European Neuropsychopharmacology 81 (2024) 20–27

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

Impact of genetic, sociodemographic, and clinical features on antidepressant treatment trajectories in the perinatal period

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ARTICLE INFO

Keywords:
Antidepressant
Affective disorder
Discontinuation
Genetic liability
Perinatal period
Epidemiology

ABSTRACT

Pregnant women on antidepressants must balance potential fetal harm with the relapse risk. While various clinical and sociodemographic factors are known to influence treatment decisions, the impact of genetic factors remains unexplored. We conducted a cohort study among 2,316 women with diagnosed affective disorders who had redeemed antidepressant prescriptions six months before pregnancy, identified from the Danish Integrated Psychiatric Research study. We calculated polygenic risk scores (PGSs) for major depression (MDD), bipolar disorder (BD), and schizophrenia (SCZ) using individual-level genetic data and summary statistics from genome-wide association studies. We retrieved data on sociodemographic and clinical features from national registers. Applying group-based trajectory modeling, we identified four treatment trajectories across pregnancy and postpartum: Continuers (38.2 %), early discontinuers (22.7 %), late discontinuers (23.8 %), and interrupters (15.3 %). All three PGSs were not associated with treatment trajectories; for instance, the relative risk ratio for continuers versus early discontinuers was 0.93 (95 % CI: 0.81–1.06), 0.98 (0.84–1.13), 1.09 (0.95–1.27) for per 1-SD increase in PGS for MDD, BD, and SCZ, respectively. Sociodemographic factors were generally not associated with treatment trajectories, except for the association between primiparity and continuing antidepressant use. Women who received ≥2 classes or a higher dose of antidepressants had a higher probability of being late discontinuers, interrupters, and continuers. The likelihood of continuing antidepressants or restarting antidepressants postpartum increased with the previous antidepressant treatment duration. Our findings indicate that continued antidepressant use during pregnancy is influenced by the severity of the disease rather than genetic predisposition as measured by PGSs.

1. Introduction

Affective disorders are common among women of childbearing age (Howard et al., 2014; Pedersen et al., 2014). Owing to increased risks of adverse health outcomes in the mother and child with untreated or undertreated affective disorders in pregnancy (Jarde et al., 2016; Wisner et al., 2009), appropriate treatment is crucial. Antidepressants are the mainstay drug treatment; approximately 2 to 8 % of women in Europe (Zoega et al., 2015) and 10 % in the USA fill at least one antidepressant prescription during pregnancy (Cooper et al., 2007). However, pregnant

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https://doi.org/10.1016/j.euroneuro.2024.01.010
Received 14 June 2023; Received in revised form 24 January 2024; Accepted 26 January 2024
Available online 6 February 2024

women prescribed antidepressants face the dilemma of continuing their treatment to balance any possible risks to the unborn child against the potential risk of mood instability.

Treatment decisions during pregnancy and postpartum (the perinatal period) are complex, and more insight into the factors that drive this decision is beneficial. Moreover, studies on adverse child outcomes and mothers' perinatal relapse risk often compare women who continue antidepressants with women who discontinue (Liu et al., 2017; Liu et al., 2022; Suarez et al., 2022; Sujan et al., 2017). Therefore, it is essential to gain better insight into the characteristics of these women. A few studies have investigated antidepressant treatment trajectories during pregnancy (Cabaillot et al., 2021; Molenaar et al., 2020; Trinh et al., 2022; Wikman et al., 2020). Studies have shown that women who restart antidepressants during pregnancy are characterized by having a severe pre-pregnancy psychiatric history (Trinh et al., 2022; Wikman et al., 2020), but also a higher socioeconomic status (Wikman et al., 2020). Moreover, a study from the Netherlands found that women with a higher socioeconomic status were more likely to continue their treatment during pregnancy (Molenaar et al., 2020). Overall, results from these studies suggest that clinical and sociodemographic features influence the decision to continue antidepressants, whereas a distinct genetic influence remains largely unexplored. A recent genome-wide study identified a polygenic profile for antidepressant response (Pain et al., 2022). However, this study is based on moderate sample size and studies with larger sample sizes are warranted to improve the prediction accuracy. The genetic liability to psychiatric disorders has been associated with depression severity (Kwong et al., 2021) and antidepressant treatment response (Meerman et al., 2022), therefore potentially influencing the decision to continue antidepressants, which has not been studied in previous studies. Importantly, no study has jointly investigated how various factors related to sociodemographic and clinical features, as well as genetic liability for mental disorders, influence antidepressant treatment courses during the perinatal period.

In this study, we aimed to identify different treatment trajectories during pregnancy and up to 12 months after childbirth among women with antidepressant treatment within 6 months before pregnancy. Further, we investigated whether genetic liability for psychiatric disorders, measured as polygenic risk scores (PGSs), and sociodemographic and clinical features influenced the identified antidepressant treatment patterns.

