Antidepressant Medication Continuation During Pregnancy and Perinatal Outcomes, Including Gestational Weight Gain, Gestational Diabetes and Birth Weight

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Abstract

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Background: Every year, approximately 7–8% of pregnant women in the US (~300,000 women) use antidepressants. Use of certain antidepressants in non-pregnant populations has been associated with weight loss, whereas others have been associated with weight gain; in pregnant women, the association of antidepressant use and gestational weight gain has not been thoroughly investigated. Some studies have observed greater risk of gestational diabetes (GDM) and smaller birthweight associated with prenatal antidepressant use. However, most studies compared women using antidepressants with unexposed pregnant women from the general population, most of whom did not have depression or anxiety, likely leading to confounding by indication.

Objective: To assess the association of antidepressant continuation in pregnancy with gestational weight gain, GDM, and infant birthweight among women using antidepressants before pregnancy.

Methods: We conducted a retrospective cohort study of singleton live births from 2001–2014 to women enrolled in an integrated healthcare system using electronic health data and linked Washington State birth records. This included women with ≥1 antidepressant prescription, filled ≤6 months before pregnancy. Women with any antidepressant fill during pregnancy were considered “exposed” (n=1,772); those without were “unexposed” (n=1,249). We calculated mean differences and relative risks (RR) using generalized estimating equations with inverse probability of treatment weighting to account for baseline characteristics, including indicators of pre-pregnancy mental health status.

Results: Women who continued versus discontinued antidepressants during pregnancy had similar risks of inadequate and excessive gestational weight gain (RR 0.95, 95% confidence interval [CI] 0.80–1.13 and RR 1.06, 95% CI 0.98–1.14, respectively). Continuing antidepressant use in pregnancy was not associated with greater risk of GDM (RR: 1.10, 95% CI: 0.84–1.44), with the potential exception of venlafaxine continuation (RR 1.52, 95% CI 0.87–2.68). We observed greater risk of small for gestational age associated with antidepressant continuation among female infants (RR: 1.65, 95% CI: 1.09-2.50), but not among male infants (RR: 0.86, 95% CI: 0.58-1.27). After restricting continuers to women with fills in all three trimesters, we observed a decreased risk of large for gestational age (RR: 0.68, 95% CI: 0.52–0.91) and macrosomia (RR: 0.49, 95% CI: 0.25–0.99) among continuers compared with discontinuers. There was a suggestion of lower risk of large for gestational age among female infants (RR: 0.74, 95% CI: 0.55-1.00) but not among male infants (RR: 0.91, 95% CI: 0.66-1.26).

Conclusions: Our study indicates that women and their providers do not need to be concerned about antidepressant continuation causing dramatic increases in risk of the outcomes studied here. We observed evidence of moderately increased risk of GDM and small for gestational age specific to some subgroups of continuers, but additional research is needed to confirm these findings.

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We thank Sharon Fuller for pulling the information from the KPWA database to build our cohort, as well as programming all our initial variables. We thank Dr. Greg Simon and Christine Stewart for their advice about how to best operationalize mental health indicators, including pragmatic advice about how to retrieve this information from the databases. We also acknowledge the Mental Health Research Network for their resources that we used to define mental health diagnoses, procedures, and medications. We thank James Fraser for his help with Institutional Review Board applications to both Kaiser Permanente Washington and the Washington State Department of Health.

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CHAPTER 1:

Antidepressant continuation in pregnancy in relation to maternal gestational weight gain

Antidepressant continuation in pregnancy in relation to maternal gestational weight gain

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ABSTRACT

Background: Approximately 7-8% of pregnant women in the US use antidepressants. In non-pregnant women, some antidepressants are associated with weight gain, whereas others are associated with weight loss. Excessive gestational weight gain can lead to greater risk of macrosomia and birth injury. Inadequate gestational weight gain may result in low birthweight. The few studies of gestational weight gain and antidepressant use in pregnancy were underpowered and unable to account for maternal mental health, possibly leading to confounding by indication.

Objective: To assess the association of antidepressant continuation in pregnancy with gestational weight gain among women using antidepressants before pregnancy.

Methods: We conducted a retrospective cohort study of singleton live births from 2001–2014 to women enrolled in an integrated healthcare delivery system. Data were obtained from electronic health records and linked Washington State birth records. Among women with ≥1 antidepressant fill ≤6 months prior to pregnancy onset, women with an antidepressant fill during pregnancy were considered “continuers” (n=1686); women without were “discontinuers” (n=1198). We calculated mean differences in gestational weight gain and relative risks (RR) of inadequate and excessive weight gain (defined according to Institute of Medicine criteria). We used generalized estimating equations with inverse probability of treatment weighting to account for baseline characteristics, including mental health indicators.

Results: As compared with women who discontinued antidepressants, women who continued in pregnancy had similar mean weight gain (mean difference: 1.3 lbs, 95% confidence interval [CI]: -0.1 to 2.8 lbs) and similar risks of inadequate and excessive gestational weight gain (RR: 0.95, 95% CI: 0.80–1.13 and RR: 1.06, 95% CI: 0.98–1.14, respectively). Findings were comparable in analyses of specific antidepressant medications and specific trimesters of exposure.

Conclusions: Our findings suggest that women and providers do not need to be concerned about antidepressant continuation in pregnancy negatively impacting gestational weight gain.

INTRODUCTION

Antidepressants are some of the most commonly used medications during pregnancy, with approximately 7–8% of pregnant women in the US exposed, translating to 280,000 to 320,000 exposed pregnancies per year.[1-3] Depression and anxiety are the main indications for use.[3] The American College of Obstetricians and Gynecologists and the American Psychiatric Association caution that the potential risks of antidepressant use in pregnancy are not well understood because most studies have not adequately accounted for maternal mental health status.[4]

Gestational weight gain is an outcome for which the effect of antidepressant use in pregnancy is unknown. In non-pregnant populations, studies suggest that some antidepressants (e.g. mirtazapine, paroxetine, sertraline) are associated with weight gain, whereas others (e.g. bupropion, fluoxetine) are associated with weight loss.[5-10] Antidepressants may lead to either weight gain or weight loss by changing appetite and metabolism[11] through differing action on monoamines, which are known to affect appetite, satiety, and feeding behavior.[5,12,13] The few studies of the association of gestational weight gain with antidepressant use in pregnant populations were not able to sufficiently account for underlying maternal depression and anxiety or were inadequately powered.[14-17] Not accounting for underlying maternal depression and anxiety may lead to confounding by indication, as depression and anxiety may be independently associated with either inadequate or excessive gestational weight gain.[18,19]

Inadequate gestational weight gain is important because it increases risk of low birthweight and subsequent life course adverse health consequences for the infant, whereas excessive gestational weight gain is associated with greater risk of gestational diabetes, macrosomia, and birth injuries, as well as greater lifetime risk of obesity and type 2 diabetes for the woman and her child.[20-23] Given the large number of exposed women and the scope of possible adverse consequences, there is a need for further studies of the association of antidepressant use during pregnancy with gestational weight gain.

To address these uncertainties, we utilized electronic health data and linked state birth records to assess the association of continuing, versus discontinuing, antidepressant use during pregnancy with gestational weight gain. We used inverse probability of treatment weighted (IPTW) models to account for maternal characteristics, including mental health, and assessed associations for individual antidepressants and trimesters of exposure.

METHODS

Overview

We conducted a retrospective cohort study with data from Kaiser Permanente Washington (KPWA, formerly Group Health Cooperative), an integrated healthcare delivery system in Washington State. We required all women to be enrolled ≥6 months prior to onset of pregnancy and an antidepressant prescription fill during that period, which allowed the analyses to: (1) address the clinical decision of whether to continue antidepressants in pregnancy that women and their providers face, and (2) limit bias due to confounding by indication. Electronic health data from KPWA were linked to Washington State birth records and provided the information necessary for our study.[24] The study was approved by the KPWA Institutional Review Board and the Washington State Department of Health Institutional Review Board (both with waivers of consent).

Study Population and Design

Our cohort was drawn from live births from January 1, 2001 through December 31, 2014 to women enrolled in KPWA. KPWA maintains extensive data on its members including patient enrollment, demographics, encounters, diagnoses, procedures, and prescription fills. Nearly two-thirds of members receive comprehensive care from KPWA healthcare providers through the Integrated Group Practice, and for these members we were able to ascertain additional data on vital signs and responses to mental health questionnaires. We required KPWA births to be linked to a Washington State birth record because this was the source for gestational age information necessary to determine timing of antidepressant fills relative to pregnancy onset. Because some women contributed multiple births to our cohort (<1% had three births, 7% had two births, and 93% had one birth) our unit of analysis was technically “births” rather than “women”, but we have used the terms interchangeably here.

We wanted to limit the study population to women taking antidepressants for depression or anxiety, as 80–90% of antidepressant use among women is for these indications.[1,3] Because women without a healthcare encounter before pregnancy did not have a chance to receive a diagnostic code for depression or anxiety (Supplementary Table 1.1), we did not require such a code. However, we excluded 138 women who did not have a depression or anxiety diagnostic code in the past two years but had a

code for another health condition that is an accepted antidepressant indication (Figure 1.1, diagnostic codes in Supplementary Table 1.2).

We defined the time window in which exposure to antidepressants was relevant to gestational weight gain as the start of pregnancy through four weeks before delivery (Figure 1.2). This allowed time for a potential effect of exposure on outcome. We excluded 30 women with their first antidepressant fill in pregnancy after this exposure window (Figure 1.1).

Pre-pregnancy body mass index (BMI), an index that estimates adiposity based on pre-pregnancy weight and maternal height, was needed to calculate adequacy of gestational weight gain. Our analyses of adequacy of gestational weight gain were restricted to births during 2003–2014, when maternal height was available on the birth certificate (Figure 1.1).

Exposure

Medication exposure information came from pharmacy dispensing data, and included antidepressant name, date of prescription fill, and number of days supplied. We considered women with any antidepressant prescription fill during the exposure window to be “continuers” and women without a fill to be “discontinuers” (Figure 1.2).

Exposure included selective serotonin reuptake inhibitors (SSRIs; citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline), serotonin-norepinephrine reuptake inhibitors (SNRIs; desvenlafaxine, venlafaxine), and other antidepressants (bupropion, mirtazapine). We did not include trazodone or tricyclic antidepressants because they are primarily used to treat sleep and pain disorders, respectively. We did not require continuers to fill the same antidepressant during the six months prior to pregnancy and the exposure window. Antidepressants are most commonly filled in 30, 60, or 90 days’ supply at Kaiser Permanente Washington. Women with an antidepressant fill that overlapped into pregnancy but without a fill during pregnancy were categorized as discontinuers, an assumption we addressed with a sensitivity analysis (described below).

Outcomes

Weight gain was ascertained from the birth certificate, along with pre-pregnancy BMI, as previously defined. Adequacy of gestational weight gain was defined according to the Institute of Medicine guidelines,[25] which recommend adequate weight gain ranges according to pre-pregnancy BMI category.

Covariates

The following covariates were also ascertained from birth records: parity, maternal race/ethnicity, maternal education, and pre-pregnancy weight.

We obtained covariates from KPWA electronic health databases including: (1) at the time of delivery: birth year, maternal age, and baby's sex, and (2) prior to pregnancy: membership in the Integrated Group Practice, Medicaid insurance coverage, chronic disease diagnoses, smoking and substance abuse diagnoses, mental health diagnoses, psychotropic prescription medication fills, prescription fills of medications that may be associated with weight gain, and utilization of psychotherapy, psychiatry, and inpatient psychiatric hospitalization (definitions in Supplementary Tables 1.1, 1.3, and 1.4). We allowed collection of covariate data to go back in time as long as women were continuously enrolled.[26]

The Patient Health Questionnaire-9 (PHQ-9) is a commonly-used, 9-item, self-reported depression screening questionnaire.[27] PHQ-9 records were only available for women in the Integrated Group Practice, where they were used from approximately 2008 onwards. During this time period, KPWA did not practice universal depression screening, but rather the PHQ-9 was typically used when the patient initially presented with symptoms of depression and periodically during follow-up to monitor response to therapy.

Statistical Analysis

We described characteristics of eligible women by exposure status. We then calculated standardized mean differences (SMDs) both with and without IPTW. SMDs quantify the difference between two groups without being affected by sample size.[28]

Because PHQ-9 scores were available only for a sub-set of women in our cohort, we described PHQ-9 scores in the two years prior to pregnancy but did not include them in models.

We used generalized estimating equations with an exchangeable correlation matrix for all regression analyses, to account for the correlation among multiple births to the same woman.[29] We calculated mean differences and 95% confidence intervals (CIs) of the association of continuing antidepressant use in pregnancy, as compared with discontinuing use, with gestational weight gain using an identity link function. For the analyses of inadequate and excessive gestational weight gain with antidepressant continuation in pregnancy, we used a modified Poisson (log) link function to calculate relative risks (RRs) and 95% CIs.

We used IPTW models in order to include more potential confounders than a multivariable adjusted model would be able to include (Methods Appendix 1.1).[28] Briefly, IPTW uses propensity scores to weight observations in the model by their likelihood of exposure to improve balance in baseline covariates between exposed and unexposed.

Covariates were chosen *a priori* based on our knowledge and previous literature, after considering sample size limitations. For the overall analyses for all our outcomes, we weighted the IPTW model by all variables in Variable Set 3 (Supplementary Table 1.5).

We conducted sub-analyses comparing women who continued specific antidepressants with discontinuers (the group of women who discontinued any antidepressant, as in the overall analysis). Additionally, we compared outcomes in women who continued antidepressant use in specific trimesters (regardless of use in other trimesters) with the same group of discontinuers used in the overall analysis. We used the smaller Variable Set 2 for these sub-analyses due to smaller numbers of exposed women (Supplementary Table 1.5). For analyses of paroxetine and venlafaxine, the analyses with the smallest number of users, we chose a parsimonious model based on which characteristics had SMDs comparing continuers and discontinuers of ≥0.10 (see Supplementary Table 1.6 for SMD values), and from these variables, we included those associated with a >10% change in the mean difference in gestational weight gain after their addition to the crude model (Variable Set 1 in Supplementary Table 1.5). For consistency, we used this model for analyses of all outcomes for these two antidepressants.

Sensitivity analyses

We conducted sensitivity analyses with IPTW models weighted for characteristics in Variable Set 2 (Supplementary Table 1.5). First, we defined exposure as receiving ≥2 antidepressant fills to address potential exposure misclassification, which could arise if women who only filled once in pregnancy never actually took the medication. Second, we restricted the sample to women with an anxiety or depression diagnostic code in the two years before pregnancy. Third, we adjusted for gestational age, because studies that accounted for underlying mental health status have found an association of prenatal antidepressant use with shorter gestational age.[30,31] We did not adjust for gestational age in our main analysis, as it is in the causal pathway, and adjustment could lead to collider-stratification bias.[32] Fourth, to address the possibility of lingering effects of medication in the body and the assumption that women whose last fill overlapped pregnancy stopped before pregnancy, we conducted a sensitivity analysis that re-categorized these women as continuers. Fifth, we ran analyses separately for continuers with less than 50% of days covered with antidepressant fills and continuers with greater than or equal to 50% of days covered, to address the issue of duration-response by proportion of days exposed. For fills that only partially overlapped with pregnancy, we prorated the days covered. For these analyses, we only included women who had a fill for one specific antidepressant during the exposure window because it was difficult to distinguish sequential from simultaneous use for women who filled multiple antidepressants. Sixth, we ran a multivariable-adjusted model, adjusted for characteristics in Variable Set 2, to assess whether the associations were generally similar. For our continuous weight gain outcome, we adjusted for pre-pregnancy BMI instead of pre-pregnancy weight to address residual confounding, restricting to years when BMI was available.

All statistical analyses were conducted in R version 3.4.2 (R Core Team [https://www.r-project.org]).

Chart Review

We conducted a chart review for a sub-set of our cohort to investigate whether women whose last prescription fill was near the start of pregnancy were truly exposed or unexposed (sub-set described in Methods Appendix 1.2). Out of this sub-set, we randomly sampled 50 women whose last fill in the

perinatal period was before pregnancy but overlapped into pregnancy (classified as discontinuers in the primary analysis) and 50 women whose last fill was in the first 30 days of pregnancy (classified as continuers in the primary analysis). We reviewed charts to assess the timing of discontinuing antidepressant use, to inform whether our exposure classification system for these women was correct.

RESULTS

The source population included 57,743 births. After applying inclusion and exclusion criteria, the eligible population for analyses of mean gestational weight gain consisted of 2,884 births (Figure 1.1), including 1,686 to women who continued antidepressants in pregnancy and 1198 to women who discontinued. The number eligible for the analyses of adequacy of gestational weight gain was 2,632 births (continuers: 1,534, discontinuers: 1,098).

Characteristics of exposed and unexposed women

Women who continued antidepressant medication during pregnancy were similar to discontinuers with respect to baseline factors, with a few exceptions: antidepressant continuers were slightly older, less likely to be nulliparous, and more likely to be non-Hispanic white and have higher education than women who discontinued antidepressants (Table 1.1). Continuers were also more likely than discontinuers to have had a psychiatry visit or filled an antidepressant prescription more than one year before pregnancy (Supplementary Table 1.6). The average length of enrollment prior to pregnancy, during which we allowed collection of covariate data, was 4.2 years (standard deviation [SD]: 4.1 years) for continuers and 4.5 years (SD: 4.3 years) for discontinuers. After weighting, SMDs in baseline characteristics were not meaningfully different between continuers and discontinuers (Supplementary Figures 1.1 and 1.2).

Among continuers, we had a record of a PHQ-9 screening before pregnancy for 361 (~61% of women who could have a record, based on data availability) compared with 284 records among discontinuers (~67% of women who could have a record). Out of a range of zero (no depression) to 27 (severe depression), the mean pre-pregnancy score was 9.5 (SD: 6.6) for continuers and 10.3 (SD: 6.7) for discontinuers.

Counts of continuers filling specific antidepressants and extent of exposure in pregnancy are included in Supplementary Tables 1.7 and 1.8.

Pregnancy weight gain

Continuers had an unadjusted mean gestational weight gain of 30.5 lbs (SD: 16.8 lbs), which was similar to discontinuers (mean: 30.3, SD: 16.1 lbs; Table 1.2). After accounting for potential confounders using IPTW, women who continued antidepressants had a similar amount of weight gain as discontinuers (mean difference: 1.3 lbs, 95% CI: -0.1 to 2.8 lbs, Table 1.2). There was not strong evidence of an association for specific antidepressants or trimesters of exposure.

Approximately 17% of antidepressant continuers and 18% of discontinuers had inadequate gestational weight gain (Table 1.3). There was no association between antidepressant continuation and risk of inadequate weight gain after weighting by confounders (RR: 0.95, 95% CI: 0.80-1.13). Findings from other trimester- and medication-specific analyses were similar. Fifty-four percent of women who continued their antidepressant in pregnancy and 51% of discontinuers had excessive gestational weight gain (RR: 1.06, 95% CI: 0.98-1.14; Table 1.4). We did not find evidence of altered risk of excessive gestational weight gain associated with use of specific antidepressants or during specific trimesters.

Sensitivity analyses

In all sensitivity analyses, as in our main analyses, we did not find evidence of an association between antidepressant continuation in pregnancy and mean gestational weight gain or inadequate or excessive gestational weight gain (Supplementary Tables 1.9, 1.10 and 1.11).

Chart review

We reviewed medical records for 50 women with an antidepressant fill before pregnancy that included enough days' supply to overlap into pregnancy. Forty-two charts (84%) contained information about when the women discontinued their antidepressant. Of those, 36 (72%) had a record stating they discontinued after the start of pregnancy, and the records for the other six stated they discontinued before pregnancy.

Among those who discontinued after the start of pregnancy, 24 (67%) stopped between 4 and 8 weeks gestation. A positive pregnancy test typically prompted discontinuation.

Among 50 charts for women with an antidepressant fill in the first 30 days of pregnancy but no subsequent fill during pregnancy, for 47 we found information indicating they discontinued their antidepressant after the start of pregnancy; the other three did not contain information about timing of discontinuation. Of those who discontinued after the start of pregnancy, 29 (62%) stopped between 4 and 8 weeks gestation, and as in women with overlapping prescriptions, this also typically followed a positive pregnancy test.

DISCUSSION

Overall, we did not find any appreciable difference in gestational weight gain comparing women who continued and discontinued taking antidepressant medications during pregnancy, at least for antidepressants that were commonly used in our study.

Previous literature on the association of antidepressant use with gestational weight gain is sparse; the few available studies were underpowered, did not adequately account for confounding by indication and did not conduct statistical testing comparing the specific groups we are interested in here. In a prospective cohort study by Wisner et al., 23 women who were continuously exposed to SSRIs gained an average of 28.6 lbs, 16 who were exposed for part of pregnancy gained an average of 31.4 lbs, and three women with depression throughout pregnancy who did not take an SSRI gained an average of 17.7 lbs.[14] Suri et al. observed that depressed pregnant women taking antidepressants (n=49) on average gained 32.6 lbs, while depressed women not treated with an antidepressant (n=22) gained an average of 32.1 lbs.[15] A 2002 study by Nulman et al. found that 40 women diagnosed with major depression who used fluoxetine in pregnancy gained an average of 36.2 lbs, while non-depressed women who did not take antidepressants in pregnancy gained an average of 30.6 lbs.[16] Another study by Nulman et al. published in 2012 found that among pregnant women with depression, the 62 who continued venlafaxine gained an average of 37.4 lbs, the 62 who continued SSRIs gained an average of 33.5 lbs, and the 54 who discontinued gained an average of 36.9 lbs.[17] The study by Wisner et al. and the earlier study by Nulman et al. suggest greater gestational weight gain associated with antidepressant use, whereas the

later Nulman et al. and the Suri et al. studies do not find a substantial difference in weight gain, consistent with our findings. The first two studies had particularly small numbers (and therefore their estimates were more prone to variability) and included women at higher-risk of adverse outcomes than those in our study. To our knowledge, no studies have assessed risk of inadequate or excessive gestational weight gain associated with antidepressant use in pregnancy.

An association between antidepressants and weight gain is biologically plausible. Antidepressants have high affinity for the histamine receptor H_1 and serotonin receptor 5-HT_{2C}, both of which are thought to impact weight gain.[13] Evidence in non-pregnant populations suggests increased risk of weight gain with use of paroxetine, sertraline, and mirtazapine, particularly with use for ≥4 months.[5-7] Conversely, use of bupropion has been associated with long-term weight loss, and fluoxetine has been associated with weight loss in the first few months of use.[5,7,33,34] However, antidepressant use may have less effect on weight gain in pregnant women, as pregnancy is a unique period when 25–35 pounds of weight gain is biologically normal and healthy. This could explain why we did not observe greater gestational weight gain associated with antidepressant use, even in users of paroxetine and sertraline. We were not able to assess risk in mirtazapine users separately due to small numbers.

Strengths of our study include the use of a large, well-defined study population, availability of prescription fill data (a better indication that the woman took the medication than prescription data alone), extensive information about mental health utilization as an indicator of severity, results of mental health screening tests for a portion of the population, and the ability to conduct a number of sensitivity analyses, which were largely consistent with our findings.

