dysphoric disorder, postpartum- and perimenopausal depression.

The current study shows an association between any history of depression and an increased risk of perimenopausal depression. This does not support our hypothesis that hormone fluctuations are the link between postpartum depression and perimenopausal depression. Further studies are needed before a firm conclusion can be drawn.

5. Conclusion

A history of depression, no matter the timing, is associated with markedly higher hazard of depression during perimenopause, when compared to individuals with no history of depression. The findings of this study suggest that depression in the postpartum period does not specifically influence the risk of depression during perimenopause, compared to depression during other time periods. This indicates the need for awareness on everyone with a history of depression in relation to the detection and treatment of perimenopausal depression.

Contributors

Emilie Venborg participated in the development of the study concept and design, the statistical analysis and interpretation of results, the drafting of the manuscript and the critical revision of the manuscript for important intellectual content.

Merete Osler participated in the development of the study concept and design, the acquisition of data, the interpretation of results, and the critical revision of the manuscript for important intellectual content.

Terese Sara Høj Jørgensen participated in the development of the study concept and design, the interpretation of results, and the critical revision of the manuscript for important intellectual content.

All authors saw and approved the final version, and no other person made a substantial contribution to the paper. All authors have full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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Ethical approval

According to Danish law, ethical approval is not required for purely register-based studies.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. To access the anonymized dataset used in this study, researchers need to apply the Danish Conscript board steering committee and Statistics Denmark. Only aggregated data, where no identification of persons is possible i.e. minimum five observations in each cell, can be removed from the server containing the data accessed through Statistics Denmark. Thus, we cannot provide an anonymized copy of the dataset as individuals may be identified based on the information in the data e.g. birthday, depression status etc. Access to the data through Statistics Denmark is only granted for authorized research and analysis environments of a more permanent nature with a chief researcher and several researchers/analysts. Foreign researchers affiliated to a Danish authorized environment can also get access. Authorization is granted by the Director General. Please find more information in the document 'Access to micro data at Statistics Denmark_2014' on https://www.dst.dk/en/TilSalg/Forskningsservice.

Declaration of competing interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2022.12.001.

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