2. Materials and methods

2.1. Setting

We conducted a cohort study utilizing Danish national registers and the Integrative Psychiatric Research (iPSYCH2015) study (Bybjerg--Grauholm et al., 2020). Approval for the study was obtained from the Danish Scientific Ethics Committee (Project ID: 1–10–72–287–12), the Danish Data Protection Agency (Project ID: 2012–41–0110), and the Danish Neonatal Screening Biobank Steering Committee. No informed consent is required for register-based studies in Denmark. All residents in Denmark are assigned a unique ten-digit number in Denmark recorded in the Civil Registration System (Pedersen, 2011). This unique number enables us to link the registers and the iPSYCH2015 study, a large case-cohort study that includes a sub-cohort of individuals born in Denmark from May 1, 1981, to December 31, 2008 (full cohort). The iPSYCH2015 study consists of a random sample of 50,615 control subjects from the full cohort and all individuals diagnosed with a major mental disorder by December 31, 2015 ($N = 93{,}608$). The iPSYCH2015 included two data selections in 2012 and 2015, respectively. A detailed description of the iPSYCH2015 has been published elsewhere (Bybjerg-Grauholm et al., 2020). In the present study, iPSYCH2012 refers exclusively to the original data selection in 2012 and iPSYCH2015i to the second selection in 2015, while iPSYCH2015 refers to the combined iPSYCH2012 and iPSYCH2015i.

2.2. Study population

We identified 15,897 women who gave birth to at least one child (singletons or multiple births) between 1997 and 2016 through the linkage of the iPSYCH2015 study to the Medical Birth Registry (Bliddal et al., 2018) (Fig. 1). Of them, 6555 women had an affective disorder diagnosed any time before the start of pregnancy, determined by the first day of the last menstrual period (LMP). Using the Psychiatric Central Research Register (Mors et al., 2011), we defined affective disorders as an inpatient or outpatient treatment for mood disorders recorded (ICD-8 codes 296.x9, 298.09, 298.19, 300.49, and 301.19, excluding 296.89; ICD-10 codes F30–F39) or neurotic, stress-related, and somatoform disorders (ICD-8 codes: 300.x9, 305.x9, 305.68, and 307.99, excluding 300.49; ICD-10 codes F40–48). We excluded 35 women who emigrated or died within 12 months after delivery to ensure we had data on antidepressant use in the postpartum period. To capture recent antidepressant use, we restricted our study population to women who filled antidepressant prescriptions 6 months before pregnancy. Overall, 2659 pregnancies by 2316 women fulfilled all criteria. We included the first 2316 eligible pregnancies, considering the dependency of pregnancies by the same woman.

2.3. Antidepressant treatment before, during, and after pregnancy

We extracted information on antidepressant use from the National Prescription Registry, which contains information on the Anatomical Therapeutic Chemical (ATC) classification codes and the date of prescriptions filled in community pharmacies in Denmark since 1995 (Kildemoes et al., 2011). The ATC code for antidepressants was N06A. We determined the antidepressant exposure and non-exposure periods using the PRE2DUP method (Tanskanen et al., 2015), a novel approach based on mathematical modeling and considering drug stockpiling and personal purchasing patterns.

We adopted our trajectory analysis from our previous study on antidepressant treatment during pregnancy(Trinh et al., 2023) but extended the period to one year postpartum. We defined antidepressant treatment status (yes or no) for one-week intervals from 168 days (24 weeks) before pregnancy to 364 days (52 weeks) after delivery, totaling 113 weeks (including 37 weeks during pregnancy). We considered a woman exposed to antidepressants in a specific week if the date of dispensation occurred in the week or when the duration of antidepressant prescriptions overlapped that week. For 260 (11.2 %) pregnancies with gestational age < 37 weeks, maximum likelihood estimation was applied to handle missing data for each week from delivery to gestational week 37.

2.4. Polygenic risk scores

The Danish Newborn Screening Biobank stores dried blood spots taken after birth from nearly all infants born in Denmark since 1981 (Norgaard-Pedersen and Hougaard, 2007). DNA was extracted from the biobank and whole-genome amplified in triplicate (Hollegaard et al., 2011). DNA was genotyped with PsychChip arrays from Illumina (Grove et al., 2019) in the iPSYCH2012 sample and PsychArray V1.0 (Bybjerg-Grauholm et al., 2020) in iPSYCH2015i. Non-genotyped markers were imputed using the Haplotype Reference Consortium (HRC) (McCarthy et al., 2016). Quality control and imputation were performed using the bioinformatics pipeline Ricopili (Lam et al., 2019).