Our study had several limitations. There were small numbers of women who had used some specific antidepressant medications, which limited power to detect moderate associations. Women with more severe depression or anxiety may have been more likely to continue antidepressants than those with lower severity, which could have led to residual confounding. If women with only one antidepressant fill in pregnancy did not actually consume the medication, there could be misclassification of exposure, potentially attenuating our risk estimates. Our chart review indicated that most women whose last prescription of an antidepressant medication overlapped the beginning of pregnancy had some exposure (typically 2–6 weeks of exposure after conception), but we classified them as unexposed. Considering

that this is a short length of exposure very early in pregnancy, it may have been ideal to exclude them from both the exposed and unexposed groups. Also, our study population was largely non-Hispanic white and commercially insured, and we were limited to live births, which may limit generalizability of the findings.

Additional risks and benefits should be considered when deciding whether to continue antidepressants in pregnancy, including infant outcomes and the woman's mental health, but our study suggests that pregnant women and their providers likely do not need to be concerned about continuation of commonly used antidepressants affecting gestational weight gain.

Table 1.1. Selected baseline characteristics of women with births eligible for the analysis of mean gestational weight gain.

Covariates	No antidepressant fill in pregnancy (n=1198)	Antidepressant fill in pregnancy (n=1686)	Unweighted SMD	Inverse probability of treatment weighted SMD
Maternal age at delivery, mean (SD)	29.7 (5.8)	31.4 (5.5)	0.301	0.009
Number of prior pregnancies (parity), n (%)				
Zero	534 (44.6)	622 (36.9)	0.159	<0.001
One	417 (34.8)	596 (35.6)	0.010	0.005
Two or more	241 (20.1)	462 (27.5)	0.142	0.016
Maternal race/ethnicity, n (%)				
Hispanic	83 (7.4)	98 (5.9)	0.046	0.006
Non-Hispanic Asian	33 (3.1)	26 (1.6)	0.084	0.005
Non-Hispanic black	47 (4.3)	36 (2.1)	0.105	0.004
Non-Hispanic Native American	15 (1.8)	25 (2.0)	0.020	0.004
Non-Hispanic Native Hawaiian or Other Pacific Islander	20 (2.2)	21 (1.3)	0.036	0.003
Non-Hispanic white	993 (83.4)	1473 (88.2)	0.124	0.005
Maternal education level, n (%)				
High school diploma/general equivalency degree or less	255 (21.4)	305 (18.2)	0.081	0.004
Some college	471 (39.6)	617 (36.9)	0.056	0.002
Bachelor's degree or more	464 (39.0)	752 (44.9)	0.120	0.001
Medicaid, n (%)	47 (3.9)	54 (3.2)	0.039	0.001
Pre-pregnancy weight in lbs, mean (SD)	166.2 (44.5)	169.1 (43.5)	0.066	0.007
During the two years prior to pregnancy, n (%)				
Alcohol abuse disorder diagnostic code	52 (4.3)	74 (4.4)	0.002	0.009
Tobacco use disorder diagnostic code	159 (13.3)	234 (13.9)	0.018	<0.001
Drug abuse disorder diagnostic code	48 (4.0)	60 (3.6)	0.023	<0.001
Depression disorder diagnostic code	868 (72.5)	1233 (73.1)	0.015	0.002
Anxiety disorder diagnostic code	463 (38.6)	716 (42.5)	0.078	0.003
Obsessive compulsive disorder diagnostic code	22 (1.8)	56 (3.3)	0.094	0.020
Post-traumatic stress disorder diagnostic code	40 (3.3)	55 (3.3)	0.004	0.002
Bipolar disorder diagnostic code	56 (4.7)	76 (4.5)	0.008	0.008
During the year prior to pregnancy, n (%)				
Any fill of antipsychotic medication	21 (1.8)	38 (2.3)	0.036	0.002
Any fill of benzodiazepine medication	266 (22.2)	410 (24.3)	0.050	0.002
Any fill for mood stabilizer medication	59 (4.9)	89 (5.3)	0.016	0.015
Any fill for medication associated with weight gain	174 (14.5)	258 (15.3)	0.022	<0.001
Any fill for diabetes medication	36 (3.0)	62 (3.7)	0.037	<0.001
Any psychotherapy visit	225 (18.9)	285 (16.9)	0.049	0.003
Any psychiatry visit	173 (14.4)	217 (12.9)	0.045	0.004
Any inpatient psychiatric hospitalization	9 (0.8)	17 (1.0)	0.028	0.011

SD: Standard deviation; SMD: Standardized mean difference

If the SMD was ≥0.10, a standard cut point,[28] we considered the two groups to be substantially different. Weighted SMDs <0.10 indicate that we had achieved good balance in terms of measured baseline characteristics between births to exposed and unexposed women.

This table contains the study population for the analysis of mean gestational weight gain. The study population for the analyses of adequacy of gestational weight gain excluded some births presented in this table (Figure 1.1).

This table includes a subset of all covariates that were used to create the inverse probability of treatment weights and included in the overall regression models (Variable Set 3 in Supplementary Table 1.5). The full version of this table (with all included characteristics) is Supplementary Table 1.6.

Diagnostic codes for conditions are listed in Supplementary Table 1.1. Specific medications in medication categories are listed in Supplementary Table 1.3. Definitions of mental health care utilization are described in Supplementary Table 1.4.

Table 1.2. Association of antidepressant continuation in pregnancy with mean maternal gestational weight gain.

	No.	Weight gain (lbs) Mean (SD)	Crude mean difference in lbs (95% CI)	Inverse probability of treatment weighted mean difference (95% CI)
No antidepressant fill in pregnancy	1198	30.3 (16.1)	ref	ref
Any antidepressant fill in pregnancy	1686	30.5 (16.8)	0.4 (-0.8 to 1.7)	1.3 (-0.1 to 2.8)[a]
SSRIs	1459	30.5 (16.7)	0.5 (-0.9 to 1.8)	1.0 (-0.4 to 2.4)[b]
Citalopram	362	31.7 (15.3)	1.4 (-0.5 to 3.2)	1.3 (-0.9 to 3.5)[b]
Fluoxetine	487	30.2 (17.7)	0.6 (-1.7 to 3.0)	1.2 (-1.9 to 4.2)[b]
Paroxetine	152	27.8 (14.9)	-2.5 (-5.0 to 0.0)	-2.0 (-4.5 to 0.6)[c]
Sertraline	525	30.1 (17.1)	0.2 (-1.7 to 2.0)	0.9 (-1.1 to 2.9)[b]
Bupropion	234	29.0 (17.2)	-1.0 (-3.5 to 1.6)	1.0 (-1.7 to 3.6)[b]
Venlafaxine	103	29.0 (18.9)	-1.3 (-5.2 to 2.6)	-1.2 (-6.1 to 3.8)[c]
Any first trimester fill	1461	30.8 (16.8)	0.7 (-0.6 to 2.0)	1.1 (-0.2 to 2.5)[b]
Any second trimester fill	1188	29.8 (15.7)	-0.4 (-1.7 to 0.8)	0.2 (-1.2 to 1.6)[b]
Any third trimester fill	1130	29.5 (15.7)	-0.7 (-2.0 to 0.6)	-0.1 (-1.4 to 1.3)[b]
Fill in all trimesters	860	29.8 (15.6)	-0.5 (-1.9 to 0.9)	0.2 (-1.3 to 1.7)[b]

lbs: pounds; SD: standard deviation; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors

Numbers for specific medications may add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four), and categories are overlapping.

SSRI antidepressants also include escitalopram and fluvoxamine, and other types of antidepressant types include mirtazapine and desvenlafaxine, but there were too few births exposed to these medications to present separately here.

[a]Weighted by characteristics included in Variable Set 3 in Supplementary Table 1.5.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 1.5.

[c]Weighted by characteristics included in Variable Set 1 in Supplementary Table 1.5.

Table 1.3. Association of antidepressant continuation in pregnancy with inadequate maternal gestational weight gain.

	No.	No. (%) with inadequate weight gain	Crude RR (95% CI)	Inverse probability of treatment weighted RR (95% CI)
No antidepressant fill in pregnancy	1098	197 (18%)	ref	ref
Any antidepressant fill in pregnancy	1534	256 (17%)	0.93 (0.79-1.10)	0.95 (0.79-1.13)[a]
SSRIs	1329	218 (16%)	0.91 (0.77-1.09)	0.94 (0.78-1.12)[b]
Citalopram	344	51 (15%)	0.84 (0.63-1.11)	0.93 (0.67-1.29)[b]
Fluoxetine	455	76 (17%)	0.92 (0.72-1.17)	0.99 (0.77-1.28)[b]
Paroxetine	109	21 (19%)	1.07 (0.70-1.62)	0.90 (0.57-1.44)[c]
Sertraline	480	86 (18%)	1.00 (0.79-1.26)	0.99 (0.77-1.29)[b]
Bupropion	215	43 (20%)	1.12 (0.83-1.50)	0.96 (0.67-1.38)[b]
Venlafaxine	90	19 (21%)	1.19 (0.79-1.82)	1.35 (0.85-2.16)[c]
Any first trimester fill	1316	216 (16%)	0.91 (0.77-1.09)	0.93 (0.78-1.11)[b]
Any second trimester fill	1091	197 (18%)	1.01 (0.85-1.20)	1.01 (0.84-1.22)[b]
Any third trimester fill	1032	192 (19%)	1.04 (0.87-1.25)	1.04 (0.86-1.26)[b]
Fill in all trimesters	774	148 (19%)	1.06 (0.88-1.29)	1.07 (0.87-1.32)[b]

RR: relative risk; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors
Numbers for specific medications may add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four), and categories are overlapping.
SSRI antidepressants also include escitalopram and fluvoxamine, and other types of antidepressant types include mirtazapine and desvenlafaxine, but there were too few births exposed to these medications to present separately here.

[a]Weighted by characteristics included in Variable Set 3 in Supplementary Table 1.5.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 1.5.

[c]Weighted by characteristics included in Variable Set 1 in Supplementary Table 1.5.

Table 1.4. Association of antidepressant continuation in pregnancy with excessive maternal gestational weight gain.

	No.	No. (%) with excessive weight gain	Crude RR (95% CI)	Inverse probability of treatment weighted RR (95% CI)
No antidepressant fill in pregnancy	1098	564 (51%)	ref	ref
Any antidepressant fill in pregnancy	1534	828 (54%)	1.05 (0.98-1.13)	1.06 (0.98-1.14)[a]
SSRIs	1329	719 (54%)	1.06 (0.98-1.14)	1.06 (0.98-1.15)[b]
Citalopram	344	194 (56%)	1.09 (0.98-1.22)	1.07 (0.94-1.22)[b]
Fluoxetine	455	247 (54%)	1.06 (0.96-1.18)	1.04 (0.93-1.17)[b]
Paroxetine	109	53 (49%)	0.94 (0.76-1.15)	0.93 (0.73-1.18)[c]
Sertraline	480	252 (53%)	1.02 (0.92-1.13)	1.05 (0.94-1.17)[b]
Bupropion	215	111 (52%)	1.00 (0.86-1.15)	1.10 (0.94-1.27)[b]
Venlafaxine	90	49 (54%)	1.10 (0.94-1.30)	1.05 (0.83-1.33)[c]
Any first trimester fill	1316	713 (54%)	1.05 (0.98-1.14)	1.06 (0.98-1.15)[b]
Any second trimester fill	1091	570 (52%)	1.02 (0.94-1.10)	1.03 (0.94-1.12)[b]
Any third trimester fill	1032	537 (52%)	1.01 (0.93-1.10)	1.02 (0.93-1.11)[b]
Fill in all trimesters	774	402 (52%)	1.01 (0.92-1.10)	1.02 (0.93-1.13)[b]

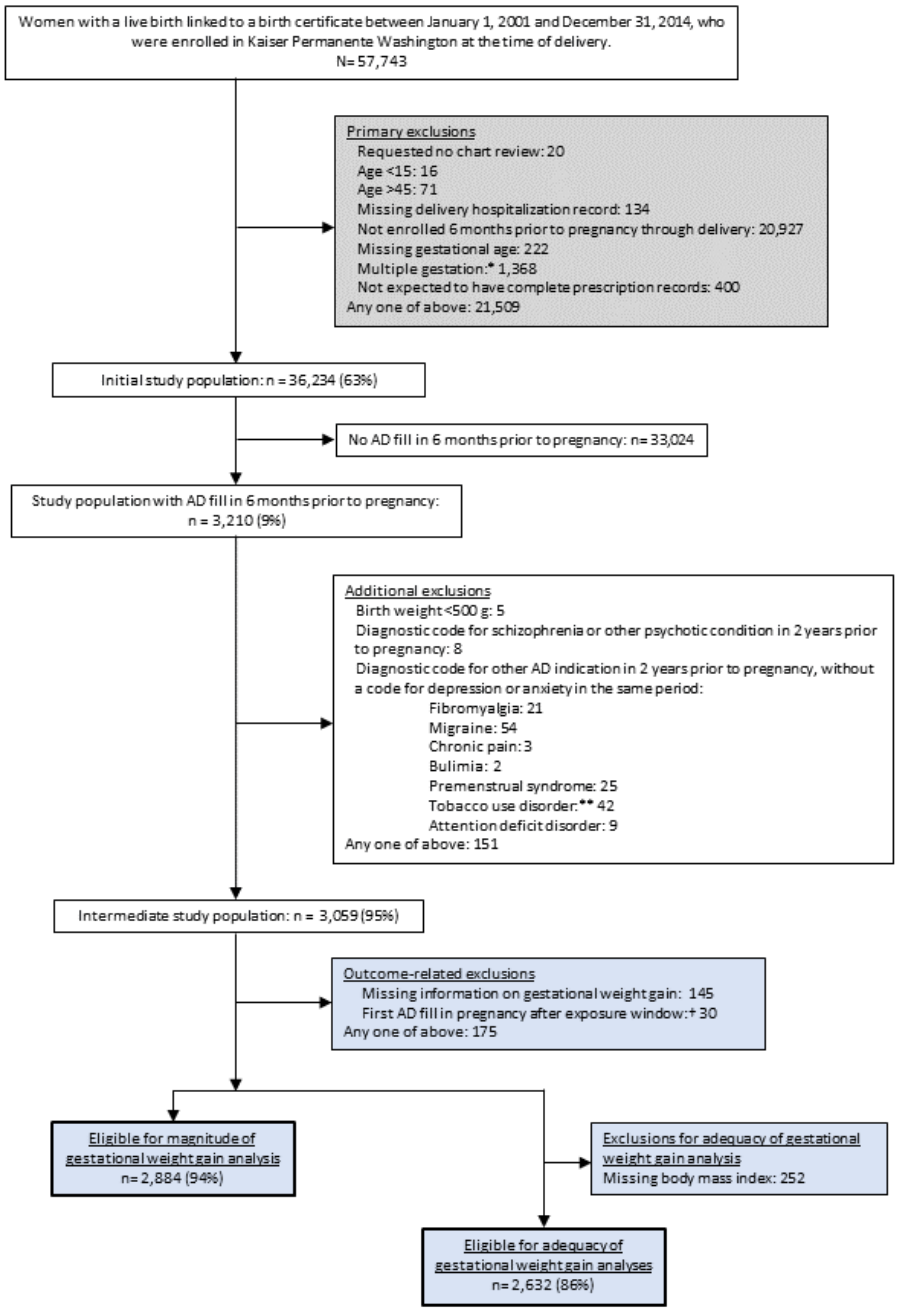
RR: relative risk; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors
Numbers for specific medications may add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four), and categories are overlapping.
SSRI antidepressants also include escitalopram and fluvoxamine, and other types of antidepressant types include mirtazapine and desvenlafaxine, but there were too few births exposed to these medications to present separately here.

[a]Weighted by characteristics included in Variable Set 3 in Supplementary Table 1.5.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 1.5.

[c]Weighted by characteristics included in Variable Set 1 in Supplementary Table 1.5.

Figure 1.1. Identification of women with singleton, live births and a fill for an antidepressant in the six months prior to pregnancy for analyses of magnitude and adequacy of gestational weight gain.



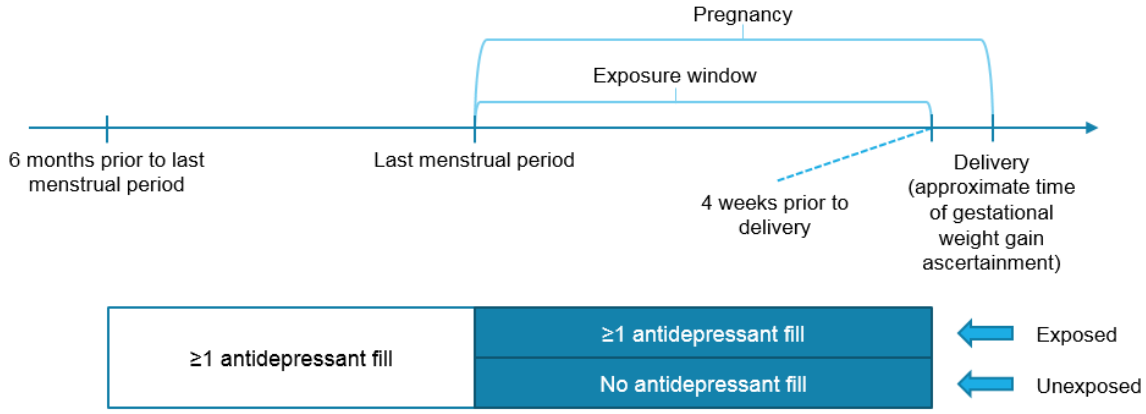
AD: Antidepressant; Antidepressants of interest include paroxetine, sertraline, escitalopram, citalopram, fluoxetine, fluvoxamine, desvenlafaxine, venlafaxine, bupropion, mirtazapine.

*We excluded twin and higher order births because there are different definitions for adequacy of GWG for multiples.

**We only excluded births to women who had a tobacco use disorder code in the 2 years prior to pregnancy if they also had a prescription fill for bupropion, as that is the only antidepressant indicated to treat tobacco use disorder.

†The exposure window spans the start of pregnancy through 4 weeks prior to the end of pregnancy, when total maternal gestational weight is assessed.

Figure 1.2. Study design for analyses of magnitude and adequacy of gestational weight gain.



Supplementary Materials

Supplementary Table 1.1. Disorder diagnostic codes for model covariates.

Characteristic	ICD-9 Code Start of Range	End of Range
Anxiety	300	300.02
	300.2	300.29
	309.21	309.21
	309.24	309.24
Obsessive compulsive disorder (type of anxiety disorder)	300.3	300.3
Posttraumatic stress disorder (type of anxiety disorder)	309.81	309.81
Depression	296.2	296.39
	296.82	296.82
	298.0	298.0
	300.4	300.4
	301.12	301.12
	311	311
	309.0	309.1
	309.28	309.28
Bipolar disorders	296	296.19
	296.4	296.81
	296.89	296.89
	301.11	301.11
	301.13	301.13
Alcohol abuse	291	291.9
	303	303.99
	305.0	305.09
Other drug abuse	292	292.99
	304	304.99
	305.2	305.99
Diabetes mellitus		
During the 6 months prior to pregnancy:	249.0	250.99
	357.2	357.2
	362.01	362.07
	366.41	366.41
Or, during pregnancy, prior to 24 weeks gestation:	249.0	250.99
	362.01	362.07
	357.2	357.2
	366.41	366.41
	648.0	648.0
Chronic hypertension	401.0	405.99
Chronic hypertension diagnosis during the 6 months prior to pregnancy through delivery:	642.0	642.29
	642.70	642.79
Or, hypertension, not otherwise specified diagnosis prior to 20 weeks gestation:	642.9	642.99

Definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Table 1.2. Disorder diagnostic codes for exclusion variables.

Characteristic	ICD-9 Code Start of Range	ICD-9 Code End of Range
Schizophrenic disorders	295	295.99
Other psychoses	297.1	297.1
	297.3	297.9
	301.22	301.22
Other indications for AD use		
Fibromyalgia	729.1	729.1
Migraine	346	346.99
Chronic pain	338.2	338.29
	338.4	338.4
Bulimia	307.51	307.51
Tobacco use	305.1	305.1
	649.0	649.09
Attention deficit disorder	314.0	314.01

Definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Table 1.3. Specific medications included in medication categories for model covariates.

Medication category	Specific medications included
Tricyclics and tetracyclics	amitriptyline
	amoxapine
	clomipramine
	desipramine
	imipramine
	doxepin
	nortriptyline
	protriptyline
	trimipramine
	maprotiline
Benzodiazepines	alprazolam
	chlordiazepoxide
	clonazepam
	clorazepate
	diazepam
	estazolam
	flurazepam
	halazepam
	lorazepam
	oxazepam
	prazepam
	quazepam
	temazepam
	triazolam
	midazolam
	bromazepam
Hypnotic sleep medication	zolpidem
	eszopiclone
	zaleplon
	ramelteon
Mood stabilizers	lithium
	valproic acid
	valproate
	divalproex
	carbamazepine
	lamotrigine
	oxcarbazepine
	gabapentin
	topiramate
	tiagabine
	zonisamide

First generation antipsychotics	chlorpromazine fluphenazine haloperidol loxapine molindone thiothixene perphenazine pimozide thioridazine thiothixene trifluoperazine
Second generation antipsychotics	aripiprazole asenapine clozapine iloperidone olanzapine paliperidone quetiapine risperidone ziprasidone
Other anti-anxiety	hydroxyzine meprobamate meprobamate pregabalin buspirone
Diabetes medications	regular insulin insulin aspart insulin glulisine insulin lispro insulin isophane insulin degludec insulin detemir insulin glargine insulin glargine NovoLog Mix 70/30 (insulin aspart protamine-insulin aspart) Humalog Mix 75/25 (insulin lispro protamine-insulin lispro) Humalog Mix 50/50 (insulin lispro protamine-insulin lispro) Humulin 70/30 (human insulin NPH-human insulin regular) Novolin 70/30 (human insulin NPH-human insulin regular)

Ryzodeg (insulin degludec-insulin aspart)
pramlintide
acarbose
miglitol
metformin
metformin-alogliptin
metformin-canagliflozin
metformin-dapagliflozin
metformin-empagliflozin
metformin-glipizide
metformin-glyburide
metformin-linagliptin
metformin-pioglitazone
metformin-repaglinide
metformin-rosiglitazone
metformin-saxagliptin
metformin-sitagliptin
alogliptin
alogliptin-metformin
alogliptin-pioglitazone
linagliptin
linagliptin-empagliflozin
linagliptin-metformin
saxagliptin
saxagliptin-metformin
sitagliptin
sitagliptin-metformin
sitagliptin and simvastatin
albiglutide
dulaglutide
exenatide
exenatide extended-release
liraglutide
nateglinide
repaglinide
repaglinide-metformin
dapagliflozin
dapagliflozin-metformin
canagliflozin
canagliflozin-metformin
empagliflozin
empagliflozin-linagliptin
empagliflozin-metformin
glimepiride

	glimepiride-pioglitazone glimeperide-rosiglitazone gliclazide glipizide glipizide-metformin glyburide glyburide-metformin chlorpropamide tolazamide tolbutamide rosiglitazone rosiglitazone-glimepiride rosiglitizone-metformin pioglitazone pioglitazone-alogliptin pioglitazone-glimepiride pioglitazone-metformin
Drugs that may cause weight gain[35,36]	Metoprolol Atenolol Propranolol Amlodipine Clonidine Pioglitazone Rosiglitazone fexofenadine cetirizine diphenhydramine prednisone (oral) methylprednisolone (oral) cortisone (oral)

Some definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Table 1.4. Mental healthcare utilization definitions for model covariates.

