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ORIGINAL RESEARCH

Antidepressant Fill and Dose Trajectories in Pregnant Women with Depression and/or Anxiety: A Norwegian Registry Linkage Study

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Background: Few studies investigated longitudinal antidepressant exposure during pregnancy and included dosage in the assessment.

Methods: We conducted a nationwide, registry-linkage study in Norway using data on antidepressant prescription fills in pregnancies lasting ≥32 weeks in women with a delivery between 2009 and 2018 who had a depression/anxiety diagnosis and antidepressant fills prior to pregnancy. Information on antidepressant exposure by week (measured by filled prescriptions) and prescribed average daily dose was used in longitudinal k-means trajectory modelling for a 108-week time window from six months prior to pregnancy to one year after delivery. Factors associated with trajectory group membership were examined using multinomial logistic regression models.

Results: We included 8,460 pregnancies in 8,092 women. Four antidepressant fill trajectories were identified based on filled antidepressant prescriptions: two distinct discontinuing patterns, one at around the start of pregnancy (30.4%) and one around the end of pregnancy (33.8%); one continuing pattern (20.6%); and one interrupting pattern (15.2%). Using average usual daily dose, we identified low dose discontinuing (60.3%), medium dose reducing (20.6%) and high dose continuing (15.2%) patterns. The multinomial logistic regressions showed that the fill trajectory group membership was strongly associated with: antidepressant type and dose prior to pregnancy and co-medication prior to pregnancy, maternal age, marital status, parity, previous pregnancy loss, and pregnancy planning.

Conclusion: Longitudinal trajectory modelling revealed distinct antidepressant fill and dosage patterns in the period around pregnancy. Knowledge about factors associated with utilization trajectories might be useful for health-care personnel counselling women about antidepressant use in pregnancy.

Keywords: longitudinal k-means trajectory modelling, antidepressant fill trajectories, depression, anxiety, pregnancy, drug utilization

Introduction

Evidence of the effectiveness and safety of medication use by the population of pregnant women is mostly based on postmarketing observational studies as this group is generally excluded from premarketing clinical trials.[1] Medication use in a real-world setting is characterized by the diversity of patient characteristics, dosage, treatment duration, and compliance.[2] Nordic registry data on medication dispensations with linkage to birth registries enable tracking of prescription drugs dispensed to pregnant women in an outpatient setting. It is imperative to maximize the potential of these data to map medication use patterns in pregnant women.

Antidepressants (AD) are increasingly being used by pregnant women. In Europe, approximately 2–8% of pregnant women fill AD prescriptions at some time during pregnancy, mostly for depression/anxiety disorders.[3] Pregnancy also remains

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a major determinant of AD treatment discontinuation.[4–6] AD discontinuation might be associated with a risk of relapse of the mother and negatively affects the child. Pregnant women are generally advised to discuss with their prescribing physician about pharmacological treatment options during pregnancy; however, many women experience high decisional conflict in the decision-making.[7–11] Most available studies investigating the effectiveness and safety of AD during pregnancy, however, have defined AD exposure in a simplistic way using a fixed time window and without taking into account the nature of long-term treatment and changes in dosage as well as indication.[12–14] A recent study using Danish registry linked data also highlighted the differences in psychiatric outcomes with regard to the timing of discontinuation during pregnancy.[10] In addition, studies using register-based data usually rely on the simple assumptions of one defined daily dose (DDD) or one tablet per day to model duration of treatment.[15,16] Recently, a novel method generating drug use patterns from prescription dispensations (PRE2DUP) was developed and validated on the Finnish prescription register.[16] This method produced better estimates of actual drug use patterns by generating expected duration of treatment using various factors, such as packaging parameters and filling history.[17,18] Therefore, the application of the PRE2DUP method is promising to improve modelling of drug utilization and treatment periods, even though it has not been applied in perinatal pharmacoepidemiologic research.

The aim of this study was twofold: (1) to apply PRE2DUP in Norwegian data and model antidepressant fill and dose trajectories in women with depression and/or anxiety from six months before to one year after delivery and (2) to identify factors associated with the defined trajectories.

Methods

Data Sources

This study was based on registry linked data (2009–2018) from: the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Database (NorPD), the Norway Control and Payment of Health Reimbursement (KUHR) and the Norwegian Patient Registry (NPR).[19,20]

In brief, MBRN is based on mandatory notification of all pregnancies lasting longer than 12 weeks in Norway since 1967 and contains various information about the mother and her infant(s).[20,21]

The NorPD is a nationwide registry of drug dispensations at the pharmacies to individual patients treated in primary care since 2004. Information in NorPD includes patient identification, dispensing date, drug substance coded against the Anatomical Therapeutic Chemical (ATC) classification system, standard unit (eg, tablet, mL), strength of the standard unit (eg, 300 mg per tablet), package size (eg, 100 tablets per full package), number of packages and DDDs dispensed, and reimbursement codes. No information on the dosage nor duration of treatment is included; drugs are generally supplied as full packages, but their combination with partial packages is possible according to the duration of treatment specified in the prescription.[2,19]

The KUHR was based on reimbursement claims by health-care professionals in primary and secondary care to the Norwegian Economics Administration with person-specific data available since 2006. Diagnostic codes follow the WHO International Classification of Diseases, version 10 (ICD-10) and International Classification of Primary Care, version 2 (ICPC-2) mainly used by general practitioners.

The NPR contains information on admission to hospitals and outpatient consultations with specialist health care of individual patients from 2008. The data include date of admission, and discharge, primary and secondary diagnosis (recorded using ICD-10).