We estimated the genetic liability using PGS, a single summary measure of inherited susceptibility that aggregates all available common variants currently estimated to be associated with variation in disorder risk(Purcell et al., 2009). We calculated PGSs for major depression (MDD), bipolar disorder (BD), and SCZ. We derived LDpred2-auto (Privé et al., 2020a) PGSs based on single nucleotide polymorphism (SNP) weights from genome-wide association studies (GWAS) summary statistics (Howard et al., 2019; Mullins et al., 2021; Trubetskoy et al.,

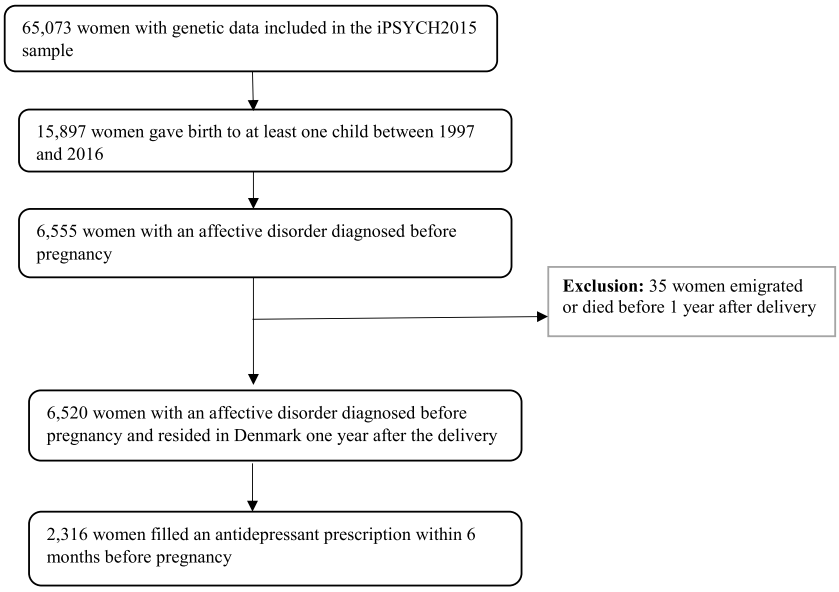

Fig. 1. Flowchart illustrating the identification of the study population.

2022), derived excluding the iPSYCH sample. The PGSs were based on the overlapping set of HapMap3 SNPs for MDD (1108,585 SNPs), BD (1109,886 SNPs), and SCZ (1097,826 SNPs). To increase the prediction ability of the PGSs, we also calculated PGSs for MDD, BD and SCZ using the iPSYCH individual data as described previously (Albiñana et al., 2021). These PGSs were derived using 5-fold cross-validation to avoid over-fitting the model. We finally combined the PGS obtained from summary statistics and individual-level data for each disorder through a linear combination, where the regression coefficients were inferred using two-fold cross-validation. The combined PGS has been demonstrated to improve prediction accuracy for psychiatric disorders in the iPSYCH data and was, therefore, used for our analyses. Details on the methods to create combined PGS can be found elsewhere (Albiñana et al., 2021).

3. Sociodemographic and clinical features

We investigated sociodemographic factors, including parental country of origin, place of residence at delivery, age at pregnancy, primiparity, marital status, level of education, and calendar year of pregnancy. We considered clinical features *prior to 6 months before pregnancy*, including age at the first affective disorder, duration of antidepressant treatment, and other diagnosed psychiatric disorders in addition to affective disorders. We further considered clinical features *within 6 months before pregnancy* as a proxy of the severity of psychiatric disorders: self-harm, inpatient treatment for psychiatric disorders, filling prescriptions for two or more classes of antidepressants, having an average daily dose of antidepressants above 1 fluoxetine dose equivalent (FDE, i.e., 40 mg fluoxetine)(Hayasaka et al., 2015), and co-prescribed medications (antipsychotics, opioids, anxiolytics and hypnotics, and antiseizure medications). The ATC codes for co-prescribed medications can be found in eTable 1.

3.1. Statistical analysis

We applied a semiparametric, group-based modeling strategy to classify women into subgroups based on the identification of heterogeneous antidepressant treatment trajectories. We implemented this technique using "traj" (Nagin et al., 2018) in Stata version 16.0 (StataCorp, College Station, TX, USA). We fitted group-based trajectory models with 1 to 6 groups and tested each model with linear, quadratic, and cubic terms to determine the best shapes that fit the data. We then decided the optimal number of trajectory groups based upon four criteria: (1) Bayesian information criterion (BIC) and Akaike Information Criteria (AIC), with a lower BIC/AIC indicating a better model fit. The BIC log Bayes factor approximation was defined as $2 \times [\Delta BIC]$ (subtracting a less complex model from a more complex model)(Walters et al., 2011) and $2 \times [\Delta BIC]$ higher than 10 is considered as solid evidence in favor of the more complex model; (2) Model adequacy, evidenced by an average posterior probability of $\geq$0.7 in each group identified; (3) Sufficient group size that constituted at least 10 % of the total sample; and (4) Clinical relevance. Women were assigned to the trajectory with the maximum posterior group probability.

Multinomial logistic regression models were used to estimate crude and mutually adjusted relative risk ratios (RRRs) and 95 % confidence intervals (95 % CIs) to assess the associations of genetic, sociodemographic, and clinical features with antidepressant treatment trajectories. We standardized the PGSs using the mean and standard deviation of PGSs in women born during 1981–1997 from the subcohort: (observed value - mean)/standard deviation. Effect estimates were presented per 1-SD increase (continuous variable) and quartiles compared to the lowest quartiles. We included the first 10 principal components (derived from genome-wide genetic data) in the models to adjust for population stratification. We implemented a principal component analysis on the iPSYCH2015 sample and computed the Gnanadesikan-Kettenring robust Mahalanobis distances of the principal components.(Privé et al., 2020b) The only covariate with missing data was the place of residence at delivery; 3.5 % of women had missing values, and we applied the missing indicator method to indicate missing values.