Mental health utilization type	Definition
Psychotherapy	Includes individual and group therapy. Any of the following CPT codes: 90801, 90802, 90806-9, 90812-15, 90847, 90849, 90853, or 90857, and for 2013 and 2014: 90791, 90832, 90833, 90834, or 90836-9 Does not include: 90804, 90805, 90810, 90811, 90862, and for 2013 and 2014: 90792
Psychiatry	A record of an outpatient visit that meets the two following conditions: 1. Visit is with a provider who is licensed to prescribe medication (MD, DO, ARNP, PA, or PA-C). 2. Visit is with a provider whose specialty is Mental Health or Psychiatry, *or* the encounter takes places in a Mental Health, Behavioral Health Services, or Psychiatry Department.
Inpatient psychiatric hospitalization	Any inpatient encounter with a mental health diagnosis as the principle diagnosis.

Some definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Table 1.5. Sets of characteristics included in models.

Covariates	Variable Set 1[a]	Variable Set 2[b]	Variable Set 3[c]
Year of delivery, continuous (years)	0	X	X
Maternal age at delivery, continuous (years)	X	X	X
Male infant, yes/no	0	X[d]	X
Number of prior pregnancies (parity): Zero One Two or more	X	X	X
Maternal race/ethnicity: Hispanic Non-Hispanic Asian Non-Hispanic black Non-Hispanic Native American Non-Hispanic Native Hawaiian or Other Pacific Islander Non-Hispanic white	X[e]	X[f]	X
Maternal education level: High school diploma/general equivalency degree or less Some college Bachelor's degree or more	0	X	X
Medicaid, yes/no	0	X	X
Integrated Group Practice, yes/no	0	X	X
Chronic hypertension, yes/no	0	0	X
Established diabetes, yes/no	0	0	X
Pre-pregnancy weight, continuous (lbs)	0	X[g]	X[g]
Alcohol abuse disorder diagnostic code during the two years prior to pregnancy	0	0	X
Tobacco use disorder diagnostic code during the two years prior to pregnancy	0	X	X
Drug abuse disorder diagnostic code during the two years prior to pregnancy	0	0	X
Depression disorder diagnostic code during the two years prior to pregnancy	0	X	X
Anxiety disorder diagnostic code during the two years prior to pregnancy	0	X	X
Obsessive compulsive disorder diagnostic code during the two years prior to pregnancy	0	0	X
Post-traumatic stress disorder diagnostic code during the two years prior to pregnancy	0	0	X
Bipolar disorder diagnostic code during the two years prior to pregnancy	0	X	X
Any fill of antipsychotic medication during the year prior to pregnancy	0	X	X
Any fill of benzodiazepine medication during the year prior to pregnancy	0	X	X
Any fill for hypnotic sleep medication during the year prior to pregnancy	0	X	X
Any fill for mood stabilizer medication during the year prior to pregnancy	0	X	X
Any fill for trazodone during the year prior to pregnancy	0	X	X
Any fill for tricyclic antidepressant medication during the year	0	X	X

prior to pregnancy			
Any fill for other anxiety medication during the year prior to pregnancy	0	X	X
Any fill for medication associated with weight gain during the year prior to pregnancy	0	X	X
Any fill for diabetes medication during the year prior to pregnancy	0	X	X
Any psychotherapy visit during the year prior to pregnancy	0	X	X
Any psychiatry visit during the year prior to pregnancy	0	X	X
Any inpatient psychiatric hospitalization during the year prior to pregnancy	0	0	X
Any fill of antipsychotic medication more than one year prior to pregnancy	0	0	X
Any fill of benzodiazepine medication more than one year prior to pregnancy	0	0	X
Any fill for hypnotic sleep medication more than one year prior to pregnancy	0	0	X
Any fill for mood stabilizer medication more than one year prior to pregnancy	0	0	X
Any fill for trazodone more than one year prior to pregnancy	0	0	X
Any fill for tricyclic antidepressant medication more than one year prior to pregnancy	0	0	X
Any fill for other anxiety medication more than one year prior to pregnancy	0	0	X
Any fill for medication associated with weight gain more than one year prior to pregnancy	0	0	X
Any fill for diabetes medication more than one year prior to pregnancy	0	0	X
Any fill for antidepressant medication more than one year prior to pregnancy	X	0	X
Any psychotherapy visit more than one year prior to pregnancy	0	0	X
Any psychiatry visit more than one year prior to pregnancy	X	0	X
Any inpatient psychiatric hospitalization more than one year prior to pregnancy	0	0	X

Categorical characteristics are included in models as categorized, unless otherwise stated.

Diagnostic codes for conditions are listed in Supplementary Table 1.1. Specific medications in medication categories are listed in Supplementary Table 1.3. Definitions of mental health care utilization are described in Supplementary Table 1.4.

[a]Variable Set 1 is used for analyses of paroxetine and venlafaxine only, where the small number of exposed women limited how many variables we could include in the models.

[b]Variable Set 2 is used for sub- and sensitivity analyses (including the multivariable-adjusted analyses) for all outcomes, other than for analyses of paroxetine and venlafaxine.

[c]Variable Set 3 is only used for the overall analyses.

[d]In sensitivity analyses for all outcomes that stratify by infant sex, we did not adjust for infant sex.

[e]We combined non-Hispanic Asian, Hispanic, Non-Hispanic Native American, non-Hispanic Native Hawaiian or Other Pacific Islander, and non-Hispanic black into one group (“Other”) for these analyses due to small numbers.

[f]We combined non-Hispanic Asian, non-Hispanic Native American, and non-Hispanic Native Hawaiian or Other Pacific Islander into one group ("Other") for these analyses due to small numbers.

[g]Pre-pregnancy weight is not adjusted for in analyses of adequacy of gestational weight gain, as body mass index is inherent in the definition of inadequate and excessive gestational weight gain. Also, pre-pregnancy weight is not adjusted for in sensitivity analyses that instead adjust for body mass index.

Supplementary Table 1.6. Full version of baseline characteristics of women with births eligible for the analysis of mean gestational weight gain.

Covariates	No antidepressant fill in pregnancy (n=1198)	Antidepressant fill in pregnancy (n=1686)	Unweighted SMD	Inverse probability of treatment weighted SMD
Year of delivery in years, mean (SD)	2008 (3.8)	2008 (3.7)	0.030	0.002
Maternal age at delivery, mean (SD)	29.7 (5.8)	31.4 (5.5)	0.301	0.009
Male infant, n (%)	598 (50.0)	875 (52.0)	0.040	0.008
Number of prior pregnancies (parity), n (%)				
Zero	534 (44.6)	622 (36.9)	0.159	<0.001
One	417 (34.8)	596 (35.6)	0.010	0.005
Two or more	241 (20.1)	462 (27.5)	0.142	0.016
Maternal race/ethnicity, n (%)				
Hispanic	83 (7.4)	98 (5.9)	0.046	0.006
Non-Hispanic Asian	33 (3.1)	26 (1.6)	0.084	0.005
Non-Hispanic black	47 (4.3)	36 (2.1)	0.105	0.004
Non-Hispanic Native American	15 (1.8)	25 (2.0)	0.020	0.004
Non-Hispanic Native Hawaiian or Other Pacific Islander	20 (2.2)	21 (1.3)	0.036	0.003
Non-Hispanic white	993 (83.4)	1473 (88.2)	0.124	0.005
Maternal education level, n (%)				
High school diploma/general equivalency degree or less	255 (21.4)	305 (18.2)	0.081	0.004
Some college	471 (39.6)	617 (36.9)	0.056	0.002
Bachelor's degree or more	464 (39.0)	752 (44.9)	0.120	0.001
Medicaid, n (%)	47 (3.9)	54 (3.2)	0.039	<0.001
Integrated Group Practice, n (%)	739 (61.7)	1013 (60.1)	0.033	0.002
Established diabetes, n (%)	35 (2.9)	46 (2.7)	0.012	<0.001
Chronic hypertension, n (%)	42 (3.5)	81 (4.8)	0.065	0.006
Pre-pregnancy weight in lbs, mean (SD)	166.2 (44.5)	169.1 (43.5)	0.066	0.007
During the two years prior to pregnancy, n (%)				
Alcohol abuse disorder diagnostic code	52 (4.3)	74 (4.4)	0.002	0.009
Tobacco use disorder diagnostic code	159 (13.3)	234 (13.9)	0.018	<0.001
Drug abuse disorder diagnostic code	48 (4.0)	60 (3.6)	0.023	<0.001
Depression disorder diagnostic code	868 (72.5)	1233 (73.1)	0.015	0.002
Anxiety disorder diagnostic code	463 (38.6)	716 (42.5)	0.078	0.003
Obsessive compulsive disorder diagnostic code	22 (1.8)	56 (3.3)	0.094	0.020
Post-traumatic stress disorder diagnostic code	40 (3.3)	55 (3.3)	0.004	0.002
Bipolar disorder diagnostic code	56 (4.7)	76 (4.5)	0.008	0.008
During the year prior to pregnancy, n (%)				
Any fill of antipsychotic medication	21 (1.8)	38 (2.3)	0.036	0.002

Any fill of benzodiazepine medication	266 (22.2)	410 (24.3)	0.050	0.002
Any fill for hypnotic sleep medication	48 (4.0)	76 (4.5)	0.025	0.001
Any fill for mood stabilizer medication	59 (4.9)	89 (5.3)	0.016	0.015
Any fill for trazodone	107 (8.9)	174 (10.3)	0.047	<0.001
Any fill for tricyclic antidepressant medication	71 (5.9)	88 (5.2)	0.031	0.003
Any fill for other anxiety medication	80 (6.7)	118 (7.0)	0.013	0.001
Any fill for medication associated with weight gain	174 (14.5)	258 (15.3)	0.022	<0.001
Any fill for diabetes medication	36 (3.0)	62 (3.7)	0.037	<0.001
Any psychotherapy visit	225 (18.9)	285 (16.9)	0.049	0.003
Any psychiatry visit	173 (14.4)	217 (12.9)	0.045	0.004
Any inpatient psychiatric hospitalization	9 (0.8)	17 (1.0)	0.028	0.011
More than one year prior to pregnancy, n (%)				
Any fill of antipsychotic medication	21 (1.8)	41 (2.4)	0.047	0.009
Any fill of benzodiazepine medication	246 (20.5)	402 (23.8)	0.080	0.011
Any fill for hypnotic sleep medication	54 (4.5)	81 (4.8)	0.014	0.006
Any fill for mood stabilizer medication	57 (4.8)	86 (5.1)	0.016	0.017
Any fill for trazodone	123 (10.3)	164 (9.7)	0.018	0.007
Any fill for tricyclic antidepressant medication	103 (8.6)	162 (9.6)	0.035	0.004
Any fill for other anxiety medication	116 (9.7)	195 (11.6)	0.061	0.001
Any fill for medication associated with weight gain	278 (23.2)	425 (25.2)	0.047	0.004
Any fill for diabetes medication	30 (2.5)	59 (3.5)	0.058	0.003
Any fill for antidepressant medication	565 (47.2)	1043 (61.9)	0.298	0.002
Any psychotherapy visit	321 (26.8)	511 (30.3)	0.078	0.008
Any psychiatry visit	149 (12.4)	296 (17.6)	0.144	0.010
Any inpatient psychiatric hospitalization	16 (1.3)	18 (1.1)	0.025	0.008

SD: Standard deviation; SMD: Standardized mean difference

3% of observations were missing prenatal weight, and <1% of observations were missing race/ethnicity, parity, and education. All other observations did not have missing values.

If the SMD was ≥0.10, a standard cut point,[28] we considered the two groups to be substantially different. Weighted SMDs <0.10 indicate that we had achieved good balance in terms of measured baseline characteristics between births to exposed and unexposed women.

This table contains the study population for the analysis of mean gestational weight gain. The study population for the analyses of adequacy of gestational weight gain excluded some births presented in this table (Figure 1.1).
This table includes all covariates used to create the inverse probability of treatment weights for the mean gestational weight gain overall regression models.
Diagnostic codes for conditions are listed in Supplementary Table 1.1. Specific medications in medication categories are listed in Supplementary Table 1.3. Definitions of mental health care utilization are described in Supplementary Table 1.4.

Supplementary Table 1.7. Counts and proportions of births to women with fills for specific antidepressants in pregnancy.

Antidepressant class or specific name	Antidepressant continuers N=1686 No. (%) during pregnancy
SSRIs	1459 (87%)
Citalopram	362 (21%)
Escitalopram	41 (2%)
Fluvoxamine	4 (<1%)
Fluoxetine	487 (29%)
Paroxetine	152 (9%)
Sertraline	525 (31%)
SNRIs	104 (6%)
Desvenlafaxine	1 (<1%)
Venlafaxine	103 (6%)
Bupropion	234 (14%)
Mirtazapine	11 (1%)

SSRIs: serotonin reuptake inhibitors; SNRIs: serotonin norepinephrine reuptake inhibitors

This table contains the study population for the analysis of mean gestational weight gain. The study population for the analyses of adequacy of gestational weight gain excluded some births presented in this table (Figure 1.1).

Numbers for specific medications add to >100% due to some women using multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four). This includes women who switched antidepressants or were using multiple antidepressants simultaneously.

Supplementary Table 1.8. Extent of antidepressant exposure for women continuing antidepressants: Number of antidepressant medication fills and days covered[a] during the exposure window.[b]

	Overall n (%)	Single type of antidepressant[c] n (%)	Two different antidepressants[c,d] n (%)
	n=1686	n=1493[c]	n=177 [c]
Number of fills, median (IQR)	3 (1-5)	2 (1-4)	5 (3-7)
1 fill	525 (31%)	525 (35%)	NA
2 fills	308 (18%)	280 (19%)	28 (16%)
3 fills	258 (15%)	227 (15%)	28 (16%)
4 or more fills	595 (35%)	461 (31%)	121 (68%)
	n=1686	n=1414[c]	n=248[c]
Days covered in exposure window, median (IQR)	144.5 (65.0-219.0)	133.5 (60.0-212.0)	185.5 (105.0-257.2)
<30	21 (1%)	21 (1%)	0 (0%)
≥30 to 89	525 (31%)	475 (34%)	49 (20%)
≥90 to 179	477 (28%)	401 (28%)	71 (29%)
≥180 to 239	376 (22%)	317 (22%)	50 (20%)
≥240	287 (17%)	200 (14%)	78 (30%)
Proportion of days covered in exposure window, median (IQR)	60% (27-91%)	55% (24-88%)	76% (42-108%)
<20%	281 (17%)	273 (19%)	8 (3%)
20 to 49%	448 (27%)	377 (27%)	68 (27%)
50 to 79%	354 (21%)	293 (21%)	56 (23%)
≥80%	580 (34%)	452 (32%)	112 (45%)

IQR: interquartile range

Values represent n (%) unless otherwise noted.

This table contains the study population for the analysis of mean gestational weight gain. The study population for the analyses of adequacy of gestational weight gain excluded some births presented in this table (Figure 1.1).

Antidepressants are commonly filled in 30, 60, or 90 days' supply at Kaiser Permanente Washington, and other lengths of days supplied are occasionally used.

20 women had fills of 3 different antidepressants in pregnancy, and 4 had fills of 4 different antidepressants in pregnancy. They are not included in the table.

[a]"Days covered" was defined as number of days supplied with an antidepressant within the exposure window[b]. This is available in the prescription fill records as a different variable from the number of pills because some patients are prescribed more than one pill of a given medication per day. For fills that only partially overlapped with pregnancy, we prorated the days covered. "Proportion of days covered" is defined as the number of days covered in the exposure window divided by the number of days in the exposure window.

[b]We defined the exposure window for analyses of gestational weight gain as the start of pregnancy through four weeks prior to delivery. The median length of the exposure window in our study was 245 days (~35 weeks), with an interquartile range of 238 to 252 days.

[c]The number of deliveries exposed to 1 specific antidepressant versus 2 different antidepressants in the exposure window is different when considering fills versus days covered. When describing number of fills, we only considered women with *fills* of two different antidepressants in the exposure window to be exposed to 2 different antidepressants. When describing days covered, we allowed fills prior to pregnancy that overlapped into pregnancy to contribute to the total days supplied (prorated), which

increased the number of women we considered to have exposure to 2 different antidepressants in pregnancy.

[d]For women taking 2 antidepressants, we calculated the total number of days covered by adding the number of days covered for each antidepressant (we did not attempt to account for overlap, even though some of these women may have been taking the 2 antidepressants simultaneously.) This made it possible for a woman to have more than 100% of days covered according to our calculations.

Supplementary Table 1.9. Sensitivity analyses for association of antidepressant continuation in pregnancy with mean gestational weight gain.

	No. of continuers Total n= 1686	Weight gain (lbs) of continuers Mean (SD)	No. of dis-continuers Total n = 1198	Weight gain (lbs) of discontinuers Mean (SD)	Mean difference in lbs (95% CI)
Inverse probability of treatment weighted models					
Overall model from primary analysis[a]	1686	30.5 (16.8)	1198	30.3 (16.1)	1.3 (-0.1 to 2.8)
Exposure defined as ≥2 antidepressant fills[b]	1201	30.2 (16.1)	1198	30.3 (16.1)	0.7 (-0.8 to 2.1)
BMI included in model[b]	1534	30.4 (16.5)	1098	30.2 (15.8)	0.8 (-0.6 to 2.0)
Adjusting for gestational age[b]	1686	30.5 (16.8)	1198	30.3 (16.1)	1.2 (-0.2 to 2.5)
<50% of days covered with fills[b,c]	660	31.1 (18.5)	1198	30.3 (16.1)	1.3 (-0.6 to 3.2)
≥50% of days covered with fills[b,c]	754	30.5 (15.0)	1198	30.3 (16.1)	0.6 (-0.9 to 2.2)
Births to women with fills overlapping pregnancy re-categorized as exposed[b]	2076	30.5 (16.6)	808	30.1 (16.3)	1.0 (-0.4 to 2.5)
Anxiety or depression diagnosis[d] in 2 years prior to pregnancy[b]	1449	30.2 (15.8)	1011	30.3 (16.3)	0.4 (-1.0 to 1.7)
Female infant[b]	811	29.6 (15.4)	600	29.7 (16.8)	0.2 (-1.6 to 1.9)
Male infant[b]	875	31.3 (17.9)	598	30.9 (15.4)	1.1 (-0.7 to 2.9)
Multivariable-adjusted model					
Overall[e]	1665	30.5 (16.8)	1182	30.3 (16.1)	1.1 (-0.1 to 2.3)

lbs: pounds; SD: standard deviation, CI: confidence interval; BMI: body mass index
[a]Repeated from Table 1.2 for comparison. Weighted by characteristics included in Variable Set 3 in Supplementary Table 1.5.
[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 1.5.
[c]Only includes women who had a fill for one specific antidepressant during the exposure window.
[d]Anxiety and depression disorders defined in Supplementary Table 1.1.
[e]Adjusted for characteristics included in Variable Set 2 in Supplementary Table 1.5.

Supplementary Table 1.10. Sensitivity analyses for association of antidepressant continuation in pregnancy with inadequate gestational weight gain.

	No. of continuers Total n = 1534	No. (%) of continuers with inadequate weight gain	No. of dis-continuers Total n = 1098	No. (%) of dis-continuers with inadequate weight gain	RR (95% CI)
Inverse probability of treatment weighted models					
Overall model from primary analysis[a]	1534	256 (17%)	1098	197 (18%)	0.95 (0.79-1.13)
Exposure defined as ≥2 antidepressant fills[b]	1094	194 (18%)	1098	197 (18%)	1.00 (0.83-1.21)
Including gestational age in the model[b]	1534	256 (17%)	1098	197 (18%)	0.93 (0.78-1.11)
Less than 50% of days covered with fills[b,c]	594	86 (14%)	1098	197 (18%)	0.84 (0.66-1.07)
Greater than 50% of days covered with fills[b,c]	685	122 (18%)	1098	197 (18%)	0.97 (0.77-1.22)
Births to women with fills overlapping pregnancy re-categorized as exposed[b]	1895	322 (17%)	737	131 (18%)	1.00 (0.82-1.21)
Anxiety or depression diagnosis[d] in 2 years prior to pregnancy[b]	1323	217 (16%)	923	166 (18%)	0.94 (0.78-1.14)
Female infant[b]	744	141 (19%)	546	103 (19%)	1.04 (0.82-1.33)
Male infant[b]	790	115 (15%)	552	94 (17%)	0.90 (0.69-1.16)
Multivariable-adjusted model					
Overall[e]	1534	256 (17%)	1098	197 (18%)	0.94 (0.79-1.12)

CI: confidence interval; RR: relative risk

[a]Repeated from Table 1.3 for comparison. Weighted by characteristics included in Variable Set 3 in Supplementary Table 1.5.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 1.5.

[c]Only includes women who had a fill for one specific antidepressant during the exposure window.

[d]Anxiety and depression disorders defined in Supplementary Table 1.1.

[e]Adjusted for characteristics included in Variable Set 2 in Supplementary Table 1.5.

Supplementary Table 1.11. Sensitivity analyses for association of antidepressant continuation in pregnancy with excessive gestational weight gain.

	No. of continuers Total n= 1534	No. (%) of continuers with excessive weight gain	No. of dis-continuers Total n = 1098	No. (%) of dis-continuers with excessive weight gain	RR (95% CI)
Inverse probability of treatment weighted models					
Overall model from primary analysis[a]	1534	828 (54%)	1098	564 (51%)	1.06 (0.98-1.14)
Exposure defined as ≥2 antidepressant fills[b]	1094	580 (53%)	1098	564 (51%)	1.04 (0.96-1.13)
Including gestational age in the model[b]	1534	828 (54%)	1098	564 (51%)	1.07 (0.99-1.16)
Less than 50% of days covered with fills[b,c]	594	327 (55%)	1098	564 (51%)	1.05 (0.96-1.16)
Greater than 50% of days covered with fills[b,c]	685	361 (53%)	1098	564 (51%)	1.05 (0.95-1.17)
Births to women with fills overlapping pregnancy re-categorized as exposed[b]	1895	1016 (54%)	737	376 (51%)	1.05 (0.96-1.14)
Anxiety or depression diagnosis[d] in 2 years prior to pregnancy[b]	1323	710 (54%)	923	478 (52%)	1.05 (0.97-1.14)
Female infant[b]	744	394 (53%)	546	275 (50%)	1.05 (0.94-1.17)
Male infant[b]	790	356 (45%)	552	259 (47%)	1.05 (0.95-1.17)
Multivariable-adjusted model					
Overall[e]	1534	828 (54%)	1098	564 (51%)	1.06 (0.98-1.14)

CI: confidence interval; RR: relative risk

[a]Repeated from Table 1.4 for comparison. Weighted by characteristics included in Variable Set 3 in Supplementary Table 1.5.