Pregnancy Cohort

We included pregnancies with valid MBRN record which lasted ≥32 weeks and had pregnancy outcomes between 2009 and 2018 with at least one outpatient visit for depression (ICD-10: F32 and F33; ICPC-2: P76) and/or anxiety (ICD-10: F40 and F41, ICPC-2: P74); and at least one AD prescription filled at any time in the six months (ie, 168 days) prior to pregnancy start – as done previously.[22,23] Because we do not have information on the indication of AD, the last two criteria maximize the possibility that ADs were filled to treat depression/anxiety.[23] The start of pregnancy was estimated from the date of delivery and gestational length estimated via ultrasound or reported last menstrual period date in case

ultrasound is missing.[20] We excluded pregnancies in the same women with an interpregnancy interval of less than one year to avoid nonindependent observations (N=60).[23]

Antidepressant Use Periods

We extracted AD prescription fills (ATC code N06A) for the study population and applied the PRE2DUP method to generate the expected treatment duration of each AD prescription fill. Packaging parameters, leaflet information and clinical guidelines on the management of depression/anxiety were used to assume the potential daily dose (see Appendix 1 for details).[16] For example, if the patient filled a prescription of one package containing 28 tablets of 5 mg escitalopram, the potential daily dose is assumed to be 10 mg (two tablets daily) for a period of 14 days because the usual daily dose for depression of escitalopram is 10 mg a day in adults. However, if the patient filled a prescription of one package containing 98 tablets of 20 mg escitalopram, the potential daily dose is assumed to be 20 mg (ie, strength of the tablet) for 98 days because daily dose for depression of escitalopram can go up to 20 mg and the patient is not supposed to divide the tablet into two. Next, we constructed the AD use periods (ADUPs) for each pregnancy. An ADUP refers to a time span with continuous use of ADs, and ADUPs are nonoverlapping for each pregnancy. Each ADUP consists of a pregnancy identification, start date, end date, and total dispensed amount of ADs expressed in number of fluoxetine dose equivalents (one fluoxetine dose equivalent (FDE)=40 mg fluoxetine).[24] Of note, an ADUP may be generated by more than one AD when the pregnant woman switched AD or was on an add-on therapy.

ADs were divided into the sub-classes of selective serotonin reuptake inhibitors (SSRIs, ATC code N06AB), serotonin–norepinephrine reuptake inhibitors (SNRIs, ATC code N06AX) and others (including any AD other than SSRIs or SNRIs).

Maternal Characteristics

We assessed maternal sociodemographic factors (ie, maternal age at delivery and marital status), and factors related to pregnancy and reproductive history (ie, parity, multiple pregnancies, obstetric risk factors before pregnancy (adapted from Bateman et al using age, asthma, pregestational diabetes, chronic hypertension, kidney disease, previous caesarean section, multiple gestation), previous pregnancy loss, smoking before pregnancy, pregnancy planning, comedication and comorbidities before pregnancy). These factors were categorized as presented in Table 1. Obstetric risk factors were measured by the obstetric comorbidity index adapted from Bateman et al, limited to conditions before pregnancy.[25] Pregnancy planning variable was constructed using various proxies presented in Appendix 2.

We investigated comedications (dichotomized as yes/no) with opioid analgesics, antiepileptics, antipsychotics, benzodiazepine/z-hypnotics, psychostimulants, and comorbidities with eating disorders, bipolar disorders, and other psychiatric conditions, as well as thyroid disorders in the six months before pregnancy (details in Appendix 2).

AD treatments are more likely to be discontinued in patients with a lower severity of mental health conditions when they enter their course of pregnancy.[26] We constructed a variable denoting mental health condition severity based on prior research.[27] As such, pregnancies that had inpatient stays or outpatient encounters with specialists for psychiatric diagnosis and/or filled prescriptions for nervous system drugs in addition to ADs in the six months prior to pregnancy are classified as having high severity (see details in Appendix 2).[27] Conversely, severity of mental health conditions might also be reflected by AD treatment pathway and/or AD dosage. We created "treatment regimen" variables denoting AD treatment pathway (monotherapy vs polytherapy), average daily dose (dichotomized using cut-off of one fluoxetine dose equivalent), and AD type (SSRIs vs others) in the same time window.

AD Fill and Dose Trajectories

We investigated the time window including 24 weeks prior to pregnancy (approximately six months), 32 weeks into pregnancy (approximately eight months), and 52 weeks after delivery (approximately one year) for a total of 108 weeks. The rational for choosing six months for the prepregnancy period is to capture recent AD use and proximal to pregnancy, as done in prior research.[22] The one-year postpartum period was chosen because it is the vulnerable window where mothers with prior mental illnesses have significantly higher risk of having postpartum affective disorders.[28] Because

Table 1 Characteristics of Pregnancies, Overall and by Antidepressant Fill Trajectories, Norway, 2009–2018 (8,460 pregnancies)