4. Sensitivity analysis

We conducted two sensitivity analyses to test the robustness of our results. First, to further account for the indications for treatment, we excluded women comorbid with another psychiatric disorder. Second, we restricted our analyses to women who only filled selective serotonin reuptake inhibitors (SSRIs), the most frequently prescribed antidepressants, within 6 months before pregnancy.

5. Results

Of 2316 women included in this study, the mean age was 26.7 (interquartile range: 23.9–29.4) years; 76.5 % were primiparous, and 46.6 % were diagnosed with affective disorder diagnosis before age 20

Table 1
Descriptive patient characteristics by trajectory group.

Characteristics	Early discontinuers ($N = 525$)	Late discontinuers ($N = 552$)	Interrupters ($N = 354$)	Continuers ($N = 885$)
Polygenic risk scores				
MDD, mean (SD)	0.45 (0.97)	0.45 (0.93)	0.46 (0.93)	0.38 (0.95)
BD, mean (SD)	0.10 (0.99)	0.10 (0.94)	0.14 (0.94)	0.06 (0.93)
SCZ, mean (SD)	0.01 (0.97)	0.00 (0.98)	0.01 (0.88)	−0.01 (0.96)
Sociodemographic factors				
Parental country of origin				
Denmark	467 (89.0)	497 (90.0)	325 (91.5)	819 (92.5)
At least one parent outside Denmark	58 (11.0)	55 (10.0)	29 (8.2)	66 (7.5)
Place of residence at delivery				
Capital	52 (9.9)	41 (7.4)	30 (8.5)	96 (10.8)
Suburb of the capital	67 (12.8)	36 (6.5)	34 (9.6)	84 (9.5)
Municipalities with a town with ≥100,000 inhabitants	68 (13.0)	80 (14.5)	40 (11.3)	131 (14.8)
Municipalities with a town with 10,000–100,000 inhabitants	144 (27.4)	177 (32.1)	109 (30.8)	268 (30.3)
Other municipalities in Denmark	173 (33.0)	196 (35.5)	130 (36.7)	280 (31.6)
Missing	21 (4.0)	22 (4.0)	11 (3.1)	26 (2.9)
Age at conception (years)				
<24	209 (39.8)	248 (44.9)	132 (37.3)	222 (25.1)
25–29	222 (42.3)	213 (38.6)	150 (42.4)	454 (51.3)
≥30	94 (17.9)	91 (16.5)	72 (20.3)	209 (23.6)
Primiparous	390 (74.3)	418 (75.7)	252 (71.2)	711 (80.3)
Maternal marital status in the year of pregnancy				
Married or cohabiting	288 (54.9)	278 (50.4)	212 (59.9)	544 (61.5)
Single, divorced, or widow	237 (45.1)	274 (49.6)	142 (40.1)	341 (38.5)
Maternal highest education in the year of pregnancy				
Mandatory school	299 (57.0)	337 (61.1)	199 (56.2)	403 (45.5)
High school or vocational school	180 (34.3)	171 (31.0)	124 (35.0)	362 (40.9)
College or university	46 (8.8)	44 (8.0)	31 (8.8)	120 (13.6)
Calendar year of pregnancy				
1995–2009	150 (28.6)	151 (27.4)	125 (35.3)	217 (24.5)
2011–2012	185 (35.2)	222 (40.2)	121 (34.2)	304 (34.4)
2013–2016	190 (36.2)	179 (32.4)	108 (30.5)	364 (41.1)
Year of recruitment				
iPSYCH2012	473 (90.1)	501 (90.8)	328 (92.7)	803 (90.7)
iPSYCH2015i	52 (9.9)	51 (9.2)	26 (7.3)	82 (9.3)
Clinical factors				
Age at first affective disorder (years)				
≤19	244 (46.5)	274 (49.6)	171 (48.3)	390 (44.1)
20–24	215 (41.0)	209 (37.9)	137 (38.7)	373 (42.1)
≥25	66 (12.6)	69 (12.5)	46 (13.0)	122 (13.8)
Duration of antidepressant treatment prior to 6 months before the pregnancy				
<1 year	260 (49.5)	276 (50.0)	139 (39.3)	208 (23.5)
1–2 years	111 (21.1)	130 (23.6)	87 (24.6)	144 (16.3)
>2 years	154 (29.3)	146 (26.4)	128 (36.2)	533 (60.2)
Maternal psychiatric diagnosis before pregnancy				
Substance abuse disorder	52 (9.9)	52 (9.4)	30 (8.5)	86 (9.7)
Psychotic disorders	43 (8.2)	44 (8.0)	24 (6.8)	89 (10.1)
Personality disorders	172 (32.8)	182 (33.0)	129 (36.4)	333 (37.6)
Child-onset disorders	66 (12.6)	78 (14.1)	42 (11.9)	101 (11.4)
Other psychiatric disorders	95 (18.1)	100 (18.1)	61 (17.2)	195 (22.0)
Maternal self-harm within 6 months before pregnancy	12 (2.3)	19 (3.4)	17 (4.8)	23 (2.6)
Psychiatric inpatient treatment within 6 months before pregnancy	29 (5.5)	53 (9.6)	20 (5.6)	63 (7.1)
Classes of antidepressant treatment within 6 months before pregnancy				
One class	496 (94.5)	499 (90.4)	334 (94.4)	822 (92.9)
Two or more classes	29 (5.5)	53 (9.6)	20 (5.6)	63 (7.1)
Dose of antidepressant within 6 months before pregnancy measured by the number of fluoxetine dose equivalent				
≤1	422 (80.4)	355 (64.3)	245 (69.2)	476 (53.8)
>1	103 (19.6)	197 (35.7)	109 (30.8)	409 (46.2)
Co-prescribed medications within 6 months before pregnancy				
Antipsychotics	75 (14.3)	105 (19.0)	54 (15.3)	191 (21.6)
Opioids	43 (8.2)	39 (7.1)	26 (7.3)	57 (6.4)
Anxiolytics and hypnotics	58 (11.0)	79 (14.3)	57 (16.1)	125 (14.1)
Antiseizure medications	41 (7.8)	50 (9.1)	44 (12.4)	120 (13.6)