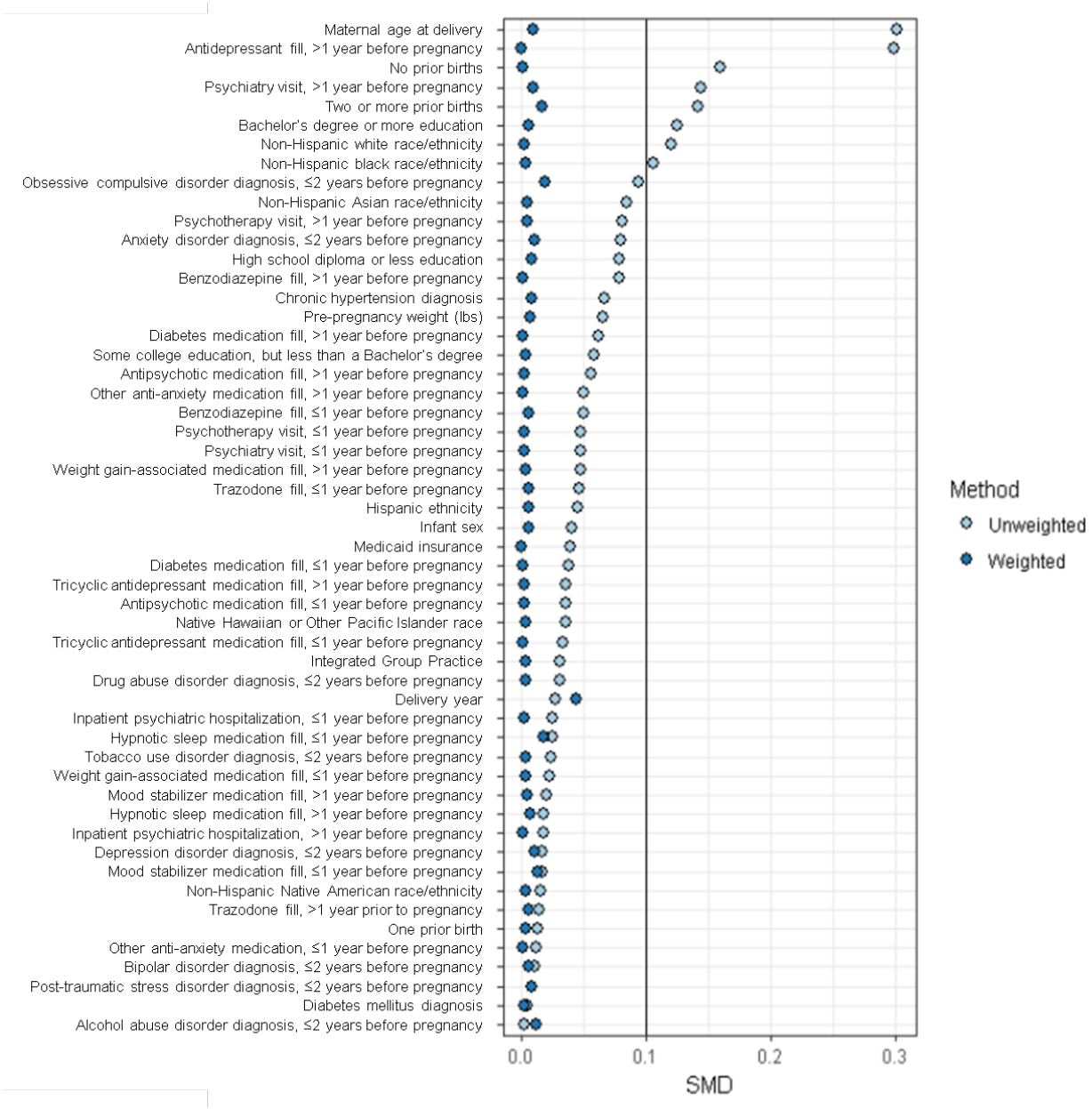
[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 1.5.

[c]Only includes women who had a fill for one specific antidepressant during the exposure window.

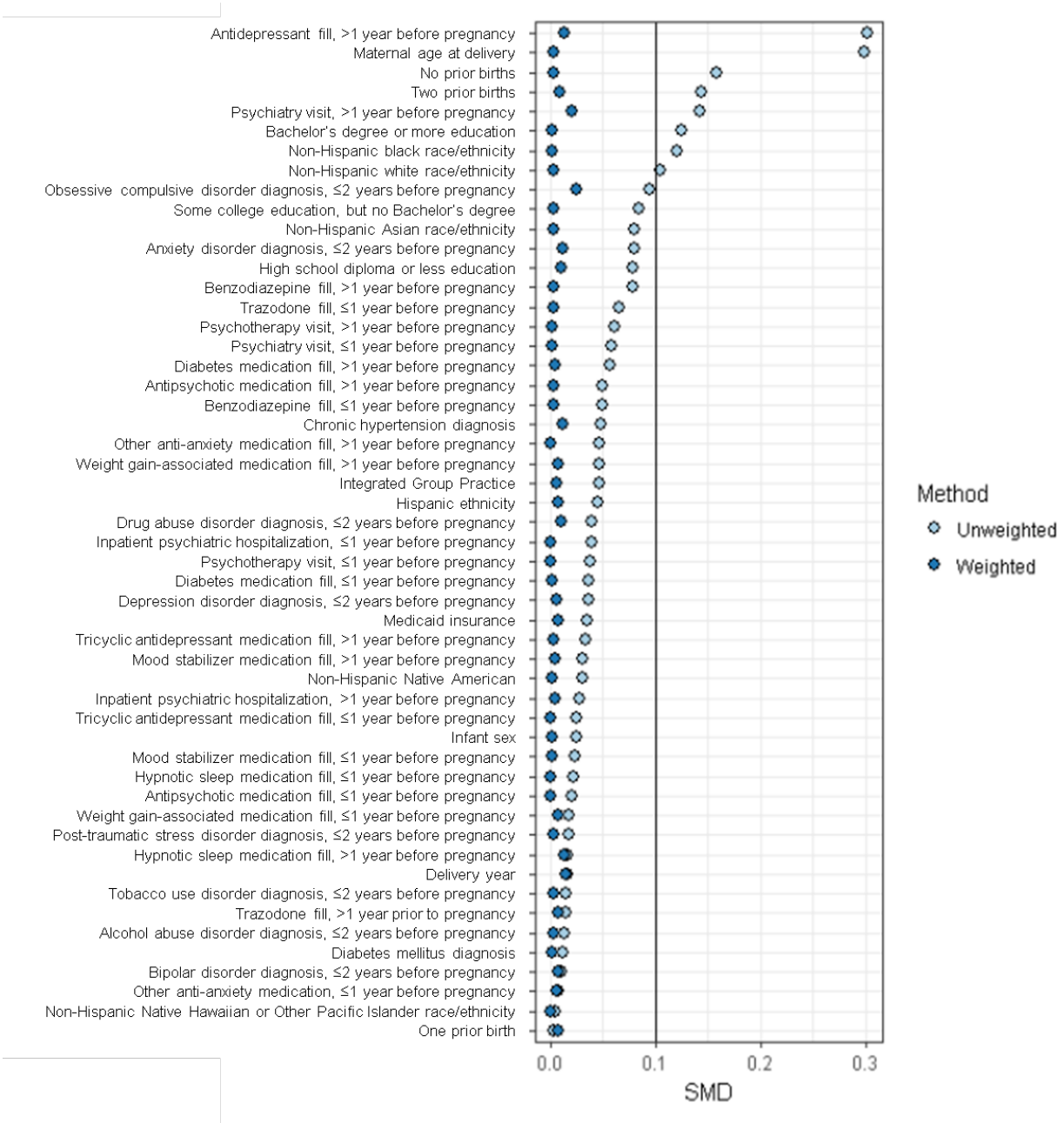
[d]Anxiety and depression disorders defined in Supplementary Table 1.1.

[e]Adjusted for characteristics included in Variable Set 2 in Supplementary Table 1.5.

Supplementary Figure 1.1. Unweighted and weighted standardized mean differences (SMDs) comparing characteristics in births to women who continued or discontinued antidepressants in pregnancy in the study population for the mean gestational weight gain analysis.



Supplementary Figure 1.2. Unweighted and weighted standardized mean differences (SMDs) comparing characteristics in births to women who continued or discontinued antidepressants in pregnancy in the study population for the adequacy of gestational weight gain analyses.



Methods Appendix 1.1. Description of inverse probability of treatment weighting methods.
Propensity scores were estimated using a logistic regression model in which antidepressant use in pregnancy was regressed on potential confounders.[28] We generated a likelihood of exposure for each birth, conditional on confounders, which was used to weight the population by the inverse probability of exposure. To avoid lowering precision, we did not include variables expected to be associated with exposure but not outcome.[37] For the exposed group, we created stabilized IPTWs by dividing the prevalence of exposure in the study population by the propensity score for each observation. For the unexposed group, we calculated stabilized IPTWs as *(1–prevalence of exposure)/(1–propensity score)*. These weights were applied to the primary regression model without adjusting for any covariates. This up-weighted the "unexpected" combinations of confounders and exposure and down-weighted the "expected" combinations of confounders and exposure, in attempt to create a pseudo-population in which exposure is not associated with confounders. To assess balance on baseline covariates, we qualitatively compared exposed and unexposed groups' overlap in propensity scores using cumulative distribution functions and histograms and checked for SMDs between groups ≥0.10.[28]

Methods Appendix 1.2. Sub-population available for chart review.
We only had access to charts for review among women in the Integrated Group Practice from 2007–2014, when the electronic medical record was implemented. Because this chart review was also used to inform other studies, we additionally excluded women with pregestational diabetes, women who were missing a record of gestational diabetes screening and delivered prior to 29 weeks gestation, and women who were missing information on gestational weight gain. Out of the 197 women with prescription fills before pregnancy with days supplied that overlapped into pregnancy who were originally eligible for our chart review, after these additional exclusions, 185 (94%) were used as the sub-population from which we randomly chose 50. Out of the 116 women with prescriptions in the first 30 days of pregnancy who were originally eligible for our chart review, after these additional exclusions, 114 (98%) were used as the sub-population from which we randomly chose 50.

CHAPTER 2:

Antidepressant continuation in pregnancy in relation to gestational diabetes

Antidepressant continuation in pregnancy in relation to gestational diabetes

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ABSTRACT

Background: In non-pregnant populations, antidepressant use is associated with greater risk of Type 2 diabetes. The few previous studies of antidepressant use in pregnancy and risk of gestational diabetes (GDM) provide conflicting findings, which may have been affected by confounding by indication.

Objective: To investigate the association of antidepressant continuation in pregnancy with GDM and blood glucose levels.

Methods: We conducted a retrospective cohort study of births from 2001–2014 to women enrolled in Kaiser Permanente Washington with ≥1 antidepressant prescription fills during the 6 months before pregnancy, utilizing electronic health data and linked Washington State birth records. Women with an antidepressant fill during pregnancy were categorized as "continuers" (n=1634); those without a fill were "discontinuers" (n=1211). We calculated relative risks (RR) for GDM and mean differences in blood glucose levels from a 50-g oral glucose challenge test (available for a subset) using inverse probability of treatment weighting to account for baseline characteristics, including rich measures of mental health status.

Results: Compared with discontinuers, continuers had comparable risk of GDM (RR: 1.10, 95% confidence interval [CI]: 0.84–1.44) and mean blood glucose levels (mean difference: 2.4 mg/dl, 95% CI -1.5 to 6.3). We observed similar results for specific antidepressants and exposure during specific trimesters, although there was a suggestion of greater risk of GDM with venlafaxine continuation (RR: 1.52, 95% CI: 0.87-2.68).

Conclusions: Our study suggests that women and their providers do not need to be concerned about increased GDM risk or higher blood glucose associated with antidepressant continuation in pregnancy, with the potential exception of venlafaxine continuation.

INTRODUCTION

Gestational diabetes (GDM) is a common pregnancy complication which affects approximately 6% of pregnant women, or 240,000 pregnancies, in the US annually.[38] Women with this condition are at greater risk of cesarean delivery and of having an infant with macrosomia or birth injuries.[20] Over the lifecourse, women with a history of GDM have an increased risk of developing type 2 diabetes,[39] and children of women with GDM are more likely to become obese and to develop type 2 diabetes.[21,22]

Because antidepressant use may increase risk of type 2 diabetes in non-pregnant women,[40,41] it could raise risk of GDM in pregnant women. Antidepressant use may directly increase risk of GDM by impacting insulin resistance and secretion[40] and may also affect risk of GDM indirectly, through weight gain.[11]

Antidepressant use is relatively common in pregnancy, with 7–8% of American pregnant women taking one of these drugs. A registry-based, Swedish cohort observed moderately greater risk of GDM associated with antidepressant use in pregnancy.[42] However, this study neither adjusted for maternal mental health indicators nor restricted their comparator group to depressed women. Since depression itself may increase risk of GDM,[43,44] the study's findings may have been affected by confounding by indication. Another study indicates there is not greater risk of GDM associated with antidepressant use after accounting for depression and anxiety (presented as an abstract). [45]

To address these uncertainties, we investigated the risk of GDM and mean difference in blood glucose levels from a routine screening test in women who continued, versus discontinued, antidepressant use during pregnancy. In these comparisons, we sought to account for possible differences in maternal characteristics, including mental health, using inverse probability of treatment weighting (IPTW).

METHODS

Overview

We conducted a retrospective cohort study with data from Kaiser Permanente Washington (KPWA, formerly Group Health Cooperative), an integrated healthcare delivery system in Washington State. We required all women to be enrolled ≥6 months prior to onset of pregnancy and an antidepressant

prescription fill during that period, which allowed the analyses to: (1) address the clinical decision of whether to continue antidepressants in pregnancy that these women and their providers face, and (2) limit bias due to confounding by indication. Electronic health data from KPWA were linked to Washington State birth records and provided the information necessary for our study.[24] The study was approved by the KPWA Institutional Review Board and the Washington State Department of Health Institutional Review Board (both with waivers of consent).

Study Population and Design

Our cohort was drawn from live births from January 1, 2001 through December 31, 2014 to women enrolled in KPWA. KPWA maintains extensive data on its members including patient enrollment, demographics, encounters, diagnoses, procedures, and prescription fills. Nearly two-thirds of members receive comprehensive care from KPWA healthcare providers through the Integrated Group Practice, and for these members we were able to ascertain additional data on laboratory values, vital signs, and mental health questionnaires. We required KPWA births to be linked to a Washington State birth record because this was the source for gestational age information necessary to determine timing of antidepressant fills relative to pregnancy onset. Because some women contributed multiple births to our cohort (<1% had three births, 7% had two births, and 93% had one birth) our unit of analysis was technically "births" rather than "women", but we have used the terms interchangeably here.

We wanted to limit the study population to women taking antidepressants for depression or anxiety, as 80–90% of antidepressant use among women is for these indications.[3,18] Because women without a healthcare encounter before pregnancy did not have a chance to receive a diagnostic code for depression or anxiety (Supplementary Table 2.1), we did not require such a code. However, we excluded 138 women without a depression or anxiety diagnostic code in the past two years if they had a code for another health condition that is an accepted antidepressant indication (Figure 2.1, diagnostic codes in Supplementary Table 2.2).

Women with established diabetes (type 1 or 2) are, by definition, not at risk for GDM, so we excluded 87 women with this diagnostic code recorded between six months prior to pregnancy onset and 24 weeks gestation (Figure 2.1, diagnostic codes in Supplementary Table 2.2). Because the KPWA

guidelines recommended universal GDM screening for the majority of our study period, for women missing a procedure code for GDM screening, we assumed screening occurred at 28 weeks (testing is recommended from 24–28 weeks gestation). Nine women missing a procedure code who delivered at 28 weeks or earlier were excluded, as they may not have had a chance for screening. We defined the exposure window as the start of pregnancy through four weeks before GDM screening (according to procedure code date) to allow time for an effect of exposure on outcome (Figure 2.2). We excluded 126 women with their first antidepressant fill in pregnancy after this exposure window (Figure 2.1).

For the analysis of screening blood glucose levels, we excluded 1744 women to restrict to a subset with a screening, 1-hour, 50 g oral glucose challenge test result available in KPWA laboratory data (Figure 2.1).

Exposure

Medication exposure information came from pharmacy dispensing data and included antidepressant name, date of prescription fill, and number of days supplied. We considered women with any antidepressant prescription fill during the exposure window to be “continuers” and women without such a fill to be “discontinuers” (Figure 2.2).

Exposure included selective serotonin reuptake inhibitors (SSRIs; citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline), serotonin-norepinephrine reuptake inhibitors (SNRIs; desvenlafaxine, venlafaxine), and other antidepressants (bupropion, mirtazapine). We did not require continuers to fill the same antidepressant during the six months prior to pregnancy and the exposure window. Antidepressants are most commonly filled in 30, 60, or 90 days’ supply at Kaiser Permanente Washington. Women with an antidepressant fill that overlapped into pregnancy but without a fill during pregnancy were categorized as discontinuers, an assumption we addressed in a sensitivity analysis (described below).

Outcomes

GDM was ascertained from KPWA diagnostic codes. We required either at least two codes of GDM (ICD-9-CM 648.8) from 16 weeks gestation to delivery or any such code at the delivery hospitalization.

Because there is evidence that even incremental differences in blood glucose levels are associated with adverse maternal and infant outcomes,[46,47] we also assessed blood glucose levels (mg/dl) from a 50-g, 1-hour oral glucose challenge from GDM screening. Test results were ascertained from KPWA laboratory data.

Covariates

We ascertained the following covariates from state birth records: parity, maternal race/ethnicity, maternal education, and pre-pregnancy weight and body mass index (BMI). Primary analyses relied on pre-pregnancy weight rather than BMI, because BMI was not available on the birth certificate until 2003.

We obtained the following covariates from KPWA electronic health databases: (1) at the time of delivery: birth year, maternal age, and baby's sex, and (2) prior to pregnancy: membership in the Integrated Group Practice, Medicaid insurance coverage, smoking and substance abuse diagnoses, mental health diagnoses, psychotropic and other prescription medication fills, and utilization of psychotherapy, psychiatry, and inpatient psychiatric hospitalization (Appendices 4, 5, and 6). We allowed collection of covariate data to go back in time as long as women were continuously enrolled.[26] We also ascertained GDM testing strategy using procedure codes (testing and policy changes described in Methods Appendix 2.1).

To measure depression severity, we extracted results from the Patient Health Questionnaire-9 (PHQ-9), a commonly-used, 9-item depression screening questionnaire.[27] PHQ-9 records were only available for women in the Integrated Group Practice, where they were used from approximately 2008 onwards. During this period, KPWA did not practice universal depression screening, but rather the PHQ-9 was used when the patient initially presented with symptoms of depression and periodically during follow-up to monitor response to therapy.

Statistical Analysis

We described characteristics of eligible women by exposure status. We then calculated standardized mean differences (SMDs) both with and without IPTW. SMDs quantify the difference between two groups without being affected by sample size.[28]

Because PHQ-9 scores were available only for a sub-set of women in our cohort, we described PHQ-9 scores in the two years prior to pregnancy but did not include them in regression models.

To account for correlation among multiple births to the same woman, we used generalized estimating equations with an exchangeable correlation matrix for all regression analyses. For the analysis of GDM with antidepressant continuation in pregnancy, we used a Poisson (log) link function to calculate relative risks (RRs) and 95% confidence intervals (CIs). We calculated mean differences and 95% CIs for the association of continuing antidepressant use in pregnancy, as compared with discontinuing use, with screening blood glucose levels using an identity link function.

We used IPTW models in order to include more potential confounders than a multivariable adjusted model would be able to include (Methods Appendix 2.2).[28] Briefly, IPTW uses propensity scores to weight observations in the model by their likelihood of exposure to improve balance in baseline covariates between exposed and unexposed.

Covariates were chosen *a priori* based on our knowledge and previous literature, after considering sample size limitations. For the overall analysis of GDM, we weighted the IPTW model by all variables in Variable Set 3 (Supplementary Table 2.3). For the overall analyses of screening blood glucose levels, the IPTW model included somewhat fewer variables, due to sample size limitations (Variable Set 2).

We conducted sub-analyses comparing women who continued specific antidepressants with discontinuers (the group of women who discontinued any antidepressant, as in the overall analysis). Additionally, we compared outcomes in women who continued antidepressant use in specific trimesters (regardless of use in other trimesters) with the same group of discontinuers used in the overall analysis. We used the smaller Variable Set 2 for these sub-analyses due to smaller numbers of exposed women (Supplementary Table 2.3). For analyses of paroxetine and venlafaxine, the analyses with the smallest number of users, we chose a parsimonious model based on which characteristics had SMDs comparing continuers and discontinuers of ≥0.10 (see Supplementary Table 2.4 for SMD values), and from these variables, we included those associated with a >10% change in the RR for GDM after their addition to the crude model (Variable Set 1 in Supplementary Table 2.3). For consistency, we used this model for analyses of blood glucose levels for these two antidepressants.

Sensitivity analyses

We conducted sensitivity analyses with IPTW models weighted for characteristics in Variable Set 2 (Supplementary Table 2.3). First, we defined exposure as receiving ≥2 antidepressant fills during the exposure window to address potential exposure misclassification, which could arise if women who only filled once in pregnancy never actually took the antidepressant. Second, we restricted the sample to women with an anxiety or depression diagnostic code in the two years before pregnancy. Third, to address the possibility of lingering effects of medication in the body and the assumption that women whose last fill overlapped pregnancy discontinued before pregnancy, we conducted a sensitivity analysis that re-categorized these women as continuers. Fourth, we ran analyses separately for continuers with less than 50% of days covered with antidepressant fills and continuers with greater than or equal to 50% of days covered, to address a potential duration-response relationship by length of exposure. For fills that only partially overlapped with pregnancy, we prorated the days covered. For these analyses, we only included women who had a fill for one specific antidepressant during the exposure window because it was difficult to distinguish sequential from simultaneous use for women who filled multiple antidepressants. Fifth, we adjusted for pre-pregnancy BMI instead of pre-pregnancy weight to address residual confounding, restricting to years when BMI was available. Sixth, we assessed the association separately for male and female infants. Seventh, we ran a multivariable-adjusted model, adjusted for characteristics in Variable Set 2, to assess whether the associations were generally similar. For the GDM analysis only, we conducted analyses separately by type of GDM testing strategy received (1-step and 2-step, Methods Appendix 2.1).

All statistical analyses were conducted in R version 3.4.2 (R Core Team [https://www.r-project.org]).

RESULTS

The source population included 57,743 births. After applying inclusion and exclusion criteria, the study population eligible for the GDM analysis consisted of 2,845 births (Figure 2.1), including 1,634 to women who continued antidepressants in pregnancy and 1,211 to women who discontinued. The number eligible for the analysis of screening blood glucose levels was 1,101 births (continuers: 613, discontinuers: 488).

Women who continued antidepressant medication during pregnancy were similar to discontinuers with respect to baseline factors, with a few exceptions: antidepressant continuers were slightly older, less likely to be nulliparous, and more likely to be non-Hispanic white and have higher education than women who discontinued antidepressants (Table 2.1). Continuers were also more likely than discontinuers to have had a psychiatry visit or filled an antidepressant prescription more than one year before pregnancy (Supplementary Table 2.4). The average length of enrollment prior to pregnancy, during which we allowed collection of covariate data, was 4.3 years (standard deviation [SD]: 4.1 years) for continuers and 4.5 years (SD: 4.3 years) for discontinuers. After weighting, SMDs in baseline characteristics were not meaningfully different (≥0.10)[28] between continuers and discontinuers (Supplementary Figures 2.1 and 2.2).