Characteristic	Antidepressant Fill Trajectory			
	Trajectory A Late Discontinuers N=2859	Trajectory B Early Discontinuers N=2575	Trajectory C Continuers N=1741	Trajectory D Interrupters N=1285
Year of delivery				
2009–2013	1,480 (33.8)	1,397 (31.9)	823 (18.8)	673 (15.4)
2014–2018	1,109 (29.0)	1,187 (31.0)	918 (24.0)	612 (16.0)
Maternal age				
≤24 years	631 (22.1)	629 (24.4)	228 (13.1)	185 (14.0)
25–29 years	892 (31.2)	797 (31.0)	486 (27.9)	412 (32.1)
30–34 years	806 (28.2)	695 (27.0)	587 (33.7)	433 (33.7)
≥35 years	530 (18.5)	454 (17.6)	440 (25.3)	255 (19.8)
Marital status				
Married/cohabiting	2,344 (82.0)	2,161 (83.9)	1,531 (87.9)	1,131 (88.0)
Other	515 (18.0)	414 (16.1)	210 (12.1)	154 (12.0)
Parity				
0	1,409 (49.3)	1,223 (47.5)	748 (43.0)	516 (40.2)
1	1,450 (50.7)	1,352 (52.5)	993 (57.0)	769 (59.8)
Plurality				
Singleton	2,825 (98.8)	2,530 (98.3)	1,716 (98.6)	1,267 (98.6)
Multiple	34 (1.2)	45 (1.7)	25 (1.4)	18 (1.4)
Obstetric index[a]				
0	1,876 (65.6)	1,662 (64.5)	996 (57.2)	808 (62.9)
1	626 (21.9)	597 (23.2)	462 (26.5)	312 (24.3)
≥ 2	357 (12.5)	316 (12.3)	283 (16.3)	165 (12.8)
Previous miscarriage or stillbirth				
Yes	698 (24.4)	784 (30.5)	501 (28.8)	346 (26.9)
No	2,161 (75.6)	1,791 (69.6)	1,240 (71.2)	939 (73.1)
Smoking before pregnancy				
Missing	440 (15.4)	392 (15.2)	234 (13.4)	190 (14.8)
Yes	773 (27.0)	668 (25.9)	414 (23.8)	325 (25.3)
No	1,646 (57.6)	1,515 (58.8)	1,093 (62.8)	770 (59.9)
Pregnancy planning[b]				
Potentially yes	934 (32.7)	952 (37.0)	676 (38.8)	501 (39.0)
Potentially no	1,925 (67.3)	1,623 (63.0)	1,065 (61.2)	784 (61.0)
Severity of depression/anxiety in six months before pregnancy[c]				
High	1,610 (56.3)	1,384 (54.8)	996 (57.2)	706 (54.9)
Low	1,249 (43.7)	1,191 (46.3)	745 (42.8)	579 (45.1)
Comorbidity in six months before pregnancy				
Other psychiatric conditions than depression and/or anxiety	1,127 (39.4)	953 (37.0)	650 (37.3)	450 (35.0)
Eating disorders	89 (3.1)	48 (1.9)	50 (2.9)	40 (3.1)
Bipolar disorders	66 (2.3)	57 (2.2)	62 (3.6)	39 (3.0)
Thyroid disorders	69 (2.4)	57 (2.2)	44 (2.5)	29 (2.3)
Comedication in six months before pregnancy				
Opioid analgesic	373 (13.1)	287 (11.2)	240 (13.8)	202 (15.7)
Antiepileptics	159 (5.6)	103 (4.0)	142 (8.2)	70 (5.5)
Antipsychotics	272 (9.5)	193 (7.5)	187 (10.7)	132 (10.3)
Psychostimulants	55 (1.9)	45 (1.7)	40 (2.3)	29 (2.3)
Benzodiazepines	680 (23.8)	535 (20.8)	474 (27.2)	329 (25.6)
Thyroid hormones	109 (3.8)	99 (3.8)	101 (5.8)	56. (4.4)

(*Continued*)

Table 1 (Continued).

Characteristic	Antidepressant Fill Trajectory			
	Trajectory A Late Discontinuers N=2859	Trajectory B Early Discontinuers N=2575	Trajectory C Continuers N=1741	Trajectory D Interrupters N=1285
Treatment regimen in six months before pregnancy				
Monotherapy	2,672 (93.5)	2,471 (96.0)	1,575 (90.5)	1,203 (93.6)
Polytherapy	187 (6.5)	104 (4.0)	166 (9.5)	82 (6.4)
Average dose in six months before pregnancy				
≤1 fluoxetine dose equivalent	2,544 (89.0)	2,470 (95.9)	1,245 (71.5)	1,128 (87.8)
>1 fluoxetine dose equivalent	315 (11.0)	105 (4.1)	496 (28.5)	157 (12.2)
Use of SSRI in the six months prior to pregnancy				
Yes	1,889 (78.1)	1,509 (69.1)	1,231 (81.7)	862 (78.7)
No	530 (21.9)	674 (30.9)	276 (18.3)	233 (21.3)

Notes: [a]Index codes adapted from Bateman et al, using the variables available in MBRN (age, asthma, pregestational diabetes, chronic hypertension, kidney disease, previous caesarean section, multiple gestation) and weighting the variables as done by Bateman et al.[25] [b]Reporting use of folic acid before pregnancy (extract from MBRN), filling clomiphene (ATC code G03GB02) before pregnancy (extract from NorPD), discontinuing hormonal contraception for systemic use (ATC-code G03A, excluding contraceptive patches, G03AA13, injections, G03AC06, implants, G03AC08, and emergency contraceptives, G03AD) before pregnancy, having preconception encounters in hospital (ICD 10 – Z30: Encounter for contraceptive management). [c]Pregnancies with at least one of the following proxies in the year prior to pregnancy were classified as high severity: one or more psychiatric inpatient stay or outpatient specialist encounters with a psychiatric diagnosis (diagnoses with ICD-10: F01-F99 except for F32, F33, F40, F41) or deliberate self-harm diagnoses (ICD-10: X71-X83) as registered in NPR; having filled prescriptions for other nervous system drugs (ATC code N except N06 registered in NorPD).

pregnancies have different gestational length at delivery, we considered in the time window only the first 32 weeks, which was available to all pregnancies by design.

The following exposure definitions were utilized for each week in the 108-week time window: (1) AD exposure status, coded as 1 if at least one day during the given week was covered by an AD treatment and 0 otherwise; and (2) average daily dose expressed in number of fluoxetine dose equivalents.[22] For a given day that falls into an ADUP, the daily dose for that day is calculated by dividing total number of fluoxetine dose equivalents by the length of that ADUP in days. The average daily dose of a given week is calculated by dividing cumulative dose by number of exposed days in that week.

We applied longitudinal k-means trajectory modelling (KML) on 108 measurements of these exposure variables. KML is a commonly used approach to cluster longitudinal data, and it has been applied in perinatal pharmacoepidemiology.[29,30] The cluster centers represent the group trajectory for each cluster, and each cluster is assumed to be homogenous. KML was done using the package "kml" in R, allowing the k-means to run for 3 to 6 clusters 100 times each. The selection of the number of clusters was based on the maximization of five nonparametric quality criterion computed from package kml in R, clinical relevance of the trajectories, and minimum group size of 10%.[22] Trajectories were described as having the following types of patients: continuers (ie, the treatment was sustained from before pregnancy, throughout pregnancy and in the postpartum year), discontinuers (ie, treatment was stopped either before or during pregnancy or in the postpartum period), and interrupters (ie, treatment was discontinued during pregnancy or in the postpartum period then was resumed later on).