years.

5.1. Antidepressant treatment trajectory description

A model with four trajectories was optimal based on the criteria for model selection outlined in eTable 2. We selected cubic polynomials since they improved model fit as indicated by BIC. The average posterior probabilities were high for all 4 groups (range: 0.975–0.991). The four groups were named based on their starting position and subsequent trajectory (Fig. 2): (1) Continuers (38.2 %): the subgroup who continued their antidepressant treatment during pregnancy and postpartum; (2) Early discontinuers (22.7 %): the subgroup who discontinued antidepressants around the time of pregnancy recognition; (3) Late discontinuers (23.8 %): the subgroup who discontinued antidepressants in the third trimester; and (4) Interrupters (15.3 %): the subgroup who stopped during pregnancy and resumed it postpartum. Table 1 presents

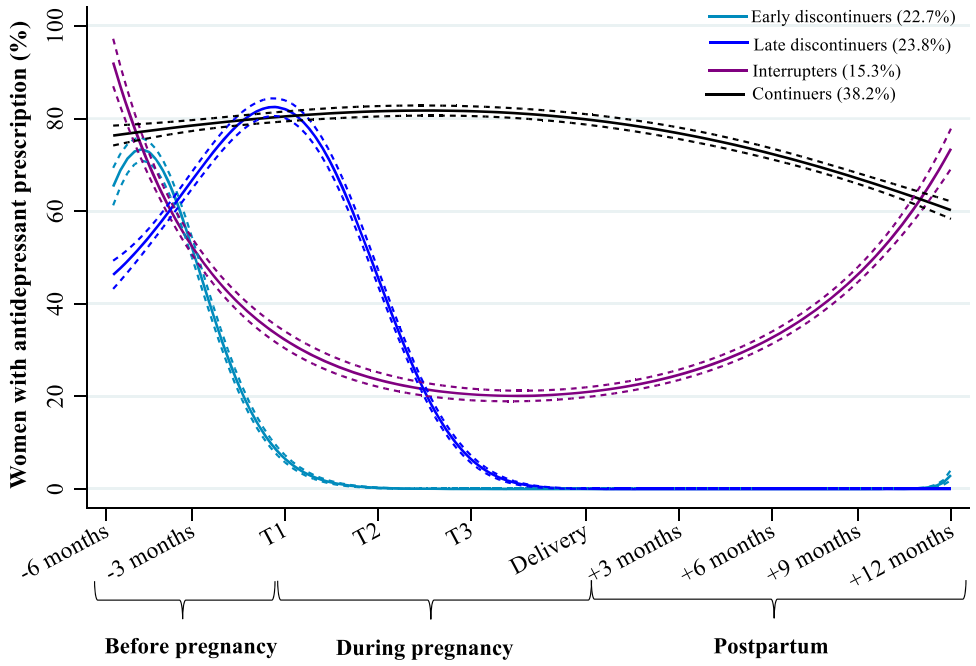

Fig. 2. Trajectories of antidepressant use in pregnancy and the postpartum period. −6 months: 6 months before pregnancy; −3 months: 3 months before pregnancy; T1: first trimester (from pregnancy to 90 days); T2: second trimester (91 days to 180 days); T3: third trimester (180 days to delivery); +3 months: 3 months after delivery; +6 months: 6 months after delivery; +9 months: 9 months after delivery; +12 months: 12 months after delivery.

the PGSs, and sociodemographic and clinical features by trajectories.