Among antidepressant continuers, we had a record of a PHQ-9 screening before pregnancy for 333 (~59% of women who could have a record, based on data availability) compared with 285 (~66% of women who could have a record) among discontinuers. The mean pre-pregnancy score was 9.7 for continuers and 10.4 for discontinuers, indicating moderate depression (SDs: 6.6 and 6.7, respectively).

Counts of continuers filling specific antidepressants and extent of exposure in pregnancy are included in Supplementary Tables 2.5 and 2.6.

The unadjusted incidence of GDM was 9% in antidepressant continuers and 7% in discontinuers (Table 2.2). In the overall study population, women continuing antidepressants did not have a greater risk of GDM after weighting by confounders (RR 1.10, 95% CI 0.84–1.44). There was some evidence that continuation of venlafaxine during pregnancy was associated with greater risk of GDM (RR 1.52, 95% CI 0.87–2.68). There was not evidence of altered risk of GDM in other medication- or trimester-specific analyses.

Continuers had an unadjusted mean blood glucose level of 117 mg/dl (SD: 30 mg/dl), similar to discontinuers (mean: 115 mg/dl, SD: 27 mg/dl; Table 2.3), and there was not a notable difference between the two groups after accounting for potential confounders using IPTW (mean difference: 2.4 mg/dl, 95% CI: -1.5 to 6.3 lbs, Table 2.3). Women continuing sertraline during pregnancy had slightly higher blood glucose levels than discontinuers (6.7 mg/dl, 95% CI: 0.3 to 13.0). We did not observe

higher blood glucose levels for continuers in analyses of other specific antidepressants or trimesters of exposure.

Sensitivity analyses

As in our main analyses, we did not find evidence of an association between antidepressant continuation in pregnancy and GDM or screening blood glucose for most sensitivity analyses, including the analyses using multivariable adjustment instead of IPTW to address confounding. There was a suggestion of greater risk of GDM associated with antidepressant continuation in women screened using the 1-step approach (RR: 1.60, 95% CI: 0.92–2.77; Supplementary Tables 2.7 and 2.8).

DISCUSSION

Overall, we did not observe greater risk of GDM (RR: 1.10, 95% CI: 0.84–1.44) or appreciable differences in mean screening blood glucose levels (2.4 mg/dl, 95% CI: -1.5 to 6.3) for women who continued, as compared with discontinued, antidepressant medications during pregnancy. There was a suggestion that risk of GDM was approximately 50% greater in women who continued venlafaxine, but this non-significant finding needs confirmation in future studies.

In addition to the 20% greater risk of developing chronic diabetes in adults with a history of antidepressant use reported in a recent meta-analysis (95% CI: 1.10-1.30),[48] a very large, registry-based study in Swedish pregnant women reported moderately greater risk of gestational diabetes associated with use of antidepressants in pregnancy (OR: 1.37, 95% CI 1.18–1.58).[42] A similar, but smaller, study in Canada that assessed risk of GDM specific to SSRI use also suggested about 30% greater risk, but this result was not statistically significant (OR: 1.31, 95% CI: 0.86–2.01).[49] Neither of these studies accounted for the presence of depression or anxiety through restriction nor adjustment. Our overall findings that addressed confounding by depression and anxiety were indicative of no elevated risk of GDM, but we were not powered to rule out the moderately greater risk suggested by these studies, given our upper confidence limit of 1.44. Consistent with our findings, a sub-analysis from a large, Canadian study (recently presented as an abstract) that restricts to women using antidepressants prior to pregnancy and adjusts for a few mental health indicators did not find greater risk of GDM associated with antidepressant

use in pregnancy (OR: 1.07, 95% CI: 0.98–1.17).[45] They also reported greater risk of GDM for venlafaxine users (OR: 1.27, 95% CI: 1.09–1.49), consistent with our findings.

A major strength of this study is that we restricted to women taking antidepressants prior to pregnancy and included indicators of mental health status along with other demographic and health-related factors to minimize confounding. Other strengths include use of a large, well-defined study population and prescription fill data, which is a better indication that the woman took the medication than prescription data alone. We had access to extensive information about baseline characteristics, including mental health care utilization, which we used to create IPTWs to address confounding. Although they were only available for a portion of our population, we were reassured to see that pre-pregnancy PHQ-9 depression screening scores were very similar between continuers and discontinuers.

We were subject to several limitations. There were small numbers of women continuing certain antidepressants, leaving us underpowered to detect modest effects. Despite our efforts to address confounding by indication, we cannot rule out residual confounding. Additionally, if women with only one antidepressant fill in pregnancy did not actually consume the medication, there could be misclassification of exposure, potentially attenuating our risk estimates. In analyses of GDM, we combined women who received the 1-step testing strategy with women who received the 2-step testing strategy, and although we adjusted for type of test received, this may not have been appropriate if antidepressant use was differentially associated with GDM based on testing strategy, as suggested by a sensitivity analysis. Also, our study population was largely non-Hispanic white and commercially insured, and we were limited to live births, which may limit generalizability of the findings.

In addition to risk for gestational diabetes, there are many other factors that must be weighed in the decision about whether to continue antidepressants in pregnancy, including infant health and the woman's mental health. With regard to gestational diabetes our study suggests that women and their providers do not need to be concerned about increased risk associated with antidepressant continuation in pregnancy, at least for the agents most commonly used in this study. Larger studies are warranted to confirm our findings.

Table 2.1. Selected baseline characteristics of women with births eligible for the analysis of gestational diabetes.

Covariates	No antidepressant fill in pregnancy (n=1211)	Antidepressant fill in pregnancy (n=1634)	Unweighted SMD	Inverse probability of treatment weighted SMD
Maternal age at delivery, mean (SD)	29.6 (5.8)	31.4 (5.5)	0.301	0.012
Number of prior pregnancies (parity), n (%)				
Zero	542 (45.1)	609 (37.5)	0.156	<0.001
One	414 (34.4)	568 (34.9)	0.010	0.006
Two or more	246 (20.5)	449 (27.6)	0.126	0.009
Maternal race/ethnicity, n (%)				
Hispanic	80 (6.6)	93 (5.7)	0.038	0.008
Non-Hispanic Asian	35 (2.9)	25 (1.5)	0.093	0.002
Non-Hispanic black	48 (4.0)	37 (2.3)	0.098	0.004
Non-Hispanic Native American	13 (1.1)	25 (1.5)	0.040	0.003
Non-Hispanic Native Hawaiian or Other Pacific Islander	21 (1.7)	21 (1.3)	0.037	<0.001
Non-Hispanic white	1007 (83.6)	1425 (87.6)	0.114	0.004
Maternal education level, n (%)				
High school diploma/general equivalency degree or less	259 (21.5)	290 (17.9)	0.091	0.005
Some college	475 (39.5)	605 (37.3)	0.044	0.002
Bachelor's degree or more	470 (39.0)	726 (44.8)	0.117	0.002
Medicaid, n (%)	45 (3.7)	55 (3.4)	0.019	0.001
Pre-pregnancy weight in lbs, mean (SD)	165.8 (45.2)	168.4 (44.5)	0.058	0.007
During the two years before the start of pregnancy, n (%)				
Alcohol abuse disorder diagnostic code	53 (4.4)	69 (4.2)	0.008	0.007
Tobacco use disorder diagnostic code	157 (13.0)	223 (13.6)	0.020	0.001
Drug abuse disorder diagnostic code	49 (4.0)	59 (3.6)	0.023	0.001
Depression disorder diagnostic code	877 (72.4)	1200 (73.4)	0.023	<0.001
Anxiety disorder diagnostic code	468 (38.6)	684 (41.9)	0.066	0.004
Obsessive compulsive disorder diagnostic code	22 (1.8)	54 (3.3)	0.094	0.019
Post-traumatic stress disorder diagnostic code	39 (3.2)	52 (3.2)	0.002	0.003
Bipolar disorder diagnostic code	57 (4.7)	71 (4.3)	0.017	0.007
During the year before the start of pregnancy, n (%)				
Any fill of antipsychotic medication	22 (1.8)	38 (2.3)	0.036	0.003
Any fill of benzodiazepine medication	272 (22.5)	395 (24.2)	0.041	0.003
Any fill for mood stabilizer medication	59 (4.9)	87 (5.3)	0.021	0.014
Any fill for medication associated with weight gain	172 (14.2)	246 (15.1)	0.024	0.003
Any fill for diabetes medication	27 (2.2)	37 (2.3)	0.002	0.003
Any psychotherapy visit	227 (18.7)	281 (17.2)	0.040	0.001
Any psychiatry visit	175 (14.4)	258 (15.8)	0.037	0.004
Any inpatient psychiatric hospitalization	9 (0.7)	16 (1.0)	0.026	0.016

Receipt of 1-step gestational diabetes testing strategy	208 (17.2)	267 (16.3)	0.022	0.002

SD: Standard deviation; SMD: Standardized mean difference

If the SMD was ≥0.10, a standard cut point,[28] we considered the two groups to be substantially different. Weighted SMDs <0.10 indicate that we had achieved good balance in terms of measured baseline characteristics between births to exposed and unexposed women.

This table contains the study population for the analysis of gestational diabetes. The study population for the analysis of blood glucose levels from the 1-hour, 50 g oral glucose tolerance test excluded many births presented in this table (Figure 1).

This table includes a subset of all covariates that were used to create the inverse probability of treatment weights and included in the overall regression models (Variable Set 3 in Supplementary Table 2.3). The full version of this table (with all included characteristics) is Supplementary Table 2.4.

Diagnostic codes for conditions are listed in Supplementary Table 2.1. Specific medications in medication categories are listed in Supplementary Table 2.9. Definitions of mental health care utilization are described in Supplementary Table 2.10.

Table 2.2. Association of antidepressant continuation in pregnancy with gestational diabetes.

	No.	No. (%) with gestational diabetes	Crude RR (95% CI)	Inverse probability of treatment weighted RR (95% CI)
No antidepressant fill in pregnancy	1211	90 (7%)	ref	ref
Any antidepressant fill in pregnancy	1634	149 (9%)	1.23 (0.95–1.58)	1.10 (0.84–1.44)[a]
SSRIs	1417	126 (9%)	1.20 (0.92–1.56)	1.10 (0.84-1.44)[b]
Citalopram	349	28 (8%)	1.06 (0.70–1.61)	0.80 (0.51-1.25)[b]
Fluoxetine	484	35 (7%)	0.98 (0.67–1.42)	0.99 (0.65-1.51)[b]
Paroxetine	151	12 (8%)	1.07 (0.60–1.91)	0.99 (0.56–1.74)[c]
Sertraline	491	54 (11%)	1.37 (0.98–1.92)	1.27 (0.89-1.82)[b]
Bupropion	225	22 (10%)	1.30 (0.82–2.06)	1.08 (0.65-1.80)[b]
Venlafaxine	104	15 (14%)	1.95 (1.17–3.26)	1.52 (0.87-2.68)[c]
Any first trimester fill	1483	141 (10%)	1.27 (0.98–1.65)	1.16 (0.89-1.52)[b]
Any second trimester fill	1181	115 (10%)	1.31 (1.00–1.71)	1.12 (0.85–1.47)[b]
Any third trimester fill	1067	93 (9%)	1.18 (0.89–1.57)	1.00 (0.74–1.34)[b]
Fill in all trimesters	871	83 (10%)	1.30 (0.97–1.74)	1.09 (0.80-1.48)[b]

RR: relative risk; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors
Numbers for specific medications may add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four), and categories are overlapping. This includes women who switched antidepressants or were using multiple antidepressants simultaneously.
Users of escitalopram, fluvoxamine, desvenlafaxine, and mirtazapine were also included in analyses but there were too few births among women exposed to these medications to present them separately.

[a]Weighted by characteristics included in Variable Set 3, listed in Supplementary Table 2.3.

[b]Weighted by characteristics included in Variable Set 2, listed in Supplementary Table 2.3.

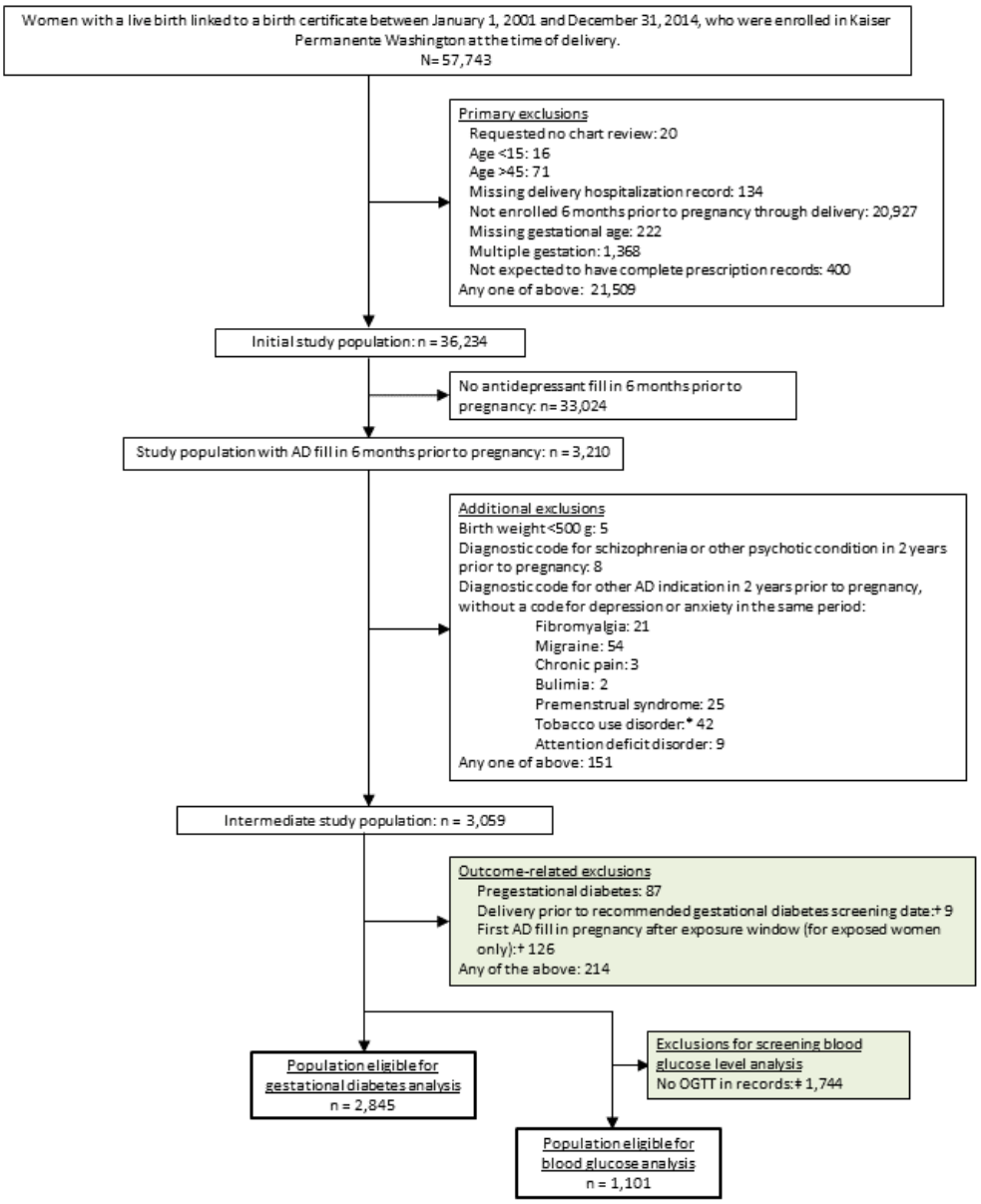
[C]Weighted by characteristics included in Variable Set 1, listed in Supplementary Table 2.3.

Table 2.3. Association of antidepressant continuation in pregnancy with blood glucose levels from a screening, 1-hour, 50 g oral glucose tolerance test.

	No.	Blood glucose levels in mg/dl Mean (SD)	Crude mean difference in mg/dl (95% CI)	Inverse probability of treatment weighted mean difference in mg/dl (95% CI)
No antidepressant fill in pregnancy	488	115 (27)	ref	ref
Any antidepressant fill in pregnancy	613	117 (30)	2.0 (-1.4 to 5.5)	2.4 (-1.5 to 6.3)[a]
SSRIs	540	117 (28)	1.5 (-1.9 to 4.9)	1.9 (-1.9 to 5.7)[a]
Citalopram	102	115 (23)	0.4 (-4.6 to 5.4)	-0.3 (-5.7 to 5.2)[a]
Fluoxetine	233	116 (29)	-0.2 (-4.8 to 4.5)	-0.9 (-6.0 to 4.1)[a]
Paroxetine	76	119 (29)	3.6 (-3.6 to 10.7)	2.6 (-4.7 to 9.9)[b]
Sertraline	161	119 (28)	3.9 (-1.1 to 8.9)	**6.7 (0.3 to 13.0)[a]**
Bupropion	84	121 (45)	5.6 (-4.3 to 15.6)	3.4 (-8.9 to 15.7)[a]
Venlafaxine	28	120 (30)	4.4 (-6.4 to 15.2)	4.5 (-6.9 to 16.0)[b]
Any first trimester fill	543	118 (31)	2.8 (-0.8 to 6.3)	3.0 (-1.1 to 7.2)[a]
Any second trimester fill	449	117 (28)	2.4 (-1.1 to 6.0)	2.7 (-1.8 to 7.2)[a]
Any third trimester fill	408	117 (28)	2.6 (-1.1 to 6.3)	1.9 (-3.1 to 7.0)[a]
Fill in all trimesters	328	119 (28)	3.7 (-0.2 to 7.6)	5.5 (-2.3 to 13.3)[a]

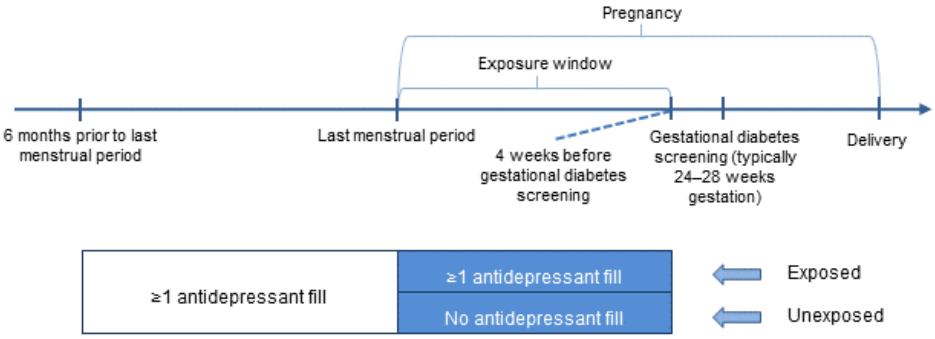
SD: standard deviation; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors
Numbers for specific medications may add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four), and categories are overlapping. This includes women who switched antidepressants or were using multiple antidepressants simultaneously.
Users of escitalopram, fluvoxamine, desvenlafaxine, and mirtazapine were also included in analyses but there were too few births among women exposed to these medications to present them separately.
[a]Weighted by characteristics included in Variable Set 2, listed in Supplementary Table 2.3.
[b]Weighted by characteristics included in Variable Set 1, listed in Supplementary Table 2.3.

Figure 2.1. Identification of women with singleton, live births and a fill for an antidepressant in the six months prior to pregnancy for analyses of gestational diabetes and screening blood glucose levels.



AD: Antidepressant; Antidepressants of interest include paroxetine, sertraline, escitalopram, citalopram, fluoxetine, fluvoxamine, desvenlafaxine, venlafaxine, bupropion, mirtazapine.
OGTT: Oral glucose tolerance test
*We only excluded deliveries to women who had a tobacco use disorder code in the 2 years prior to pregnancy if they also had a prescription fill for bupropion, as that is the only antidepressant indicated to treat tobacco use disorder.
†The exposure window spans the start of pregnancy through 4 weeks prior to gestational diabetes screening. For women missing information on date of gestational diabetes screening, we assumed they were screened at 28 weeks, based on screening guidelines. If these women delivered at or before 28 weeks gestation, we excluded them from the cohort, because they may not have had a chance for gestational diabetes screening.
‡For the analysis of screening blood glucose level, we used results from the 1-hour, 50-g oral glucose challenge. We expected 50-g OGTTs to only be present in our laboratory data for women in the Integrated Group Practice from 2001–2011, after which the Integrated Group Practice switched to 75-g OGTTs.

Figure 2.2. Study design for analyses of gestational diabetes and screening blood glucose levels.



Supplementary Materials

Supplementary Table 2.1. Disorder diagnostic codes for model covariates.

Characteristic	ICD-9-CM Code Start of Range	End of Range
Anxiety	300	300.02
	300.2	300.29
	309.21	309.21
	309.24	309.24
Obsessive compulsive disorder (type of anxiety disorder)	300.3	300.3
Posttraumatic stress disorder (type of anxiety disorder)	309.81	309.81
Depression	296.2	296.39
	296.82	296.82
	298.0	298.0
	300.4	300.4
	301.12	301.12
	311	311
	309.0	309.1
	309.28	309.28
Bipolar disorders	296	296.19
	296.4	296.81
	296.89	296.89
	301.11	301.11
	301.13	301.13
Alcohol abuse	291	291.9
	303	303.99
	305.0	305.09
Other drug abuse	292	292.99
	304	304.99
	305.2	305.99
Chronic hypertension	401.0	405.99
Chronic hypertension diagnosis during the 6 months prior to pregnancy through delivery:	642.0	642.29
	642.70	642.79
Or, hypertension, not otherwise specified diagnosis prior to 20 weeks gestation:	642.9	642.99

Some definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Table 2.2. Disorder diagnostic codes for exclusion variables.

Characteristic	ICD-9-CM Code Start of Range	End of Range
Schizophrenic disorders	295	295.99
Other psychoses	297.1	297.1
	297.3	297.9
	301.22	301.22
Other indications for AD use		
Fibromyalgia	729.1	729.1
Migraine	346	346.99
Chronic pain	338.2	338.29
	338.4	338.4
Bulimia	307.51	307.51
Tobacco use	305.1	305.1
	649.0	649.09
Attention deficit disorder	314.0	314.01
Diabetes mellitus		
During the 6 months prior to pregnancy:		
	249.0	250.99
	357.2	357.2
	362.01	362.07
	366.41	366.41
Or, during pregnancy, prior to 24 weeks gestation:	249.0	250.99
	362.01	362.07
	357.2	357.2
	366.41	366.41
	648.0	648.0

Some definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Table 2.3. Sets of characteristics included in models.