We described and compared the maternal characteristics and AD treatment prior to pregnancy across different AD fill and dose trajectories. We evaluated the association between these covariates and group membership of AD fill trajectories using univariate (Model 1) and multivariate (Model 2) multinomial logistic regressions to compute relative risk ratios and 95% confidence intervals restricted to pregnancies without missing data on covariates.[31] The only covariate with missing data was smoking status; 14.9% of women had missing values. Model 2 included all measured covariates in the study. The early discontinuer group was chosen as reference because this group was more likely to have mild symptoms. Given the similarities in the timing of discontinuation during pregnancy, we also compared interrupters vs late discontinuers.

Sensitivity Analyses

We conducted a set of sensitivity analyses to test the robustness of our results.

First, because in the main analysis we combined overlapping dispensations to generate ADUPs, we explored the possible effect of a grace period of 30 days (ie, combining drug use periods separated by less than 30 days in a single ADUP) on our results.

Second, we performed sensitivity analysis assuming consumption of two DDDs per day as suggested by previous work, if the patient filled a package with unit strength = DDD (eg, tablets of 10 mg escitalopram).[22,32,33] The main analysis assumed consumption of one DDD per day if the standard unit strength of the dispensed AD is equal to the DDD, however, this assumption might not reflect the actual prescribed dose of ADs in more severe cases or pregnancy-specific dosage adjustments.

Third, because pregnancies in the same women are not independent, we performed sensitivity analyses restricted to the first pregnancy recorded where multiple pregnancies within same woman were present in the study population (N=8,092 pregnancies).

Fourth, we extended the look-back time window to retrieve pregnancies in the study cohort to one year instead of six months to assess the potential impact of inclusion criteria (N=10,317 pregnancies).

Fifth, group-based trajectory modelling (GBTM) describes a longitudinal dataset in terms of a mixture of group trajectories, without regard of within-group variability which has been applied in perinatal research.[34] We applied GBTM in sensitivity analysis to determine if modelling strategy affected our findings.

All sensitivity analyses were performed on AD exposure in the 108-week time period. Data management and statistical analyses were performed with Stata/MP 16.0 and R 4.0.5 software for Windows.

Results

Description of Study Population

Among 592,189 pregnancies registered in the MBRN during 2009–2018 period, we included 8,460 pregnancies within 8,092 women in the study (Figure 1). Of these, 98.3% pregnancies resulted in live births and 46.1% were primiparous. The mean maternal age at start of the pregnancy was 29.5 years (standard deviation (SD)=5.5, min=16, max=48). The mean gestational age at delivery was 39.1 weeks (SD=1.7, min=32, max=44). Regarding AD treatment prior to pregnancy, 93.6% was on monotherapy, mostly with SSRIs (65.9%). The top five filled ADs prior to pregnancy included escitalopram (43.8% of prescription fills), venlafaxine (13.4%), sertraline (12.0%), fluoxetine (6.4%) and citalopram (5.6%).

AD Fill Trajectories

Using AD exposure status, four trajectories were selected to describe AD fills of our population (Figure 2A): (A) late discontinuers (start decreasing AD use at the beginning of pregnancy and stop around the end of pregnancy), 33.8%; (B) early discontinuers (start decreasing AD use before pregnancy and stop around the start of pregnancy), 30.4%; (C) continuers,20.6%; and (D) interrupters (same as late discontinuers but resuming AD use in postpartum period), 15.2%.

AD Dose Trajectories

Based on the KML modelling using average daily prescribed dose, we selected the three dose-dependent trajectory groups (Figure 2B): low dose (0.2–0.4 FDE) discontinuing (A) 60.3%, medium dose (0.6–0.8 FDE) reducing (B) 28.8% and high dose (1.0–1.2 FDE) continuing (C) 10.9%.

Factors Associated with AD Fill Trajectories

The maternal characteristics of the study population and trajectories generated from KML are shown in Tables 1 and S1. Some notable characteristics (applied for both fill and dose trajectories) are: discontinuers groups tend to be younger, not living with their partners, and were pregnant for the first time compared to other groups. In contrast, continuers had the highest proportion of pregnancies with high severity of mental health conditions, having comorbidities with other psychiatric conditions and comedications, receiving polytherapy and higher dose of AD prior to pregnancy. Interrupters were more likely to fill opioid