5.2. PGSs and their associations with antidepressant treatment trajectories

The RRRs for continuers versus early discontinuers were 0.93 (95 % CI: 0.81–1.06), 0.98 (0.84–1.13), 1.09 (0.95–1.27) per 1-SD increase in PGS for MDD, BD, and SCZ, respectively. Similarly, PGSs for MDD, BD, and SCZ were not associated with the likelihood of being late discontinuers or interrupters (Table 2). Furthermore, when dividing the samples into quartiles, the probability of being in antidepressant treatment groups did not change by quartiles of PGSs for MDD, BD, and SCZ (eFig. 1 in the supplementary).

5.3. Sociodemographic and clinical features associated with antidepressant treatment trajectories

Primiparous women were more likely to be continuers versus early discontinuers than parous women (RRR=1.43, 95 % CI: 1.05–1.94) (Table 2). Parental country of origin, place of residence at delivery, age at pregnancy, marital status, and education were not associated with antidepressant treatment trajectories.

Women who had received ≥2 antidepressant classes within 6 months before pregnancy were highly likely to discontinue late in pregnancy, restart antidepressants postpartum or continue their antidepressants versus early discontinuation (RRR=1.98, 95 % CI: 1.27–3.09 for late discontinuers, RRR=1.78, 95 % CI: 1.08–2.94 for interrupters, and RRR=2.64, 95 % CI:1.72–4.04 for continuers). Likewise, those who were on a high dose of antidepressants before pregnancy were also more likely to be late discontinuers (RRR=2.33, 95 % CI: 1.74–3.12), interrupters (RRR=1.63, 95 % CI: 1.17–2.26), and continuers (RRR=3.60, 95 % CI: 2.73–4.74) versus early discontinuers. Moreover, the likelihood of being interrupters or continuers increased with the duration of antidepressant treatment (p for trend was <0.001 for both continuers and interrupters). Maternal self-harm within 6 months before pregnancy was independently associated with a higher possibility of being interrupters and psychiatric admission with being late discontinuers and continuers. Antidepressant treatment groups did not differ by other clinical features examined, including age at first affective disorder diagnosis, other psychiatric diagnoses, and co-prescribed medications before pregnancy (Table 2).

6. Sensitivity analyses

The associations of three PGSs, sociodemographic factors, and clinical features with antidepressant treatment trajectories in the perinatal period were consistent by restricting to women with no psychiatric comorbidities (eTable 3) and analyses among women who were treated with SSRIs only in 6 months before the pregnancy (eTable 4), although the 95 % CIs were broader and some estimates were no more statistically significant due to smaller sample sizes.

7. Discussion

The present study identified four antidepressant treatment trajectories across the perinatal period: continuers, early discontinuers, late discontinuers, and interrupters. Less than 40 % of women continued antidepressant treatment in the perinatal period, confirming previous findings that pregnancy is a period where many women make important treatment decisions (Petersen et al., 2011). There was no evidence that PGSs for MDD, BD, and SCZ were associated with these trajectories, but women with a diagnosed affective disorder and filled an antidepressant prescription before pregnancy (our study population) had a higher MDD PGS and BD PGS than pregnant women not included in the study, as expected (eTable 5). Primiparous women were more likely to continue antidepressants, but antidepressant treatment trajectories did not differ by other socioeconomic factors. Characteristics for women who were most likely to continue or resume antidepressants differed from women who discontinued antidepressants before pregnancy regarding individual treatment courses. These differences were seen for more treatment-specific aspects related to antidepressant use, including duration, classes, and doses.

We did not find evidence of genetic liability for three psychiatric disorders, MDD, BD and SCZ, measured as PGSs, influencing

Table 2
Adjusted relative risk ratios (RRR) in the multivariable model predicting trajectory group[a].