Covariates	Variable Set 1[a]	Variable Set 2[b]	Variable Set 3[c]
Year of delivery, continuous (years)	0	X	X
Maternal age at delivery, continuous (years)	X	X	X
Male infant, yes/no	0	X	X
Number of prior pregnancies (parity): Zero One Two or more	0	X[d]	X
Maternal race/ethnicity: Hispanic Non-Hispanic Asian Non-Hispanic black Non-Hispanic Native American Non-Hispanic Native Hawaiian or Other Pacific Islander Non-Hispanic white	0	X[e]	X
Maternal education level: High school diploma/general equivalency degree or less Some college Bachelor's degree or more	0	X	X
Medicaid, yes/no	0	X	X
Integrated Group Practice, yes/no	0	X	X
Chronic hypertension, yes/no	0	0	X
Pre-pregnancy weight, continuous (lbs)	0	X[f]	X
Alcohol abuse disorder diagnostic code during the two years prior to pregnancy	0	0	X
Tobacco use disorder diagnostic code during the two years prior to pregnancy	0	X	X
Drug abuse disorder diagnostic code during the two years prior to pregnancy	0	0	X
Depression disorder diagnostic code during the two years prior to pregnancy	0	X	X
Anxiety disorder diagnostic code during the two years prior to pregnancy	0	X	X
Obsessive compulsive disorder diagnostic code during the two years prior to pregnancy	0	0	X
Post-traumatic stress disorder diagnostic code during the two years prior to pregnancy	0	0	X
Bipolar disorder diagnostic code during the two years prior to pregnancy	0	X	X
Any fill of antipsychotic medication during the year prior to pregnancy	0	X	X
Any fill of benzodiazepine medication during the year prior to pregnancy	0	X	X
Any fill for hypnotic sleep medication during the year prior to pregnancy	0	X	X
Any fill for mood stabilizer medication during the year prior to pregnancy	0	X	X
Any fill for trazodone during the year prior to pregnancy	0	X	X
Any fill for tricyclic antidepressant medication during the year prior to pregnancy	0	X	X

Any fill for other anxiety medication during the year prior to pregnancy	0	X	X
Any fill for medication associated with weight gain during the year prior to pregnancy	0	X	X
Any fill for diabetes medication during the year prior to pregnancy	0	X	X
Any psychotherapy visit during the year prior to pregnancy	0	X	X
Any psychiatry visit during the year prior to pregnancy	0	X	X
Any inpatient psychiatric hospitalization during the year prior to pregnancy	0	0	X
Any fill of antipsychotic medication more than one year prior to pregnancy	0	0	X
Any fill of benzodiazepine medication more than one year prior to pregnancy	0	0	X
Any fill for hypnotic sleep medication more than one year prior to pregnancy	0	0	X
Any fill for mood stabilizer medication more than one year prior to pregnancy	0	0	X
Any fill for trazodone more than one year prior to pregnancy	0	0	X
Any fill for tricyclic antidepressant medication more than one year prior to pregnancy	0	0	X
Any fill for other anxiety medication more than one year prior to pregnancy	0	0	X
Any fill for medication associated with weight gain more than one year prior to pregnancy	0	0	X
Any fill for diabetes medication more than one year prior to pregnancy	0	0	X
Any fill for antidepressant medication more than one year prior to pregnancy	X	0	X
Any psychotherapy visit more than one year prior to pregnancy	0	0	X
Any psychiatry visit more than one year prior to pregnancy	0	0	X
Any inpatient psychiatric hospitalization more than one year prior to pregnancy	0	0	X
Receipt of 1-step gestational diabetes testing strategy[g]	0	X	X

Categorical characteristics are included in models as categorized, unless otherwise stated.

Diagnostic codes for conditions are listed in Appendix 3. Specific medications in medication categories are listed in Appendix 4. Definitions of mental health care utilization are described in Appendix 5.

[a]Variable Set 1 is used for analyses of paroxetine and venlafaxine only, where the small number of exposed women limited how many variables we could include in the models.

[b]Variable Set 2 is used for all analyses of screening blood glucose level, and in sub- and sensitivity analyses (including the multivariable adjusted analysis) for gestational diabetes, other than analyses of paroxetine and venlafaxine.

[c]Variable Set 3 is only used for the overall analysis of gestational diabetes.

[d]In sensitivity analyses that stratify by infant sex, we did not also adjust for infant sex.

[e]We combined Asian, Native American, and Native Hawaiian or Other Pacific Islander into one group ("Other") for these analyses due to small numbers.

[f]Pre-pregnancy weight is not adjusted for in sensitivity analyses that instead adjust for body mass

index.

[g]Receipt of 1-step gestational diabetes testing strategy was only included in analyses of gestational diabetes, given that the analysis of screening blood glucose level was only for those receiving the 50-g test, 1-hour test, which is part of the 2-step testing strategy.

Supplementary Table 2.4. Full set of characteristics of women and births eligible for the analysis of gestational diabetes.

Covariates	No antidepressant fill in pregnancy (n=1211)	Antidepressant fill in pregnancy (n=1634)	Unweighted SMD	Inverse probability of treatment weighted SMD
Year of delivery in years, mean (SD)	2008 (3.8)	2008 (3.8)	0.046	0.001
Maternal age at delivery, mean (SD)	29.6 (5.8)	31.4 (5.5)	0.322	0.012
Male infant, n (%)	608 (50.2)	840 (51.4)	0.024	0.007
Number of prior pregnancies (parity), n (%)				
Zero	542 (45.1)	609 (37.5)	0.156	<0.001
One	414 (34.4)	568 (34.9)	0.010	0.006
Two or more	246 (20.5)	449 (27.6)	0.126	0.009
Maternal race/ethnicity, n (%)				
Hispanic	80 (6.6)	93 (5.7)	0.038	0.008
Non-Hispanic Asian	35 (2.9)	25 (1.5)	0.093	0.002
Non-Hispanic black	48 (4.0)	37 (2.3)	0.098	0.004
Non-Hispanic Native American	13 (1.1)	25 (1.5)	0.040	0.003
Non-Hispanic Native Hawaiian or Other Pacific Islander	21 (1.7)	21 (1.3)	0.037	<0.001
Non-Hispanic white	1007 (83.6)	1425 (87.6)	0.114	0.004
Maternal education level, n (%)				
High school diploma/general equivalency degree or less	259 (21.5)	290 (17.9)	0.091	0.005
Some college	475 (39.5)	605 (37.3)	0.044	0.002
Bachelor's degree or more	470 (39.0)	726 (44.8)	0.117	0.002
Medicaid, n (%)	45 (3.7)	55 (3.4)	0.019	0.001
Integrated Group Practice, n (%)	753 (63.2)	987 (60.4)	0.036	0.006
Chronic hypertension, n (%)	36 (3.0)	67 (4.1)	0.061	0.004
Pre-pregnancy weight in lbs, mean (SD)	165.8 (45.2)	168.4 (44.5)	0.058	0.007
During the year prior to pregnancy, n (%)				
Any fill of antipsychotic medication	22 (1.8)	38 (2.3)	0.036	0.003
Any fill of benzodiazepine medication	272 (22.5)	395 (24.2)	0.041	0.003
Any fill for hypnotic sleep medication	50 (4.1)	70 (4.3)	0.008	<0.001
Any fill for mood stabilizer medication	59 (4.9)	87 (5.3)	0.021	0.014
Any fill for trazodone	110 (9.1)	164 (10.0)	0.032	0.003
Any fill for tricyclic antidepressant medication	69 (5.7)	82 (5.0)	0.030	0.003
Any fill for other anxiety medication	78 (6.4)	113 (6.9)	0.019	0.002
Any fill for medication associated with weight gain	172 (14.2)	246 (15.1)	0.024	0.003
Any fill for diabetes medication	27 (2.2)	37 (2.3)	0.002	0.003

Any psychotherapy visit	227 (18.7)	281 (17.2)	0.040	0.001
Any psychiatry visit	175 (14.4)	258 (15.8)	0.037	0.004
Any inpatient psychiatric hospitalization	9 (0.7)	16 (1.0)	0.026	0.016
During the two years prior to pregnancy, n (%)				
Alcohol abuse disorder diagnostic code	53 (4.4)	69 (4.2)	0.008	0.007
Tobacco use disorder diagnostic code	157 (13.0)	223 (13.6)	0.020	0.001
Drug abuse disorder diagnostic code	49 (4.0)	59 (3.6)	0.023	0.001
Depression disorder diagnostic code	877 (72.4)	1200 (73.4)	0.023	0.001
Anxiety disorder diagnostic code	468 (38.6)	684 (41.9)	0.066	0.004
Obsessive compulsive disorder diagnostic code	22 (1.8)	54 (3.3)	0.094	0.019
Post-traumatic stress disorder diagnostic code	39 (3.2)	52 (3.2)	0.002	0.003
Bipolar disorder diagnostic code	57 (4.7)	71 (4.3)	0.017	0.007
More than one year prior to pregnancy, n (%)				
Any fill of antipsychotic medication	22 (1.8)	39 (2.4)	0.040	0.007
Any fill of benzodiazepine medication	247 (20.4)	383 (23.4)	0.074	0.011
Any fill for hypnotic sleep medication	53 (4.4)	77 (4.7)	0.016	0.007
Any fill for mood stabilizer medication	57 (4.7)	85 (5.2)	0.023	0.015
Any fill for trazodone	124 (10.2)	156 (9.5)	0.023	0.007
Any fill for tricyclic antidepressant medication	104 (8.6)	153 (9.4)	0.027	0.001
Any fill for other anxiety medication	116 (9.6)	186 (11.4)	0.059	0.004
Any fill for medication associated with weight gain	278 (23.0)	412 (25.2)	0.053	0.002
Any fill for diabetes medication	16 (1.3)	40 (2.4)	0.083	0.001
Any fill for antidepressant medication	618 (48.9)	1016 (64.2)	0.314	0.003
Any psychotherapy visit	328 (27.1)	494 (30.2)	0.070	0.005
Any psychiatry visit	151 (12.5)	282 (17.3)	0.135	0.010
Any inpatient psychiatric hospitalization	16 (1.3)	17 (1.0)	0.026	0.006
Receipt of 1-step gestational diabetes testing strategy	208 (17.2)	267 (16.3)	0.022	0.002

SD: Standard deviation; SMD: Standardized mean difference

3% of observations were missing prenatal weight, and <1% of observations were missing race/ethnicity, parity, and education. All other observations did not have missing values.
If the SMD was ≥0.10, a standard cut point,[28] we considered the two groups to be substantially different. Weighted SMDs <0.10 indicate that we had achieved good balance in terms of measured baseline characteristics between births to exposed and unexposed women.
This table contains the study population for the analysis of gestational diabetes. The study population for the analysis of blood glucose levels from the 1-hour, 50 g oral glucose tolerance test excluded many births presented in this table (Figure 1).
This table includes all covariates used to create the inverse probability of treatment weights for the gestational diabetes overall regression models.
Diagnostic codes for conditions are listed in Supplementary Table 2.1. Specific medications in medication categories are listed in Supplementary Table 2.9. Definitions of mental health care utilization are described in Supplementary Table 2.10.

Supplementary Table 2.5. Counts and proportions of births to women with fills for specific antidepressants in pregnancy.

Antidepressant class or specific name	Antidepressant continuers N=1634 No. (%) during pregnancy
SSRIs	1417 (87%)
Citalopram	349 (21%)
Escitalopram	43 (3%)
Fluvoxamine	4 (<1%)
Fluoxetine	484 (30%)
Paroxetine	151 (9%)
Sertraline	491 (30%)
SNRIs	105 (6%)
Desvenlafaxine	1 (<1%)
Venlafaxine	104 (6%)
Bupropion	225 (14%)
Mirtazapine	10 (<1%)

SSRIs: serotonin reuptake inhibitors; SNRIs: serotonin norepinephrine reuptake inhibitors
This table contains the exposed births to women included in the analysis of gestational diabetes. The study population for the analysis of blood glucose levels from the 1-hour, 50-g oral glucose tolerance test excluded many births presented in this table (Figure 2.1).
Numbers for specific medications add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four). This includes women who switched antidepressants or were using multiple antidepressants simultaneously.

Supplementary Table 2.6. Extent of antidepressant exposure for women continuing antidepressants: Number of antidepressant medication fills and days covered[a] during the exposure window.[b]

	Overall n (%)	Single type of antidepressant[c] n (%)	Two different antidepressants[c,d] n (%)
	n=1634	n=1493[c]	n=177 [c]
Number of fills, median (IQR)	2 (1-3)	2 (1-3)	4 (3-5)
1 fill	661 (40%)	658 (45%)	NA
2 fills	409 (25%)	374 (25%)	35 (23%)
3 fills	189 (12%)	152 (10%)	37 (25%)
4 or more fills	375 (23%)	283 (19%)	77 (52%)
	n= 1634	n= 1403	n= 214
Days covered in exposure window, median (IQR)	100 (59-150)	93 (53-144)	131.5 (89-197.8)
<30	34 (2%)	32 (2%)	2 (<1%)
≥30 to 89	665 (41%)	610 (43%)	54 (25%)
≥90 to 179	770 (47%)	665 (47%)	96 (45%)
≥180 to 239	116 (7%)	85 (6%)	29 (14%)
≥240	49 (3%)	11 (<1%)	33 (15%)
Proportion of days covered in exposure window, median (IQR)	66% (36 - 92%)	61% (34 - 89%)	78% (53-120%)
<20%	168 (10%)	162 (12%)	6 (3%)
20 to 49%	432 (26%)	391 (28%)	39 (18%)
50 to 79%	420 (26%)	359 (26%)	60 (28%)
≥80%	586 (36%)	469 (33%)	103 (48%)

IQR: interquartile range

Values represent n (%) unless otherwise noted.

This table contains the exposed births to women included in the analysis of gestational diabetes. The study population for the analysis of blood glucose levels from the 1-hour, 50 g oral glucose tolerance test excluded many births presented in this table (Figure 1).

Antidepressants are commonly filled in 30, 60, or 90 days' supply at Kaiser Permanente Washington, and other lengths of days supplied are occasionally used.

8 women had fills of 3 different antidepressants in the exposure window, and 2 had fills of 4 different antidepressants in pregnancy. They are only included in the "Overall" column of the table.

[a]"Days covered" was defined as number of days supplied with an antidepressant within the exposure window[b]. This is available in the prescription fill records as a different variable from the number of pills because some patients are prescribed more than one pill of a given medication per day. For fills that only partially overlapped with pregnancy, we prorated the days covered. "Proportion of days covered" is defined as the number of days covered in the exposure window divided by the number of days in the exposure window.

[b]We defined the exposure window as the start of pregnancy through four weeks prior to gestational diabetes screening. The median length of the exposure window in our study was 168 days (~24 weeks), with an interquartile range of 159 to 174 days.

[c]The number of deliveries exposed to 1 specific antidepressant versus 2 different antidepressants in the exposure window is different when considering fills versus days covered. When describing number of fills, we only considered women with *fills* of two different antidepressants in the exposure window to be exposed to 2 different antidepressants. When describing days covered, we allowed fills prior to pregnancy that overlapped into pregnancy to contribute to the total days supplied (prorated),

which increased the number of women we considered to have exposure to 2 different antidepressants in pregnancy.

[d]For women taking 2 antidepressants, we calculated the total number of days covered by adding the number of days covered for each antidepressant (we did not attempt to account for overlap, even though some of these women may have been taking the 2 antidepressants simultaneously.) This made it possible for a woman to have more than 100% of days covered according to our calculations.

Supplementary Table 2.7. Sensitivity analyses for association of antidepressant continuation in pregnancy with gestational diabetes.

	No. of continuers Total n= 1634	No. (%) with gestational diabetes among continuers	No. of dis-continuers Total n = 1211	No. (%) with gestational diabetes among dis-continuers	RR (95% CI)
Inverse probability of treatment weighted models					
Overall model from primary analysis	1634	149 (9%)	1211	90 (7%)	1.10 (0.84–1.44)[a]
Exposure defined as ≥2 antidepressant fills	1184	109 (9%)	1211	90 (7%)	1.09 (0.82–1.44)[b]
Including BMI in model	1437	137 (10%)	1072	79 (7%)	1.15 (0.87–1.51)[b]
<50% of days covered with fills	563	43 (8%)	1211	90 (7%)	1.04 (0.72–1.50)[b,c]
≥50% of days covered with fills	840	84 (10%)	1211	90 (7%)	1.19 (0.88–1.60)[b,c]
1-step approach to gestational diabetes testing	251	41 (16%)	187	17 (9%)	1.60 (0.92–2.77)[b,d]
2-step approach to gestational diabetes testing	1147	85 (7%)	877	64 (7%)	0.96 (0.69–1.33)[b,d]
Births to women with fills overlapping pregnancy re-categorized as exposed	2021	175 (9%)	824	64 (8%)	0.95 (0.72–1.27)[b]
Anxiety or depression diagnosis in 2 years prior to pregnancy	1402	125 (9%)	1025	80 (8%)	1.05 (0.79–1.39)[b,e]
Female infant	794	74 (9%)	603	44 (7%)	1.13 (0.78-1.63)[b]
Male infant	840	75 (9%)	608	46 (8%)	1.08 (0.74-1.56)[b]
Multivariable–adjusted model					
Overall	1634	149 (9%)	1211	90 (7%)	1.12 (0.86–1.45)[f]

RR: relative risk; CI: confidence interval

[a]Repeated from Table 2 for comparison. Weighted by characteristics included in Variable Set 3 in Supplementary Table 2.3.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 2.3.

[c]Only includes women who had a fill for one specific antidepressant during the exposure window.

[d]Women whose gestational diabetes testing strategy was unclear or were missing testing records were not included.

[e]Anxiety and depression disorders defined in Supplementary Table 2.1.

[f]Adjusted for characteristics included in Variable Set 2 in Supplementary Table 2.3.

Supplementary Table 2.8. Sensitivity analyses for association of antidepressant continuation in pregnancy with blood glucose levels from a screening, 1-hour, 50 g oral glucose tolerance test.

	No. of continuers Total n= 613	Blood glucose levels in mg/dl among continuers Mean (SD)	No. of discontinuers Total n = 488	Blood glucose levels in mg/dl among discontinuers Mean (SD)	Mean difference in mg/dl (95% CI)
Inverse probability of treatment weighted models					
Overall model from primary analysis	613	117 (30)	488	115 (27)	2.4 (-1.5 to 6.3)[a,b]
Exposure defined as ≥2 antidepressant fills	435	118 (28)	488	115 (27)	2.1 (-2.7 to 6.9)[b]
Including BMI in the model	500	117 (31)	402	115 (27)	1.6 (-2.6 to 5.8)[b]
<50% of days covered with fills	216	116 (35)	488	115 (27)	1.4 (-4.9 to 7.7)[b,c]
≥50% of days covered with fills	320	118 (27)	488	115 (27)	4.1 (-1.6 to 9.7)[b,c]
Births to women with fills overlapping pregnancy re-categorized as exposed	782	117 (29)	319	116 (29)	0.2 (-4.1 to 4.4)[b]
Anxiety or depression diagnosis in 2 years prior to pregnancy	560	117 (27)	430	116 (27)	1.9 (-1.9 to 5.6)[b,d]
Female infant	297	118 (32)	259	115 (27)	5.9 (-0.3 to 12.1)[b]
Male infant	316	116 (28)	229	116 (27)	0.3 (-5.4 to 6.0)[b]
Multivariable-adjusted model					
Overall	613	117 (30)	488	115 (27)	2.3 (-1.3 to 6.0)[e]

SD: standard deviation; CI: confidence interval

[a]Repeated from Table 3 for comparison.

[b]Weighted by characteristics included in Variable Set 3 in Supplementary Table 2.3.

[c]Only includes women who had a fill for one specific antidepressant during the exposure window.

[d]Anxiety and depression disorders defined in Supplementary Table 2.1.

[e] Adjusted for characteristics included in Variable Set 2 in Supplementary Table 2.3.

Supplementary Table 2.9. Specific medications included in medication categories for model covariates.

Medication category	Specific medications included
Tricyclics and tetracyclics	Amitriptyline
	Amoxapine
	Clomipramine
	Desipramine
	Imipramine
	Doxepin
	Nortriptyline
	Protriptyline
	Trimipramine
	Maprotiline
Benzodiazepines	Alprazolam
	Chlordiazepoxide
	Clonazepam
	Clorazepate
	Diazepam
	Estazolam
	Flurazepam
	Halazepam
	Lorazepam
	Oxazepam
	Prazepam
	Quazepam
	Temazepam
	Triazolam
	Midazolam
	Bromazepam
Hypnotic sleep medication	Zolpidem
	Eszopiclone
	Zaleplon
	Ramelteon
Mood stabilizers	Lithium
	valproic acid
	Valproate
	Divalproex
	Carbamazepine
	Lamotrigine
	Oxcarbazepine
	Gabapentin
	Topiramate
	Tiagabine
	zonisamide

First generation antipsychotics	Chlorpromazine
	Fluphenazine
	Haloperidol
	loxapine
	molindone
	thiothixene
	perphenazine
	pimozide
	thioridazine
	thiothixene
	trifluoperazine
Second generation antipsychotics	aripiprazole
	asenapine
	clozapine
	iloperidone
	olanzapine
	paliperidone
	quetiapine
	risperidone
	ziprasidone
Other anti-anxiety	hydroxyzine
	meprobamate
	meprobamate
	pregabalin
	buspirone
Diabetes medications	regular insulin
	insulin aspart
	insulin glulisine
	insulin lispro
	insulin isophane
	insulin degludec
	insulin detemir
	insulin glargine
	insulin glargine
	NovoLog Mix 70/30 (insulin aspart protamine-insulin aspart)
	Humalog Mix 75/25 (insulin lispro protamine-insulin lispro)
	Humalog Mix 50/50 (insulin lispro protamine-insulin lispro)
	Humulin 70/30 (human insulin NPH-human insulin regular)
	Novolin 70/30 (human insulin NPH-human insulin regular)

Ryzodeg (insulin degludec-insulin aspart)
pramlintide
acarbose
miglitol
metformin
metformin-alogliptin
metformin-canagliflozin
metformin-dapagliflozin
metformin-empagliflozin
metformin-glipizide
metformin-glyburide
metformin-linagliptin
metformin-pioglitazone
metformin-repaglinide
metformin-rosiglitazone
metformin-saxagliptin
metformin-sitagliptin
alogliptin
alogliptin-metformin
alogliptin-pioglitazone
linagliptin
linagliptin-empagliflozin
linagliptin-metformin
saxagliptin
saxagliptin-metformin
sitagliptin
sitagliptin-metformin
sitagliptin and simvastatin
albiglutide
dulaglutide
exenatide
exenatide extended-release
liraglutide
nateglinide
repaglinide
repaglinide-metformin
dapagliflozin
dapagliflozin-metformin
canagliflozin
canagliflozin-metformin
empagliflozin
empagliflozin-linagliptin
empagliflozin-metformin
glimepiride

	glimepiride-pioglitazone glimeperide-rosiglitazone gliclazide glipizide glipizide-metformin glyburide glyburide-metformin chlorpropamide tolazamide tolbutamide rosiglitazone rosiglitazone-glimepiride rosiglitizone-metformin pioglitazone pioglitazone-alogliptin pioglitazone-glimepiride pioglitazone-metformin
Drugs that may cause weight gain[35,36]	Metoprolol Atenolol Propranolol Amlodipine Clonidine Pioglitazone Rosiglitazone fexofenadine cetirizine diphenhydramine prednisone (oral) methylprednisolone (oral) cortisone (oral)

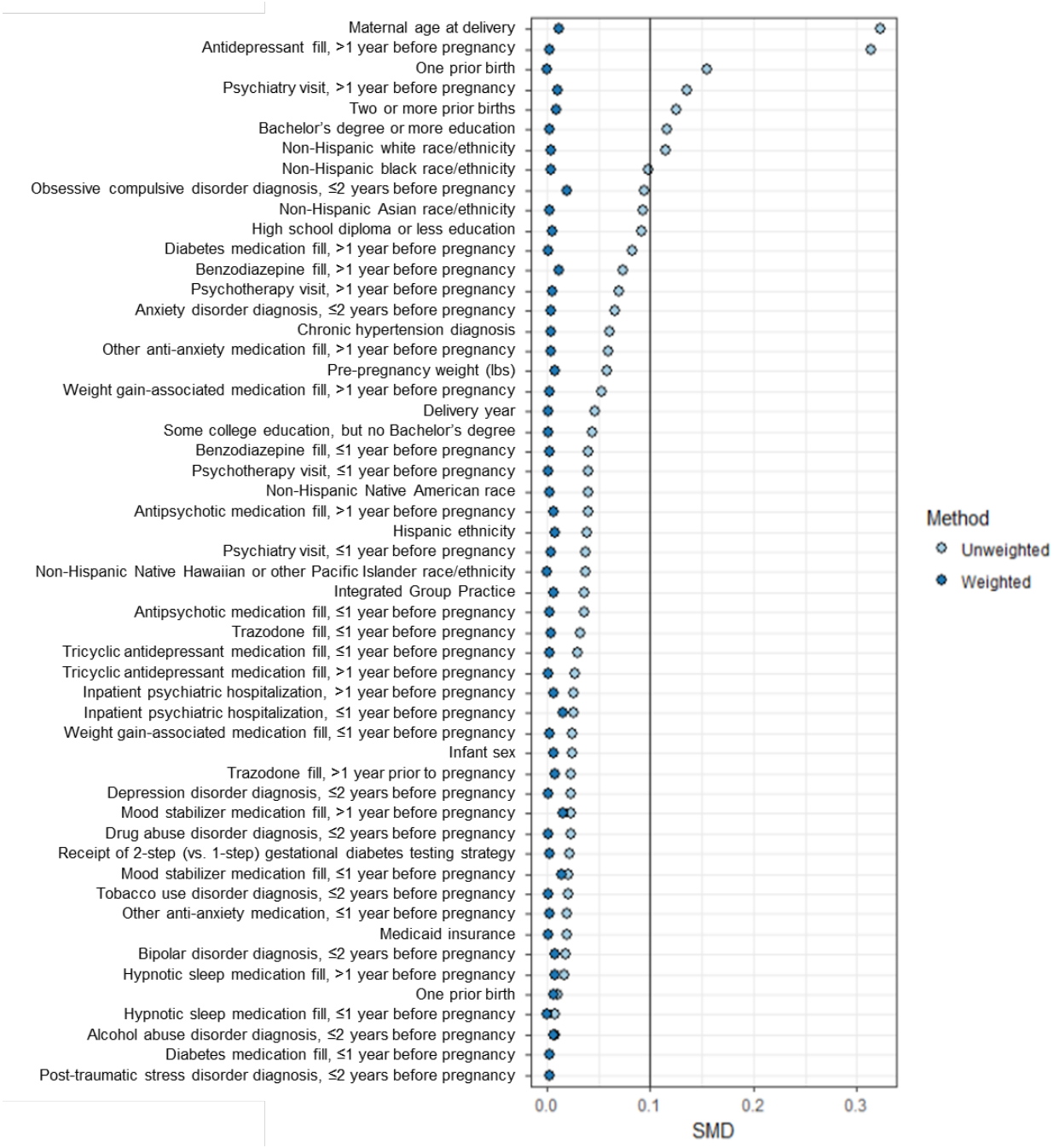
Some definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Table 2.10. Mental healthcare utilization definitions for model covariates.