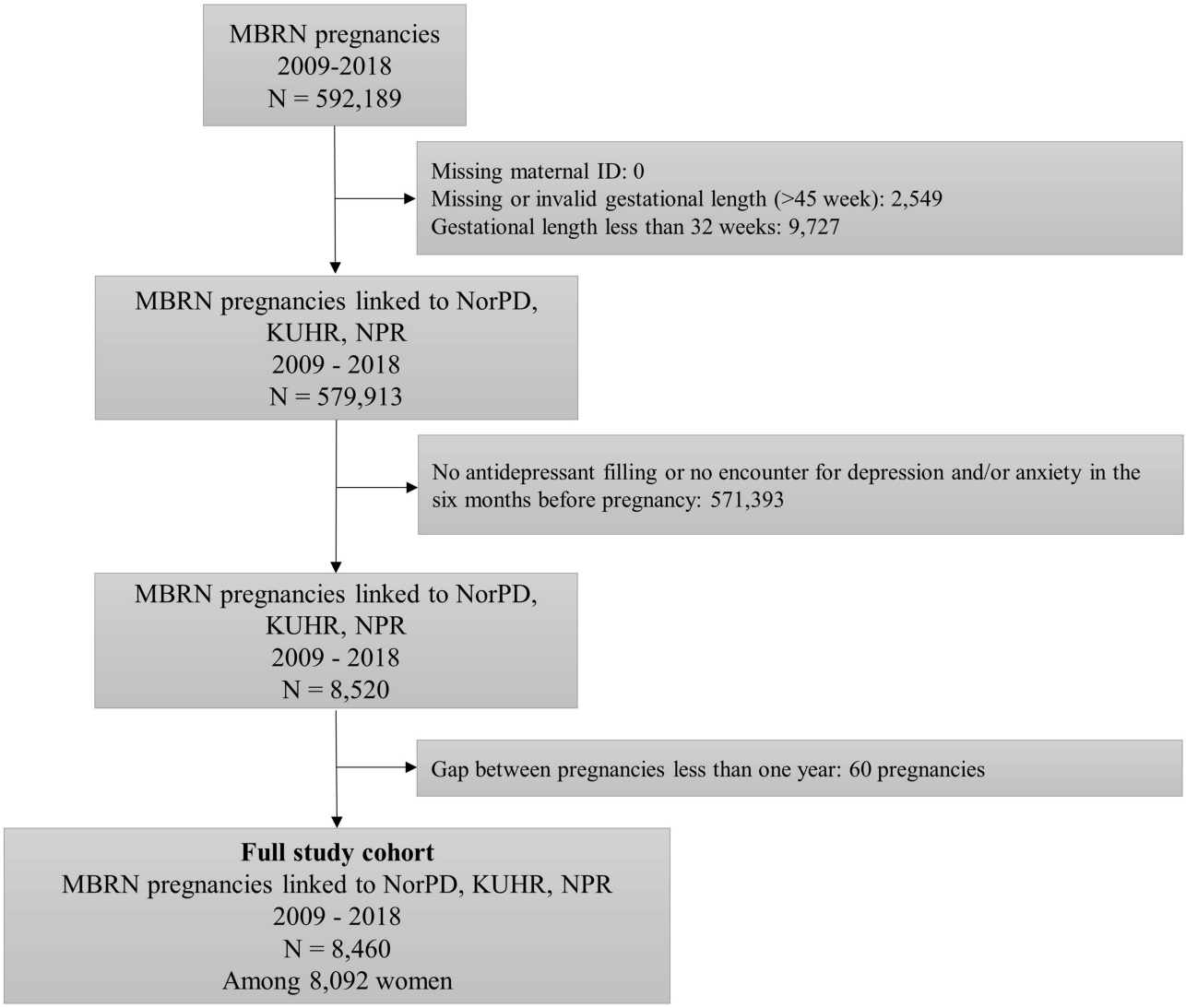


Figure 1 Flowchart of study population.
Abbreviations: MBRN, Medical Birth Registry of Norway; NorPD, Norwegian Prescription Database; KUHR, Norway Control and Payment of Health Reimbursement.

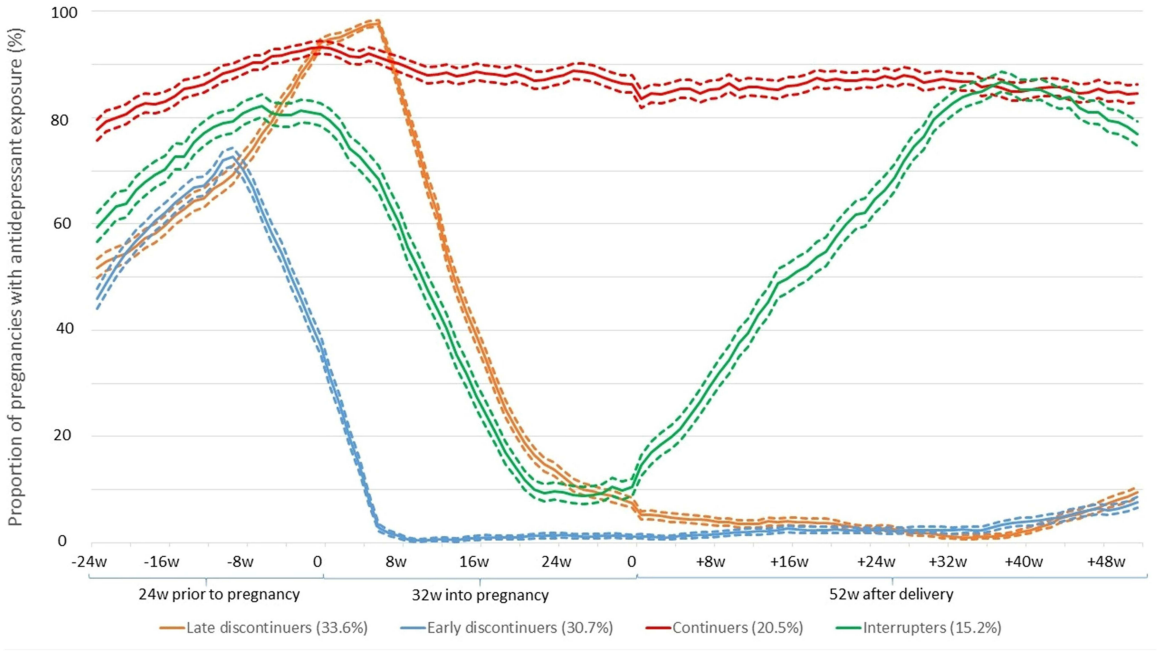
analgesics and other medications for psychiatric treatments, and also more often plan their pregnancy and live with a partner. In particular for distinct fill trajectories, early discontinuers had the highest proportion of pregnancies with a previous loss and late discontinuers had the lowest proportion of potentially planned pregnancies. Of note, the proportion of continuers were higher during the 2014–2018 period compared to that of 2009–2013 period.