Characteristic	Late discontinuers vs. early discontinuers	Interrupters vs. early discontinuers	Continuers vs. early discontinuers
Polygenic risk scores			
MDD PGS, per standard increase	1.01 (0.88–1.16)	1.00 (0.85–1.16)	0.93 (0.81–1.06)
BD PGS, per standard increase	1.00 (0.86–1.17)	1.06 (0.89–1.25)	0.98 (0.84–1.13)
SCZ PGS, per standard increase	1.00 (0.86–1.17)	1.04 (0.88–1.24)	1.09 (0.95–1.27)
Sociodemographic factors			
Parental country of origin			
Denmark	1 (ref)	1 (ref)	1 (ref)
At least one parent outside Denmark	0.93 (0.55–1.56)	0.80 (0.43–1.49)	0.83 (0.50–1.38)
Place of residence at delivery			
Capital	1 (ref)	1 (ref)	1 (ref)
Suburb of the capital	0.67 (0.37–1.22)	0.91 (0.48–1.72)	1.23 (0.75–2.02)
Municipalities with a town with ≥100,000 inhabitants	1.40 (0.81–2.42)	0.97 (0.52–1.81)	1.26 (0.80–1.96)
Municipalities with a town with 10,000–100,000 inhabitants	1.44 (0.88–2.36)	1.27 (0.73–2.19)	1.10 (0.71–1.71)
Other municipalities in Denmark	1.37 (0.84–2.25)	1.26 (0.74–2.17)	1.10 (0.71–1.71)
Missing	1.31 (0.50–3.41)	1.88 (0.61–5.85)	1.52 (0.61–3.82)
Age at conception (years)			
<24	1.11 (0.67–1.83)	0.77 (0.44–1.34)	0.86 (0.54–1.38)
25–29	0.92 (0.61–1.38)	0.77 (0.49–1.20)	1.11 (0.77–1.60)
≥30	1 (ref)	1 (ref)	1 (ref)
Primiparous (yes versus no)	1.23 (0.90–1.69)	0.87 (0.61–1.22)	1.43 (1.05–1.94)
Maternal marital status in the year of pregnancy			
Married or cohabiting	1 (ref)	1 (ref)	1 (ref)
Single, divorced, or widow	1.21 (0.93–1.56)	0.85 (0.64–1.14)	0.87 (0.68–1.12)
Maternal highest education in the year of pregnancy			
Mandatory school	1 (ref)	1 (ref)	1 (ref)
High school or vocational school	0.95 (0.70–1.28)	1.01 (0.72–1.41)	1.20 (0.90–1.58)
College or university	1.09 (0.64–1.86)	0.97 (0.54–1.76)	1.36 (0.84–2.19)
Clinical factors			
Age at first affective disorder (years)			
≤19	1.02 (0.63–1.65)	1.09 (0.64–1.87)	0.94 (0.60–1.47)
20–24	0.89 (0.57–1.38)	0.90 (0.55–1.46)	0.89 (0.59–1.35)
≥25	1 (ref)	1 (ref)	1 (ref)
Duration of antidepressant treatment prior to 6 months before the pregnancy			
<1 year	1 (ref)	1 (ref)	1 (ref)
1–2 years	1.20 (0.86–1.67)	1.61 (1.10–2.36)	1.61 (1.15–2.27)
>2 years	1.02 (0.72–1.44)	2.02 (1.37–2.98)	4.52 (3.26–6.27)
Other psychiatric diagnoses before pregnancy			
Substance abuse disorder (yes vs. no)	0.83 (0.54–1.28)	0.87 (0.52–1.44)	0.98 (0.65–1.48)
Schizophrenia (yes vs. no)	0.90 (0.54–1.50)	0.85 (0.47–1.54)	0.98 (0.61–1.56)
Personality disorders (yes vs. no)	1.00 (0.76–1.32)	1.16 (0.85–1.58)	1.09 (0.84–1.42)
Child-onset disorders (yes vs. no)	1.04 (0.71–1.52)	0.98 (0.63–1.52)	0.96 (0.66–1.40)
Other psychiatric disorders (yes vs. no)	1.04 (0.75–1.44)	0.94 (0.65–1.36)	1.12 (0.83–1.52)
Maternal self-harm within 6 months before pregnancy (yes vs. no)	1.30 (0.60–2.82)	2.53 (1.13–5.62)	1.53 (0.70–3.37)
Psychiatric inpatient treatment within 6 months before pregnancy (yes vs. no)	1.63 (0.98–2.72)	1.00 (0.53–1.89)	1.67 (0.99–2.82)
Classes of antidepressant treatment in 6 months before pregnancy			
One class	1 (ref)	1 (ref)	1 (ref)
Two or more classes	1.98 (1.27–3.09)	1.78 (1.08–2.94)	2.64 (1.72–4.04)
Dosage of antidepressant within 6 months before pregnancy			
≤1 fluoxetine dose equivalents	1 (ref)	1 (ref)	1 (ref)
>1 fluoxetine dose equivalent	2.33 (1.74–3.12)	1.63 (1.17–2.26)	3.60 (2.73–4.74)
Co-prescribed medications within 6 months before pregnancy			
Antipsychotics (yes vs. no)	1.29 (0.88–1.89)	0.95 (0.63–1.45)	1.32 (0.93–1.86)
Opioids (yes vs. no)	0.70 (0.43–1.12)	0.81 (0.48–1.38)	0.63 (0.40–0.99)
Anxiolytics and hypnotics (yes vs. no)	1.29 (0.88–1.89)	1.48 (0.98–2.24)	1.30 (0.90–1.88)
Antiseizure medications (yes vs. no)	1.00 (0.63–1.58)	1.55 (0.96–2.49)	1.20 (0.80–1.82)

[a] Adjusted for the calendar year of pregnancy and the first ten principal components; all the risk factors were mutually adjusted for in the models.

antidepressant treatment trajectories. It is possible that the decision to continue versus discontinue medications in the perinatal period is not affected by genetic liability for risk to psychiatric disorders. However, several potential alternative explanations exist for the lack of significant evidence of association, including the limited sample size of the GWAS discovery that makes PGSs less powered. Moreover, we included one measure of genetic liability but acknowledged that this may not fully capture the genetic liability.