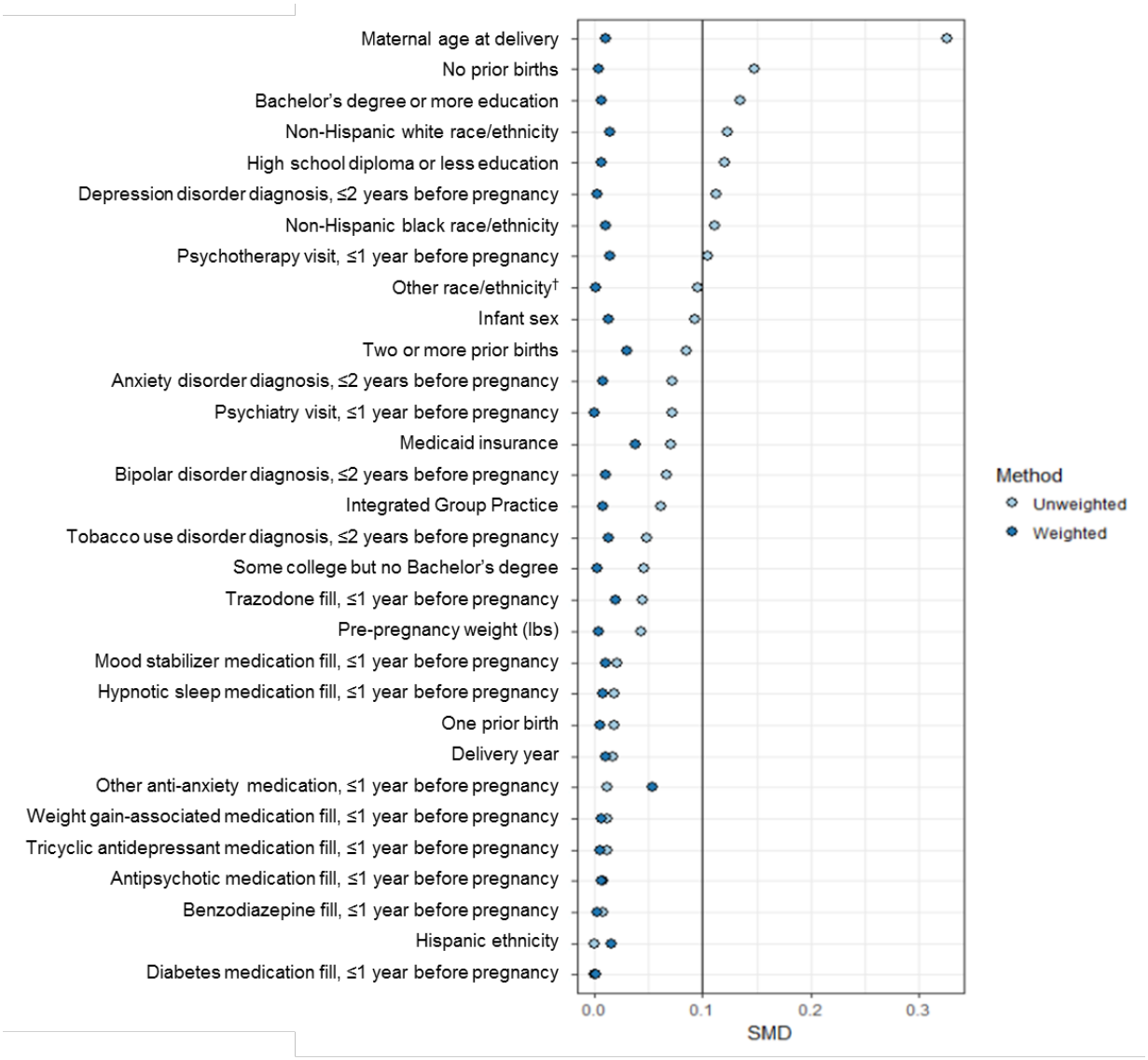
Mental health utilization type	Definition
Psychotherapy	Includes individual and group therapy. Any of the following CPT codes: 90801, 90802, 90806–9, 90812–15, 90847, 90849, 90853, or 90857, and for 2013 and 2014: 90791, 90832, 90833, 90834, or 90836–9 Does not include: 90804, 90805, 90810, 90811, 90862, and for 2013 and 2014: 90792
Psychiatry	A record of an outpatient visit that meets the two following conditions: 1. Visit is with a provider who is licensed to prescribe medication (MD, DO, ARNP, PA, or PA–C). 2. Visit is with a provider whose specialty is Mental Health or Psychiatry, *or* the encounter takes places in a Mental Health, Behavioral Health Services, or Psychiatry Department.
Inpatient psychiatric hospitalization	Any inpatient encounter with a mental health diagnosis as the principle diagnosis.

Some definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Figure 2.1. Unweighted and weighted standardized mean differences (SMDs) comparing characteristics in births to women who continued or discontinued antidepressants in pregnancy in the study population for the gestational diabetes analysis.



Supplementary Figure 2.2. Unweighted and weighted standardized mean differences (SMDs) comparing characteristics in births to women who continued or discontinued antidepressants in pregnancy in the study population for the screening blood glucose levels analysis.



†Other race/ethnicity includes Non-Hispanic Native American, Non-Hispanic Native Hawaiian or Other Pacific Islander, and Non-Hispanic Asian women.

Methods Appendix 2.1. Gestational diabetes screening strategies and policy changes.
The Integrated Group Practice changed its guidelines in April 2011 to recommend the 1-step strategy, in which all women receive a 75-g, 2-hour, diagnostic oral glucose tolerance test. Before this time in the Integrated Group Practice and in most outside clinics over all study years (affecting women seeing external providers), the standard of care was the 2-step GDM testing strategy. In the 2-step strategy, all women receive a 50-g, 1-hour oral glucose challenge, and only those who fail this screening then receive the 100-g, 3-hour, diagnostic oral glucose tolerance test. If testing strategy was unclear, we classified women based on whether they were in the Integrated Group Practice and delivery year.

Methods Appendix 2.2. Description of inverse probability of treatment weighting methods.
Propensity scores were estimated using a logistic regression model in which antidepressant use in pregnancy was regressed on potential confounders. We generated a likelihood of exposure for each birth, conditional on confounders, which was used to weight the population by the inverse probability of exposure. To avoid lowering precision, we did not include variables expected to be associated with exposure but not outcome.[37] For the exposed group, we created stabilized IPTWs by dividing the prevalence of exposure in the study population by the propensity score for each observation. For the unexposed group, we calculated stabilized IPTWs as *(1–prevalence of exposure)/(1–propensity score)*.[28] These weights were applied to the primary regression model without adjusting for any covariates. This up-weighted the "unexpected" combinations of confounders and exposure and down-weighted the "expected" combinations of confounders and exposure, in attempt to create a pseudo-population in which exposure is not associated with confounders. To assess balance on baseline covariates, we qualitatively compared exposed and unexposed groups' overlap in propensity scores using cumulative distribution functions and histograms, and checked for SMDs between groups ≥0.10.[28]

CHAPTER 3: Antidepressant continuation in pregnancy in relation to infant birthweight

Antidepressant continuation in pregnancy in relation to infant birthweight

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ABSTRACT

Background: Every year, 6-7% of pregnant women in the US (~300,000 women) use antidepressants. Many studies have assessed antidepressant use during pregnancy in relation to risk of low infant birthweight, however, most did not account for maternal mental health, possibly leading to confounding.

Objective: To assess the association of antidepressant continuation in pregnancy with infant birthweight among women using antidepressants before pregnancy.

Methods: We conducted a retrospective cohort study of singleton, live births from 2001–2014 to women enrolled in an integrated healthcare system, Kaiser Permanente Washington, using electronic health data and linked Washington State birth records. The study population was women with ≥1 antidepressant prescription filled ≤6 months before pregnancy. Women with ≥1 antidepressant fill during pregnancy were considered "exposed" (n=1,772); those without were considered "unexposed" (n=1,249). We calculated mean differences in infant birthweight and relative risks (RR) of small or large for gestational age, low birthweight (<2500 grams), and macrosomia (>4500 grams) using generalized estimating equations with inverse probability of treatment weighting to account for baseline characteristics, including pre-pregnancy mental health status.

Results: We observed slightly lower mean birthweight in babies of women who continued antidepressant use in pregnancy (mean difference: -75.7 g, 95% confidence interval [CI] -118.9 to -32.6 g). We observed greater risk of small for gestational age associated with antidepressant continuation among female infants (RR: 1.65, 95% CI: 1.09-2.50), but not among male infants (RR: 0.86, 95% CI: 0.58-1.27). After restricting continuers to women with fills in all three trimesters, we observed a decreased risk of large for gestational age (RR: 0.68, 95% CI: 0.52–0.91) and macrosomia (RR: 0.49, 95% CI: 0.25–0.99) among continuers compared with discontinuers. There was a suggestion of lower risk of large for gestational age among female infants (RR: 0.74, 95% CI: 0.55-1.00) but not among male infants (RR: 0.91, 95% CI: 0.66-1.26).

Conclusions: After accounting for maternal characteristics including mental health status, we observed female infant-specific greater risk of small for gestational age and potentially lower risk of large for

gestational age with prenatal antidepressant exposure. We also saw duration-response patterns of decreased risk of large for gestational age and macrosomia.

INTRODUCTION

At least one in every 10 pregnant women is affected by depression and anxiety, and an even higher proportion suffers from postpartum depression.[3,50,51] An Agency for Healthcare Research and Quality review weighing the risks and potential benefits of antidepressant use in pregnancy found that there was insufficient evidence to draw conclusions about the appropriate recommendation for using antidepressants in pregnancy, based on the lack of high-quality evidence.[52] A joint statement by the American College of Obstetricians and Gynecologists and the American Psychiatric Association is similarly equivocal.[4]

Many women choose to discontinue their antidepressant in pregnancy due to concerns about harming their fetus. One outcome of concern is infant birthweight, a major predictor of short-term and lifelong health. Some studies, but not all, have reported that prenatal antidepressant use was associated with lower mean birthweight and a greater risk of low birthweight (LBW, <2500 g) and small for gestational age (SGA),[53-55] but these studies did not adequately control for maternal depression or substance use. Given that these factors are associated with lower infant birthweight,[56] the findings of these studies may be at due to confounding. It is plausible that prenatal antidepressant exposure could impact infant birthweight because animal models indicate that antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs), may cause uterine blood flow restriction,[57] and that serotonin is associated with vasoconstriction.[58] Considering that selected antidepressants are associated with weight gain in non-pregnant populations, prenatal antidepressant use could also be associated with increased maternal gestational weight gain and subsequent increased risk of macrosomia (>4500 g) and large for gestational age (LGA).

We used electronic health data and linked state birth records to assess the association of continuing, versus discontinuing, antidepressant use during pregnancy and infant birthweight, including continuous birthweight, SGA, LGA, LBW, and macrosomia. To account for maternal characteristics that may bias associations of prenatal antidepressant use and perinatal outcomes, we utilized inverse probability of treatment weighted (IPTW) models. We also calculated associations by specific antidepressant medications and trimesters of exposure.

METHODS

Overview

We conducted a retrospective cohort study with data from Kaiser Permanente Washington (KPWA, formerly Group Health Cooperative), an integrated healthcare delivery system in Washington State. We required all women to be enrolled ≥6 months prior to onset of pregnancy and an antidepressant prescription fill during that period, which allowed the analyses to: (1) address the clinical decision of whether to continue antidepressants in pregnancy that these women and their providers face, and (2) limit bias due to confounding by indication. Electronic health data from KPWA were linked to Washington State birth records and provided the information necessary for our study.[24] The study was approved by the KPWA Institutional Review Board and the Washington State Department of Health Institutional Review Board (both with waivers of consent).

Study Population and Design

Our cohort was drawn from live births from January 1, 2001 through December 31, 2014 to women enrolled in KPWA. KPWA maintains extensive data on its members including patient enrollment, demographics, encounters, diagnoses, procedures, and prescription fills. Nearly two-thirds of members receive comprehensive care from KPWA healthcare providers through the Integrated Group Practice, and for these members we were able to ascertain additional data on vital signs and mental health questionnaires. We required KPWA births to be linked to a Washington State birth record because this was the source for gestational age, necessary to determine timing of antidepressant fills relative to pregnancy onset, as well as birthweight. Because some women contributed multiple births to our cohort (<1% had three births, 7% had two births, and 93% had one birth) our unit of analysis was technically "births" rather than "women", but we have used the terms interchangeably here.

We wanted to limit the study population to women taking antidepressants for depression or anxiety, as 80–90% of antidepressant use among women is for these indications.[1,3] Because women without a healthcare encounter before pregnancy did not have a chance to receive a diagnostic code for depression or anxiety, we did not require such a code (relevant diagnostic codes in Supplementary Table 3.1). However, we excluded 138 women without a depression or anxiety diagnostic code in the past two

years if they had a code for another health condition that is an accepted antidepressant indication (Figure 3.1, relevant diagnostic codes in Supplementary Table 3.2).

We defined the time window during which exposure to antidepressants was relevant to infant birthweight as the start of pregnancy through four weeks before delivery, to allow time for an effect of exposure on outcome (Figure 3.2). We excluded 30 women with their first antidepressant fill in pregnancy after this exposure window (Figure 3.1).

Exposure

Medication exposure information came from pharmacy dispensing data and included antidepressant name, date of prescription fill, and number of days supplied. We considered women with any antidepressant prescription fill during the exposure window to be "continuers" and women without such a fill to be "discontinuers" (Figure 3.2).

Exposure included SSRIs (citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline), serotonin-norepinephrine reuptake inhibitors (SNRIs; desvenlafaxine, venlafaxine), and other antidepressants (bupropion, mirtazapine). We did not include trazodone or tricyclic antidepressants because they are primarily used to treat sleep and pain disorders, respectively. We did not require continuers to fill the same antidepressant during the six months prior to pregnancy and the exposure window. Antidepressants are most commonly filled in 30, 60, or 90 days' supply at Kaiser Permanente Washington. Women with an antidepressant fill that overlapped into pregnancy but without a fill during pregnancy were categorized as discontinuers, an assumption we addressed in a sensitivity analysis (described below).

Outcomes

Infant birthweight and gestational age were ascertained from the birth certificate. LBW was defined as birthweight <2500 g and macrosomia as birthweight >4500 g. SGA and LGA were defined using sex-specific and gestational age-specific cutoffs that represent the 10^{th} and 90^{th} percentile, respectively, of the growth curve for birthweight based on the Washington State population.[59]

Covariates

We ascertained the following covariates from state birth records: parity, maternal race/ethnicity, maternal education, and pre-pregnancy weight and body mass index (BMI). Primary analyses relied on pre-pregnancy weight rather than BMI, given that BMI was not available on the birth certificate until 2003.

We obtained covariates from KPWA electronic health databases including: (1) at the time of delivery: birth year, maternal age, and infant sex, and (2) prior to pregnancy: membership in the Integrated Group Practice, Medicaid insurance coverage, chronic disease diagnoses, smoking and substance abuse diagnoses, mental health diagnoses, psychotropic prescription medication fills, and utilization of psychotherapy, psychiatry, and inpatient psychiatric hospitalization (definitions in Appendices 5, 6, and 7). We allowed collection of covariate data to go back in time as long as women were enrolled.[26]

The Patient Health Questionnaire-9 (PHQ-9) is a commonly-used, 9-item, self-reported depression screening questionnaire.[27] PHQ-9 records were only available for women in the Integrated Group Practice, where they were used from approximately 2008 onwards. During this time period, KPWA did not practice universal depression screening, but rather the PHQ-9 was typically used when the patient initially presented with symptoms of depression and periodically during follow-up to monitor response to therapy. We used baseline characteristics as covariates because adjusting for information from after the start of pregnancy could induce bias.[32]

Statistical Analysis

We described characteristics of eligible women by exposure status. We then calculated standardized mean differences (SMDs) both with and without IPTW. SMDs quantify the difference between two groups without being affected by sample size.[28]

Because PHQ-9 scores were available only for a sub-set of women in our cohort, we described PHQ-9 scores in the two years prior to pregnancy but did not include them in models.

We used generalized estimating equations with an exchangeable correlation matrix for all regression analyses, to account for the correlation among multiple births to the same woman.[29] We calculated mean differences and 95% confidence intervals (CIs) of the associations of prenatal antidepressant use with infant birthweight using an identity link function. For the analyses of LBW,

macrosomia, SGA, and LGA with antidepressant continuation in pregnancy, we used a Poisson (log) link function to calculate relative risks (RRs) and 95% CIs.

We used IPTW models in order to include more potential confounders than a multivariable adjusted model would be able to include (Methods Appendix 1).[28] Briefly, IPTW uses propensity scores to weight observations in the model by their likelihood of exposure to improve balance in baseline covariates between exposed and unexposed.

Covariates were chosen *a priori* based on our knowledge and previous literature, after considering sample size limitations. For the overall analyses for all our outcomes, we weighted the IPTW model by all variables in Variable Set 3 (Supplementary Table 3.3).

We conducted sub-analyses comparing women who continued specific antidepressants with discontinuers (the group of women who discontinued any antidepressant, as in the overall analysis). Additionally, we compared outcomes in women who continued antidepressant use in specific trimesters (regardless of use in other trimesters) with the same group of discontinuers used in the overall analysis. We used the smaller Variable Set 2 for these sub-analyses due to smaller numbers of exposed women (Supplementary Table 3.3). For analyses of paroxetine and venlafaxine, the analyses with the smallest number of users, we chose a parsimonious model based on which characteristics had SMDs comparing continuers and discontinuers of ≥0.10 (see Supplementary Table 3.4 for SMD values), and from these variables, we included those associated with a >10% change in the mean difference in birthweight after their addition to the crude model (Variable Set 1 in Supplementary Table 3.3). For consistency, we used this model for analyses of all outcomes for these two antidepressants.

Sensitivity analyses

We conducted sensitivity analyses using IPTW models, weighting for characteristics described in Variable Set 2 (Supplementary Table 3.3). First, we defined exposure as receiving ≥2 antidepressant fills to address potential exposure misclassification, which could arise if women who only filled once in pregnancy never actually took the medication. Second, we restricted the sample to women with an anxiety or depression diagnostic code in the two years before pregnancy. Third, to address the possibility of lingering effects of medication and the assumption that women whose last fill overlapped pregnancy

may have actually stopped before pregnancy onset, we conducted a sensitivity analysis that re-categorized these women as continuers. Fourth, we ran analyses separately for continuers with less than 50% of days covered with antidepressant fills and continuers with greater than or equal to 50% of days covered, to address the issue of duration-response by proportion of days exposed. For fills that only partially overlapped with pregnancy, we prorated the days covered. For these analyses, we only included women who had a fill for one specific antidepressant during the exposure window because it was difficult to distinguish sequential from simultaneous use for women who filled multiple antidepressants. Fifth, we adjusted for pre-pregnancy BMI instead of pre-pregnancy weight to address residual confounding, restricting to years when BMI was available. Sixth, we ran a multivariable-adjusted model, adjusted for characteristics in Variable Set 2 (Supplementary Table 3.3), to assess whether the associations were generally similar to IPTW analyses. Seventh, we ran analyses separately by infant sex, to assess possible differential effects of antidepressant use. For analyses of birthweight as a continuous variable, LBW, and macrosomia, we adjusted for gestational age, because studies that accounted for underlying mental health status have found an association of prenatal antidepressant use with shorter gestational age.[30,31] We did not adjust for gestational age in our main analyses of these outcomes, as it is in the causal pathway, and adjustment could lead to collider-stratification bias.[32] SGA and LGA inherently account for gestational age, so we did not include those outcomes in this sensitivity analysis.

All statistical analyses were conducted in R version 3.4.2 (R Core Team [https://www.r-project.org]).