Multiple maternal factors were associated with AD fill trajectory group membership including average dose prior to pregnancy, treatment pathway before pregnancy, AD type before pregnancy maternal age, marital status, parity, previous miscarriage or stillbirth, pregnancy planning, and comedication (including opioid, antiepileptics, antipsychotics, benzodiazepines) (see Tables 2 and S2 for details). Continuers, late discontinuers, and interrupters had 3–9 times more likely to be on high AD doses prior to pregnancy and had twofold more likely of using SSRIs prior to pregnancy compared to early discontinuers. However, interrupters had about 1.5 times more likely of fill opioids and antipsychotics prior to pregnancy, to be living with partners, planned their pregnancy and to be multiparous compared to late discontinuers.

Sensitivity Analyses

The inclusion of grace periods of 30 days generates fewer ADUPs, but did not affect the main results (Figure S1). Under the assumption of two DDDs per day if the unit strength is equal to the DDD, the trajectory groups remained similar as

A - Antidepressant fill trajectories



B – Antidepressant dose trajectories (expressed in number of fluoxetine dose equivalents – FLE with 1 FLE = 40mg fluoxetine)

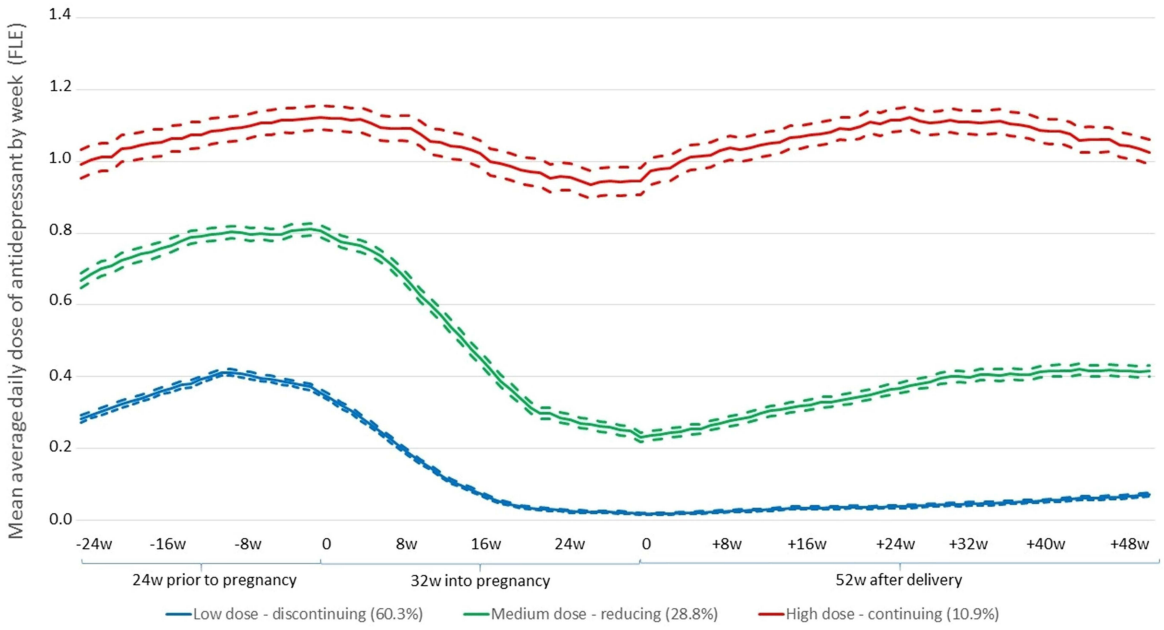


Figure 2 Trajectories of antidepressant fill (**A**) and dose (**B**) in pregnant women with depression/anxiety using longitudinal k-means trajectory modelling (2009–2018; N=8460 pregnancies). In both figures, weeks 32 to delivery were excluded.
Abbreviations: w, week; FLE, Fluoxetine equivalent.

Table 2 Association (Relative Risk Ratio, RRR) Between Maternal Characteristics and Antidepressant Fill Trajectory, Norway, 2009–2018 (7204 Pregnancies)*