Our finding of an association between primiparity and antidepressant continuation contrasts with previous studies showing that primiparity was associated with a decreased likelihood of continuation (Molenaar et al., 2020; Wikman et al., 2020). A third study found no association between parity and continuation, but primiparous women had a reduced possibility of restarting antidepressants after discontinuation (Trinh et al., 2022). The differences between ours and these studies may be ascribed to the differences in the study populations. Our study included women with a preexisting affective disorder and who gave birth at a younger age, whereas the others included all women on antidepressants regardless of the diagnosis (Molenaar et al., 2020; Wikman et al., 2020), or women of an older age.(Molenaar et al., 2020; Trinh et al., 2022; Wikman et al., 2020)

We found that longer treatment duration and higher daily doses before pregnancy were associated with being continuers and interrupters, in line with the findings from previous studies (Trinh et al., 2022; Wikman et al., 2020), and we speculate that both duration and dose represent proxy measures of disease severity, offering an explanation for these specific findings. Women who continue or resume their antidepressants are more ill than women who discontinue early before pregnancy. For women with severe disorders, stopping antidepressants

during pregnancy may lead to a greater risk of a psychiatric emergency (Liu et al., 2022). Therefore, clinical practice should provide supportive and non-stigmatizing advice for these groups of women, acknowledging that the severity of the underlying disorders is likely to have guided the individualized treatment decision. Our findings that antidepressant treatment trajectories are mainly ascribed to aspects related to the severity of the diseases also have important implications for future research. Studies on antidepressant treatment during pregnancy could consider confounding by treatment indications through adjustment for pre-pregnancy treatment doses and duration to obtain more valid estimates.

7.1. Strengths and limitations

Our study is the first to investigate how genetic liability to three major psychiatric disorders may influence antidepressant fill trajectories. The linkage between the iPSYCH2015 cohort and multiple national registers allows us to assess a wide range of genetic, sociodemographic, and clinical features with a high level of detail. We used group-based trajectory modeling to examine longitudinal antidepressant fill patterns, which overcomes the limitation of binary classification using a fixed time window.

Our study also has some limitations. First, the decisions to continue or discontinue antidepressants during pregnancy are complex. In addition to the factors we examined, other factors, such as personal preferences and concerns about fetal safety, may affect the treatment decision. (Eakley and Lyndon, 2022) We do not know whether women discontinued treatment owing to inadequate response, treatment side effects, improvement of symptoms, or discovery of pregnancy. Second, we only included affective disorder cases diagnosed in the hospitals but not by the general practitioners. Therefore, we may include more severe cases, and there is no direct measurement of disease severity in registered data. However, we demonstrated that proxies of disease severity, including duration and daily doses of antidepressant treatment, may be associated with treatment trajectories. Third, our study population was relatively younger, with a mean age at conception of 27 (interquartile range: 24–29) years, compared to, on average, 30 years of first-time mothers in Denmark,(Kyhl et al., 2015) limiting the generalizability to women of different ages. Last, in Denmark, approximately 2 % of women filled at least one antidepressant prescription during pregnancy (Rommel et al., 2021), a lower percentage compared to other countries (Zoega et al., 2015; Cooper et al., 2007). Consequently, countries with different patterns of antidepressant use during pregnancy may also demonstrate distinct trajectory groups in comparison to Denmark.

8. Conclusions

We documented four antidepressant treatment trajectories across the perinatal period. The characteristics that determine treatment patterns were not associated with genetic liability but are ascribed to aspects related to the disease severity, such as duration, dosage and number of antidepressant classes treated before pregnancy. Future studies on antidepressant treatment during pregnancy consider confounding by adjusting for pre-pregnancy treatment to obtain valid estimates.

Contributors

XL contributed to data curation, data analysis, visualization, and project administration, wrote the first draft of the manuscript, and has complete access to all study data, ensuring data integrity and accuracy of the analysis. XL, VB, and TMO contributed to conceptualization and funding acquisition. NRW, VB, and TMO contributed to supervision. All authors contributed to the result interpretation, investigation, and methodology, provided critical reviews and editing of the paper, and approved the final manuscript.

Role of funding source

XL was supported by the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement no 891079. VB and TMO are supported by the National Institute of Mental Health (NIMH) (R01MH122869). TMO is also supported by the Lundbeck Foundation (R313-2019-569). AL and NTHT are supported by the Research Council of Norway (grant no. 288696). The investigators conducted the research independently. The funders had no role in study design, data analysis, data interpretation, writing, or submission for publication.

Data sharing

The study was based on Danish nationwide registers. According to Danish legislation, individual-level data can be accessed only through secure servers, Denmark Statistics, where download or export of individual-level information is prohibited. Only aggregated data can be shared to ensure complete anonymity and protection of individuals included in the studies.

Declaration of competing interest

All authors declare no conflict of interest related to this submission.

Acknowledgments

The authors gratefully acknowledge the Psychiatric Genomics Consortium (PGC) and the research participants and employees of 23andMe, Inc., for providing the summary statistics used to generate the polygenic risk scores.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2024.01.010.

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