Characteristic	Multinomial Logistic Regression (Multivariable Adjusted for All Covariates)			
	Late Discontinuers (vs Early Discontinuers) RRR (95%CI)	Continuers (vs Early Discontinuers) RRR (95%CI)	Interrupters (vs Early Discontinuers) RRR (95%CI)	Interrupters (vs Late Discontinuers) RRR (95%CI)
Year of delivery	**1.02 (1.00–1.05)**	**1.05 (1.02–1.08)**	1.01 (0.98–1.04)	0.98 (0.96–1.01)
Maternal age	**1.02 (1.01–1.04)**	**1.06 (1.04–1.07)**	**1.04 (1.02–1.05)**	1.01 (1.00–1.03)
Married or cohabiting	0.89 (0.76–1.05)	**1.42 (1.14–1.75)**	**1.40 (1.12–1.76)**	**1.56 (1.25–1.95)**
Nonprimiparous	0.92 (0.81–1.04)	0.98 (0.84–1.14)	**1.20 (1.02–1.42)**	**1.31 (1.12–1.54)**
Multiple birth	0.70 (0.41–1.18)	0.56 (0.30–1.06)	0.75 (0.38–1.48)	1.08 (0.54–2.18)
Obstetric index[a]	0.95 (0.89–1.01)	1.02 (0.95–1.10)	**0.91 (0.83–0.99)**	0.96 (0.88–1.05)
Previous miscarriage or stillbirth	**0.71 (0.62–0.82)**	**0.77 (0.66–0.90)**	**0.75 (0.63–0.88)**	1.04 (0.88–1.23)
Smoking before pregnancy	1.07 (0.93–1.22)	0.95 (0.81–1.11)	1.02 (0.86–1.21)	0.96 (0.81–1.13)
Pregnancy planning[b]	**0.82 (0.72–0.93)**	1.08 (0.93–1.25)	1.06 (0.91–1.24)	**1.30 (1.12–1.51)**
High severity of depression/anxiety in six months before pregnancy[c]	0.96 (0.83–1.12)	0.86 (0.71–1.03)	**0.79 (0.65–0.96)**	**0.81 (0.67–0.98)**
Other psychiatric conditions than depression and/or anxiety	1.05 (0.92–1.20)	0.93 (0.80–1.10)	**0.82 (0.69–0.97)**	**0.78 (0.66–0.92)**
Eating disorders	1.37 (0.92–2.05)	1.39 (0.87–2.22)	**1.69 (1.03–2.75)**	1.23 (0.79–1.91)
Bipolar disorders	0.88 (0.58–1.34)	1.27 (0.80–2.00)	1.34 (0.82–2.20)	1.53 (0.95–2.45)
Thyroid disorders	1.12 (0.66–1.89)	0.67 (0.37–1.21)	0.75 (0.39–1.46)	0.67 (0.36; –1.26)
Opioid analgesic	**1.25 (1.03–1.52)**	**1.35 (1.08–1.69)**	**1.74 (1.38–2.19)**	**1.39 (1.12–1.73)**
Antiepileptics	**1.48 (1.10–2.00)**	**1.74 (1.25–2.42)**	1.32 (0.91–1.91)	0.89 (0.64–1.24)
Antipsychotics	1.16 (0.92–1.45)	1.20 (0.92–1.55)	**1.53 (1.16–2.01)**	**1.32 (1.02–1.70)**
Benzodiazepines	1.13 (0.96–1.33)	**1.37 (1.13–1.66)**	**1.47 (1.20–1.80)**	**1.30 (1.07–1.58)**
Psychostimulants	1.03 (0.67–1.60)	1.47 (0.89–2.43)	1.57 (0.93–2.63)	1.52 (0.92–2.50)
Thyroid hormones	1.03 (0.68–1.56)	**1.59 (1.03–2.44)**	1.15 (0.70–1.90)	1.13 (0.70–1.81)
AD polytherapy	1.22 (0.92–1.62)	**1.45 (1.07–1.97)**	1.27 (0.91–1.79)	1.04 (0.77–1.42)
Higher AD dose prior to pregnancy	**2.66 (2.07–3.43)**	**8.72 (6.81–11.16)**	**3.11 (2.34–4.13)**	1.17 (0.93–1.47)
Use of SSRIs in the six months prior to pregnancy	**1.72 (1.50–1.97)**	**2.52 (2.12–2.99)**	**1.4 (1.54–2.19)**	1.07 (0.90–1.28)

Notes: [a]Index codes adapted from Bateman et al, using the variables available in MBRN (age, asthma, pregestational diabetes, chronic hypertension, kidney disease, previous caesarean section, multiple gestation) and weighting the variables as done by Bateman et al.[25] bReporting use of folic acid before pregnancy (extract from MBRN), filling clomiphene (ATC code G03GB02) before pregnancy (extract from NorPD), discontinuing hormonal contraception for systemic use (ATC-code G03A, excluding contraceptive patches, G03AA13, injections, G03AC06, implants, G03AC08, and emergency contraceptives, G03AD) before pregnancy, having preconception encounters in hospital (ICD 10 – Z30: Encounter for contraceptive management). [c]Pregnancies with at least one of the following proxies in the year prior to pregnancy were classified as high severity: one or more psychiatric inpatient stay or outpatient specialist encounters with a psychiatric diagnosis (diagnoses with ICD-10: F01-F99 except for F32, F33, F40, F41) or deliberate self-harm diagnoses (ICD-10: X71-X83) as registered in NPR; having filled prescriptions for other nervous system drugs (ATC code N except N06 registered in NorPD). *The total number of pregnancies is lower than the total population because of missing values on smoking. Bold indicates significant association.

main analysis (Figure S2). Of note, there were fewer pregnancies classified as late discontinuers and continuers. Sensitivity analysis restricted to first pregnancy registered and extended look-back time window provided similar results as main analysis (Figures S3 and S4). GBTM yielded consistent trajectories as found in KML (Figure S5).

Discussion

Summary of Findings

This nationwide study extended the literature by examining the longitudinal patterns of AD prescription fills of nearly 9000 pregnancies with AD treatment prior to pregnancy with underlying depressive and/or anxiety disorders in Norway. Based on AD prescription fills, we identified two distinct discontinuing groups, one interrupting and one continuing the AD treatment. Using the average usual daily dose, we identified one discontinuing, one reducing and one

continuing AD pattern. Discontinuation of AD treatment during pregnancy is highly prevalent in our study population (60–80%). The identified trajectories were highly consistent when different modelling strategies were used and the findings remain robust across different assumptions. We identified various factors associated with AD fill trajectory group membership, including AD treatment regimen and comedication prior to pregnancy, as well as other maternal characteristics (notably reproductive history).

Interpretations

We investigated different longitudinal measurements for trajectory modelling. The AD exposure status seems to be suitable for determining distinct patterns.[35] The average usual daily dose, by contrast, provides additional information on the dose-dependent aspect of the trajectories.[22,35] Among pregnant women in Norway, the extent of the discontinuation of AD treatment during pregnancy, at nearly 80% seems to be greater than what has been observed in France (ie, 55.8%) but may be lower than in the UK, where only 10% of women remained on AD treatment at the beginning of their third trimester.[4,35] However, Norwegian clinical guidelines recommend against discontinuing regular psychotropic drugs without consulting the attending physician(s), and discourage switching from one psychotropic drug to another.[36] Added to that, the timing of the discontinuation of treatment varied substantially in our study population, as seen in AD fill trajectories. One third of our sample discontinued their AD treatment near the start of pregnancy, and nearly half of them stopped treatment prior to delivery. By comparison, pregnant women in France tend to discontinue their AD treatment in the second or third trimester.[35] These differences might reflect how the pregnant women with mental health diagnoses in different countries were followed-up during pregnancy. In Norway, pregnant women with mental disorders are mainly followed-up by their GPs (ie, main prescribing physicians) and in moderate to severe cases, by psychiatric specialists.[37,38]

Another of our study's main findings is that the fill trajectories are highly associated with the dose of AD prior to pregnancy, and women using lower doses were more likely to discontinue their treatment. Those results were observed by both the KML modelling on average daily dose and multinomial logistic regression. Similar findings were observed in a cohort of 15,041 pregnancies recruited in the US using OptumLabs Data Warehouse.[39] Using lower doses of AD may suggest that discontinuers have milder conditions of depression or anxiety or that ADs were potentially maintained at low dose for long time without appropriate follow-up. Even so, both interrupters and late discontinuers showed similar patterns and characteristics prior to pregnancy; they had discontinued their treatment quite late during pregnancy, potentially due to the severity of their depression and/or anxiety because their AD doses at baseline were higher than among early discontinuers. The presence of interrupters in our population raises concerns about the negative effects of intrauterine drugs and the potential recurrence of depression and/or anxiety after the discontinuation of AD treatment.[4,35] Future studies should examine associated outcomes following those distinct patterns of discontinuation.

Among the factors associated with AD fill trajectory group membership compared to early discontinuers, those related to AD treatment regimen (eg, dose and type of AD) and comedication prior to pregnancy were the strongest. That information can be easily extracted from the medical and prescription fill history and should be made available to physicians at the time of consultation. Anticipating the behaviors of pregnant women toward AD treatment during pregnancy is pivotal because early counselling may help to reduce the discontinuation of AD treatment without clinical justification.

Our study had multiple strengths. First, it had a larger sample size than in some prior studies, and it examined AD prescription fills specifically in women with depression and/or anxiety. Moreover, we used data covering an entire nation, and registry-linked data allowed us to explore various potential factors associated with the identified trajectories. Second, by employing the PRE2DUP method, we had more flexibility than had we used published methods based on the assumption of one DDD per day.[16] We expanded the PRE2DUP method to Norwegian prescription data and presented an application to a population of pregnant women. Third, by using dispensation data from pharmacy records, we eliminated the potential for recall and selection bias associated with survey data (ie, data from interviews and questionnaires). Fourth, by linking prescription data with outpatient diagnosis from primary and secondary care, we were able to model AD filling trajectories specifically in women with depression and/or anxiety. That consideration was important because AD filling status and dose trajectories may differ in women with other indications for use (eg, eating disorders).

Some limitations of our study should be discussed as well. First, medications dispensed to an individual during a hospital stay or medications administered at outpatient clinics and hospitals are not recorded in NorPD, which may result in false gaps in exposure. Second, in Norway one prescription fill can cover up to three months, if not longer when specified by the prescribers. We set the maximum duration of each dispensation of treatment to 150 days, as has been done in other studies using the PRE2DUP method, to limit the inclusion of duplicated dispensations. Ultimately, only 7% of AD prescription fills were affected. Third, we did not know when, if at all, the dispensed drugs were used by pregnant women based solely on dispensation data. Therefore, discontinuation prior to the estimated end of drug use period might lead to misclassification across discontinuation groups. A previous study has reported high agreement between AD prescription fills in NorPD and self-reported AD use in the Norwegian Mother and Child Cohort Study, especially from week 21 gestation to delivery.[40] By extension, our assumption that the dispensing date was the first day that the patient had taken the drug from the given dispensation is not necessarily true. Fourth, we lacked an ideal approach to define the potential daily dose if the patient had received an AD with a unit strength equal to the DDD (eg, patient filled tablets of 20 mg fluoxetine, with the DDD of fluoxetine equaling 20 mg, while the maximum daily dose for depression in adult may be increased to 60 mg). We tested two assumptions of one DDD and two DDDs per day; however, neither of the assumed daily amounts of consumption accurately reflects the prescribed dose or the actual dose consumed. Such discrepancies may have resulted in the misclassification of treatment continuation vs discontinuation. Even so, misclassification bias seems modest because the groups were identical when the assumed daily consumption was changed from one DDD to two DDDs. Fifth, we did not assess AD switching or add-on patterns in our study. Patients who switched and patients receiving add-on therapy were likely to be classified as continuers. Future research could use individual drug use periods to explore those patterns. Sixth, because prescribed dose was not available in our data, we could not capture changes in dose within one ADUP. Seventh and last, to overcome the potential problem of different gestational length across pregnancies, we selected pregnancies with gestational lengths exceeding 32 weeks and included only the first 32 weeks of gestation within the pregnancy window. As a result, we could not infer filling patterns at the end of pregnancy nor those of pregnancies lasting less than 32 weeks. In addition, our analyses do not capture potential discontinuation between week 32 and the end of pregnancy. However, discontinuation proximal to delivery is relatively rare because clinical guidelines in Norway strongly discourage this practice.[37]

Conclusion

Using the PRE2DUP method in Norwegian prescription data, we identified distinct AD fill and dose patterns. The AD regimen at baseline, comedication prior to pregnancy, and other maternal characteristics were strongly associated with the trajectories. Knowledge about factors associated with utilization trajectories might be useful for health-care personnel counselling women about AD use in pregnancy.

Abbreviations

AD, antidepressants; ADUP, antidepressant use period; ATC, anatomical therapeutic chemical; DDD, defined daily dose; FDE, fluoxetine dose equivalent; GBTM, group-based trajectory modelling; ICD-10, International Classification of Diseases, version 10; ICPC-2, International Classification of Primary Care, version 2; KML, longitudinal k-means trajectory modelling; KUHR, Norway Control and Payment of Health Reimbursement; MBRN, Medical Birth Registry of Norway; NPR, Norwegian Patient Registry; NorPD, Norwegian prescription database; PRE2DUP, from prescription to drug use period; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

Data Sharing Statement

The data in this project were delivered by the registry holders to the researchers as pseudonymized data files. Data are available upon request to the registry holders, provided legal and ethical approvals.

Ethics

The study was approved by the Regional Committee for Research Ethics in South Eastern Norway (approval number 2018/140/REK Sør Øst) and by the Data Protection Officer at the University of Oslo (approval number 58033). Data were handled in accordance with the General Data Protection Regulation.

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