Chart Review

We conducted a chart review for a sub-set of our cohort to investigate whether women whose last prescription fill was near the start of pregnancy were truly exposed or unexposed (sub-set described in Methods Appendix 2). Out of this sub-set, we randomly sampled 50 women whose last fill in the perinatal period was before pregnancy but overlapped into pregnancy (classified as discontinuers in the primary analysis) and 50 women whose last fill was in the first 30 days of pregnancy (classified as continuers in the primary analysis). We reviewed charts to assess the timing of discontinuing antidepressant use, to inform whether our exposure classification system for these women was correct.

RESULTS

There were 57,743 births identified in linked KPWA-Washington State birth certificate data during the study period. After applying inclusion criteria, the eligible women had 3,021 births (Figure 3.1), including 1,772 to women who continued antidepressants in pregnancy and 1,249 to women who discontinued.

Characteristics of exposed and unexposed women

Women who continued antidepressant medication during pregnancy were similar to discontinuers with a few exceptions: antidepressant continuers were slightly older, less likely to be nulliparous, and more likely to be non-Hispanic white and have higher education than women who discontinued antidepressants (Table 3.1). Continuers were also more likely than discontinuers to have had a psychiatry visit or filled an antidepressant prescription more than one year before pregnancy (Supplementary Table 3.4). The average length of enrollment prior to pregnancy, during which we allowed collection of covariate data, was 4.2 years (standard deviation [SD]: 4.1 years) for continuers and 4.5 years (SD: 4.3 years) for discontinuers. After weighting, SMDs in baseline characteristics were not meaningfully different between continuers and discontinuers (Supplementary Figure 3.1).

Among continuers, we had a record of a PHQ-9 screening before pregnancy for 363 (~61% of women who could have a record, based on data availability) compared with 285 records among discontinuers (~67% of women who could have a record). The mean pre-pregnancy score was 9.5 for continuers and 10.4 for discontinuers, both indicating moderate depression (SDs: 6.6 and 6.7, respectively).

Counts of continuers filling specific antidepressants and extent of exposure in pregnancy are included in Supplementary Tables 3.5 and 3.6.

Birth outcomes

Antidepressant continuers had babies with slightly smaller unadjusted mean birthweights, compared with discontinuers (3406 g, SD: 566 g versus 3461 g, SD: 546 g, respectively, Table 3.2), and this difference remained after accounting for confounders (mean difference: -75.7, 95% CI: 118.9 to -32.6). Women who

used citalopram or venlafaxine, or had an antidepressant fill in the second trimester, third trimester, or in all three trimesters, had the smallest babies, as compared with discontinuers (Table 3.2).

Among both continuers and discontinuers, the crude incidence of SGA was 7% (Table 3.3). In the IPTW analysis, women who continued antidepressants in pregnancy did not have greater risk of SGA than discontinuers (RR: 1.19, 95% CI: 0.89-1.58). Results were generally unchanged in analyses of specific antidepressant medications or trimesters of exposure.

The crude incidence of LGA was 10% among infants born to continuers and 11% among discontinuers (Table 3.4). After accounting for confounders, women who continued antidepressants had a non-statistically significant decreased risk of having an LGA infant as compared with discontinuers (RR: 0.82, 95% CI: 0.66-1.03). There was stronger evidence for this association when comparing continuers of any SSRI (RR: 0.77, 95% CI: 0.61-0.97), continuers of citalopram (RR: 0.62, 95% CI: 0.40-0.96), continuers in the second trimester (RR: 0.75, 95% CI: 0.59-0.96), continuers in the third trimester (RR: 0.71, 95% CI: 0.55-0.92), and continuers in all trimesters (RR: 0.68, 95% CI: 0.52-0.91) with discontinuers.

Five percent of babies born to women who continued antidepressants in pregnancy had LBW, compared with 4% among those who discontinued (Table 3.5). In the IPTW analysis, women with any antidepressant continuation in pregnancy had some evidence of higher risk of having a LBW baby, as compared with discontinuers, but this result was not statistically significant (RR: 1.36, 95% CI 0.94-1.98). There was a suggestion of substantially greater risk of LBW for continuers using bupropion (RR: 1.88, 95% CI: 0.89-3.95, respectively).

Macrosomia was rare, with a crude incidence of 2% in both continuers and discontinuers (Table 3.5). We did not observe differing risk of macrosomia comparing continuers with any antidepressant use with discontinuers in overall analyses (RR: 0.75, 95% CI: 0.44-1.27), but we observed markedly lower risk after restricting continuers to women with any fill in the second trimester (RR: 0.52, 95% CI: 0.28-0.95), any fill in the third trimester (RR: 0.50, 95% CI: 0.27-0.93), and fills in all trimesters (RR: 0.49, 95% CI 0.25-0.99).

Sensitivity analyses

In analyses defining exposure as receiving ≥2 antidepressant fills, we observed stronger associations than in the overall analysis for mean birthweight (-110.2 g, 95% CI: -155.4 to -65.1), LGA (RR: 0.71, 95% CI: 0.55-0.91), and macrosomia (RR: 0.53, 95% CI: 0.29-0.97) (Supplementary Tables 3.7, 3.8, and 3.9). When restricting continuers to women with ≥50% of days covered, we found stronger associations, as compared with discontinuers, with lower mean birthweight (mean difference: -110.5 g, 95% CI: -166.6 to -54.5 g, Supplementary Table 3.7) and suggestions of smaller risk of macrosomia (RR: 0.55, 95% CI: 0.26-1.16, Supplementary Table 3.9) and greater risk of LBW (RR: 1.54, 95% CI: 1.00-2.38, Supplementary Table 3.10), although the latter two findings were not statistically significant. Associations were attenuated for mean birthweight and LBW when restricting continuers to women with <50% of days covered with antidepressant medication.

For female infants, we observed stronger associations with antidepressant continuation than in the overall analysis, with lower mean birthweight (mean difference: -105.4 g, 95% CI: -163.0 to -47.7, Supplementary Table 3.7), increased risk of SGA (RR 1.65, 95% CI: 1.09-2.50, Supplementary Table 3.11), and a trend toward decreased risk of LGA (RR: 0.74, 95% CI: 0.55-1.00, Supplementary Table 3.8), whereas associations in male infants were attenuated (mean difference in birthweight: -50.8 g, 95% CI: -108.6 to 7.1) and potentially reversed (RR of SGA: 0.86, 95% CI: 0.58-1.27), as compared with the overall analysis. Adjustment for gestational age attenuated the associations for analyses of mean birthweight and LBW (Supplementary Tables 3.7 and 3.10).

Results were generally similar to the overall analyses in sensitivity analyses restricting to women with an anxiety or depression diagnosis, re-categorizing women with prescriptions that overlapped pregnancy as exposed, adjusting for BMI, and using multivariable models.

Chart review

We reviewed medical records for 50 women with an antidepressant fill before pregnancy that included enough days' supply to overlap into pregnancy. Forty-two charts (84%) contained information about when the women discontinued their antidepressant. Of those, 36 (72%) had a record stating they discontinued after the start of pregnancy, and the records for the other six stated they discontinued before pregnancy.

Among those who discontinued after the start of pregnancy, 24 (67%) stopped between 4 and 8 weeks gestation. A positive pregnancy test typically prompted discontinuation.

Among 50 charts for women with an antidepressant fill in the first 30 days of pregnancy but no subsequent fill during pregnancy, for 47 we found information indicating they discontinued their antidepressant after the start of pregnancy; the other three did not contain information about timing of discontinuation. Of those who discontinued after the start of pregnancy, 29 (62%) stopped between 4 and 8 weeks gestation, and as in women with overlapping prescriptions, this also typically followed a positive pregnancy test.

DISCUSSION

We observed slightly lower mean birthweight among babies of women who continued antidepressant use in pregnancy, although this less than a quarter pound difference in weight was likely not clinically important. Infants born to women who continued antidepressants in pregnancy were not at greater risk of SGA or LBW in overall analyses; however, additional analyses indicated that greater risk of SGA was present for female but not male infants, as well as potentially greater risk of LBW for those with longer duration of use during pregnancy. We also found a suggestion of lower risk of LGA for female but not male infants. We found stronger evidence of lower risk of LGA specific to continuation of SSRIs, as well as lower risk of both LGA and macrosomia with longer duration of use or use later in pregnancy. We are less certain that our findings apply to antidepressants with few users in our study (e.g. bupropion, venlafaxine, escitalopram) and given that we assessed a large number of associations, all our findings warrant confirmation.

Similar to our study, most previous studies that analyzed the difference in mean infant birthweight reported small differences that were not clinically meaningful.[14,15,55,60-63] And although a 2012 systematic review stated, “There is considerable evidence that fetuses exposed to antidepressants are delivered small for gestational age [SGA],”[64] studies that sufficiently accounted for mental health status and other potential confounders, such as substance abuse, did not report greater risk of SGA, including a study that compared discordantly-exposed siblings (RR: 1.01, 95% CI: 0.81-1.25)[31] and two studies comparing women who used antidepressants in pregnancy with women who had used antidepressants prior to

pregnancy (RR: 0.93, 95% CI: 0.73-1.19[65] and RR: 1.00, 95% CI: 0.87-1.15[66]). These studies were consistent with our overall findings, potentially because their study designs accounted for unmeasured residual confounding. To our knowledge, studies that have adequately addressed confounding have not assessed risk separately for male and female infants, so we were not able to compare our finding of greater risk of SGA specific to females with previous literature. As with studies of SGA, a recent meta-analysis observed a greater risk of LBW associated with antidepressant use in pregnancy,[67] but studies restricting to a comparator group with a history of depression found varying results, with two reporting no association (RR: 1.00, 95% CI: 0.74-1.35[66] and RR: 1.1, 95% CI: 0.9-1.3,[68] second decimal place not presented), consistent with our study, and two reporting a more than 2-fold greater risk (OR: 2.26; 95% CI: 1.31-3.91[69] and OR: 2.73, 95% CI: 0.92-8.09[70]). Findings in the latter two studies may be partially explained by residual confounding by mental health severity.

There is minimal literature focused on antidepressant use in pregnancy and excessive infant birthweight. Consistent with our findings, a large, Swedish cohort study observed that use later in pregnancy and use both early and later in pregnancy was associated with lower risk of macrosomia (OR: 0.86, 95% CI: 0.74-0.99 and OR: 0.86, 95% CI: 0.73-1.03, whereas use early in pregnancy was not associated with macrosomia (OR: 1.04, 95% CI: 0.95-1.13).[42] However, their findings for LGA were inconsistent with ours: they did not observe lower risk of LGA associated with use later in pregnancy (OR: 1.08, 95% CI: 0.97-1.20), use both early and later in pregnancy (OR: 1.15, 95% CI: 1.01-1.30), or lower risk associated with SSRI use later in pregnancy (OR: 1.06, 95% CI: 0.93-1.19), and another study observed substantially greater risk of LGA associated with any antidepressant use early in pregnancy (OR: 1.71, 95% CI: 1.20).[71] The conflicting findings, as compared with our study, could be explained by their comparisons to the general population of pregnant women, instead of restricting to those with depression or anxiety, and lack of adjustment for mental health status and other potential confounders, such as substance abuse.

Strengths of our study include the use of a large, well-defined study population, availability of prescription fill data (recorded prospectively, which prevents recall bias), and extensive information about baseline characteristics, including mental health care utilization, which we used to create IPTWs to address confounding. We also had scores from PHQ-9 depression screenings, and although they were

only available for a portion of our population, we were reassured to see that pre-pregnancy depression scores were very similar between continuers and discontinuers. Our associations were stronger with longer duration of exposure, which follows the dose-response principle, and were also stronger for exposure in the second and third trimester, which is when the largest amount of fetal growth occurs.

Our study had several limitations. There were small numbers of women continuing certain antidepressants, leaving us underpowered to detect modest effects. Despite our efforts to address confounding by indication, we cannot discount the possibility of residual confounding. If women with one antidepressant fill in pregnancy did not consume the medication, there could be misclassification of exposure, potentially attenuating our risk estimates. The chart review indicated that most women whose last prescription of an antidepressant medication overlapped the beginning of pregnancy had some exposure (typically 2–6 weeks of exposure after conception), but we classified them as unexposed. Considering that this is a short length of exposure very early in pregnancy, it may have been ideal to exclude them from both the exposed and unexposed groups. There was evidence of effect measure modification by infant sex for birthweight and SGA, and we may have induced bias by failing to stratify by it for all analyses. Also, our study population was largely non-Hispanic white and commercially insured, and we were limited to live births, which may limit generalizability of the findings.

Many outcomes beyond infant birthweight should be considered when deciding whether to continue antidepressants in pregnancy, including neonatal syndromes, childhood neurodevelopmental outcomes, and the woman's mental health and wellbeing during and immediately after pregnancy. For infant birthweight, we observed that antidepressant continuation in pregnancy was associated with greater risk of SGA only among female infants and longer duration of prenatal antidepressant exposure was associated with decreased risk of large for gestational age and macrosomia. Future research is warranted to confirm these findings, including investigating whether there is a duration-response or threshold effect, whether these findings are consistent for antidepressants with few users in our study, and whether the effects of antidepressants on birthweight are stronger in female infants. If our findings are confirmed, women and their providers may be reassured that there is not evidence of dramatic changes in birthweight associated with antidepressant use, and may need to consider a nuanced approach, considering duration of use and infant sex.

Table 3.1. Selected baseline characteristics of women with births in our cohort.

Covariates	No antidepressant fill in pregnancy (n=1249)	Antidepressant fill in pregnancy (n=1772)	Unweighted SMD	Inverse probability of treatment weighted SMD
Maternal age at delivery, mean (SD)	29.7 (5.8)	31.4 (5.4)	0.305	0.007
Number of prior pregnancies (parity), n (%)				
Zero	556 (44.9%)	656 (37.3%)	0.155	<0.001
One	426 (34.4%)	617 (35.0%)	0.014	0.004
Two or more	257 (20.7%)	488 (27.7%)	0.133	0.019
Maternal race/ethnicity, n (%)				
Hispanic	87 (7.0%)	107 (6.1%)	0.038	0.004
Non-Hispanic Asian	35 (2.8%)	27 (1.5%)	0.088	0.001
Non-Hispanic black	50 (4.0%)	38 (2.2%)	0.108	0.003
Non-Hispanic Native American	15 (1.2%)	26 (1.5%)	0.023	0.003
Non-Hispanic Native Hawaiian or Other Pacific Islander	21 (1.7%)	23 (1.3%)	0.032	0.002
Non-Hispanic white	1033 (83.2%)	1543 (87.5%)	0.120	<0.001
Maternal education level, n (%)				
High school diploma/general equivalency degree or less	273 (22.0%)	326 (18.5%)	0.087	<0.001
Some college	492 (39.7%)	653 (37.1%)	0.053	0.004
Bachelor's degree or more	474 (38.3%)	780 (44.3%)	0.124	0.003
Medicaid, n (%)	48 (3.8%)	61 (3.4%)	0.021	0.001
Pre-pregnancy weight in lbs, mean (SD)	167.2 (46.2)	170.2 (45.4)	0.066	0.009
During the two years prior to pregnancy, n (%)				
Alcohol abuse disorder	53 (4.2%)	76 (4.3%)	0.002	0.016
Tobacco use disorder	165 (13.2%)	250 (14.1%)	0.026	0.005
Drug abuse disorder	49 (3.9%)	63 (3.6%)	0.019	0.008
Depression disorder	906 (72.5%)	1300 (73.4%)	0.019	0.003
Anxiety disorder	482 (38.6%)	742 (41.9%)	0.067	0.002
Obsessive compulsive disorder	22 (1.8%)	57 (3.2%)	0.094	0.012
Post-traumatic stress disorder	41 (3.3%)	57 (3.2%)	0.004	0.001
Bipolar disorder	58 (4.6%)	78 (4.4%)	0.012	0.001
During the year prior to pregnancy, n (%)				
Any fill of antipsychotic medication	23 (1.8%)	40 (2.3%)	0.029	0.011
Any fill of benzodiazepine medication	279 (22.3%)	425 (24.0%)	0.039	0.025
Any fill for mood stabilizer medication	59 (4.7%)	95 (5.4%)	0.029	0.047
Any fill for medication associated with weight gain	178 (14.3%)	270 (15.2%)	0.028	0.023
Any fill for diabetes medication	38 (3.0%)	65 (3.7%)	0.035	0.015
Any psychotherapy visit	231 (18.5%)	303 (17.0%)	0.038	0.010
Any psychiatry visit	177 (14.2%)	281 (15.9%)	0.047	0.018
Any inpatient psychiatric	9 (0.7%)	17 (1.0%)	0.026	0.011

hospitalization

SD: Standard deviation; SMD: Standardized mean difference
If the SMD was ≥0.10, a standard cut point,[28] we considered the two groups to be substantially different. Weighted SMDs <0.10 indicate that we had achieved good balance in terms of measured baseline characteristics between births to exposed and unexposed women.
This table includes a subset of all covariates that were used to create the inverse probability of treatment weights and included in the overall regression models (Variable Set 3 in Supplementary Table 3.3). The full version of this table (with all included characteristics) is Supplementary Table 3.4. Diagnostic codes for conditions are listed in Supplementary Table 3.1. Specific medications in medication categories are listed in Supplementary Table 3.12. Definitions of mental health care utilization are described in Supplementary Table 3.13.

Table 3.2. Antidepressant continuation in pregnancy and mean infant birthweight.

	No.	Birthweight in g Mean (SD)	Crude mean difference in g (95% CI)	Inverse probability of treatment weighted mean difference in g (95% CI)
No antidepressant fill in pregnancy	1249	3461 (546)	ref	ref
Any antidepressant fill in pregnancy	1772	3406 (566)	-57.1 (-97.2 to -17.0)	-75.7 (-118.9 to -32.6)[a]
SSRIs	1536	3403 (562)	-60.3 (-101.7 to -18.9)	-84.1 (-126.9 to -41.2)[b]
Citalopram	381	3398 (512)	-68.8 (-129.3 to -8.3	-67.7 (-139.1 to 3.7)[b]
Fluoxetine	514	3399 (555)	-64.1 (-120.5 to -7.7)	-101.3 (-163.6 to -39.1)[b]
Paroxetine	162	3459 (497)	-6.8 (-90.4 to 76.8)	-37.0 (-116.4 to 42.40)[c]
Sertraline	546	3387 (612)	-72.0 (-132.6 to -11.4)	-76.1 (-137.4 to -14.7)[b]
Bupropion	242	3403 (582)	-51.6 (-131.1 to 27.9)	-50.5 (-151.9 to 50.8)[b]
Venlafaxine	110	3426 (557)	-84.8 (-186.3 to 16.6)	-119.4 (-230.7 to -8.20)[c]
Any first trimester fill	1534	3408 (565)	-55.2 (-96.6 to -13.8)	-73.1 (-116.0 to -30.2)[b]
Any second trimester fill	1249	3385 (567)	-78.1 (-121.9 to -34.2)	-101.1 (-147.1 to -55.1)[b]
Any third trimester fill	1191	3383 (550)	-77.2 (-120.8 to -33.5)	-105.0 (-151.3 to -58.6)[b]
Fill in all trimesters	908	3378 (544)	-83.6 (-130.6 to -36.6)	-107.8 (-159.6 to -55.9)[b]

g: grams; SD: standard deviation; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors

Numbers for specific medications may add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four), and categories are overlapping.

SSRI antidepressants also include escitalopram and fluvoxamine, and other types of antidepressants include mirtazapine and desvenlafaxine, but there were too few births exposed to these medications to present separately here.

[a]Weighted by characteristics included in Variable Set 3 in Supplementary Table 3.3.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 3.3.

[c]Weighted by characteristics included in Variable Set 1 in Supplementary Table 3.3.

Table 3.3. Association of antidepressant continuation in pregnancy with small for gestational age.

	No.	No. (%) with small for gestational age	Crude RR (95% CI)	Inverse probability of treatment weighted RR (95% CI)
No antidepressant fill in pregnancy	1249	82 (7%)	ref	ref
Any antidepressant fill in pregnancy	1772	130 (7%)	1.13 (0.86-1.47)	1.19 (0.89-1.58)[a]
SSRIs	1536	107 (7%)	1.07 (0.81-1.41)	1.09 (0.81-1.46)[b]
Citalopram	381	26 (7%)	1.03 (0.67-1.58)	0.87 (0.52-1.45)[b]
Fluoxetine	514	33 (6%)	0.98 (0.66-1.44)	1.03 (0.68-1.56)[b]
Paroxetine	162	10 (6%)	0.93 (0.49-1.76)	0.80 (0.39-1.66)[c]
Sertraline	546	44 (8%)	1.24 (0.87-1.77)	1.19 (0.81-1.75)[b]
Bupropion	242	22 (9%)	1.32 (0.80-2.18)	1.32 (0.80-2.19)[b]
Venlafaxine	110	9 (8%)	1.20 (0.59-2.43)	1.29 (0.61-2.71)[c]
Any first trimester fill	1534	110 (7%)	1.10 (0.84-1.45)	1.11 (0.83-1.48)[b]
Any second trimester fill	1249	89 (7%)	1.09 (0.82-1.46)	1.17 (0.86-1.59)[b]
Any third trimester fill	1191	84 (7%)	1.08 (0.80-1.45)	1.11 (0.81-1.52)[b]
Fill in all trimesters	908	62 (7%)	1.11 (0.81-1.52)	1.08 (0.77-1.53)[b]

RR: relative risk; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors
Numbers for specific medications may add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four), and categories are overlapping.
SSRI antidepressants also include escitalopram and fluvoxamine, and other types of antidepressants include mirtazapine and desvenlafaxine, but there were too few births exposed to these medications to present separately here.

[a]Weighted by characteristics included in Variable Set 3 in Supplementary Table 3.3.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 3.3.

[c]Weighted by characteristics included in Variable Set 1 in Supplementary Table 3.3.

Table 3.4. Association of antidepressant continuation in pregnancy with large for gestational age.

	No.	No. (%) with large for gestational age	Crude RR (95% CI)	Inverse probability of treatment weighted RR (95% CI)
No antidepressant fill in pregnancy	1249	139 (11%)	ref	ref
Any antidepressant fill in pregnancy	1772	180 (10%)	0.91 (0.74-1.12)	0.82 (0.66-1.03)[a]
SSRIs	1536	151 (10%)	0.88 (0.71-1.10)	**0.77 (0.61-0.97)**[b]
Citalopram	381	27 (7%)	**0.64 (0.43-0.95)**	**0.62 (0.40-0.96)**[b]
Fluoxetine	514	51 (10%)	0.89 (0.65-1.20)	0.78 (0.56-1.08)[b]
Paroxetine	162	17 (10%)	0.92 (0.56-1.52)	0.63 (0.36-1.11)[c]
Sertraline	546	58 (11%)	0.96 (0.72-1.28)	0.89 (0.65-1.22)[b]
Bupropion	242	27 (11%)	0.98 (0.65-1.46)	1.15 (0.72-1.82)[b]
Venlafaxine	110	10 (9%)	0.81 (0.44-1.48)	0.64 (0.30-1.36)[c]
Any first trimester fill	1534	157 (10%)	0.91 (0.74-1.13)	0.81 (0.65-1.02)[b]
Any second trimester fill	1249	119 (10%)	0.85 (0.67-1.08)	**0.75 (0.59-0.96)**[b]
Any third trimester fill	1191	108 (9%)	0.81 (0.64-1.04)	**0.71 (0.55-0.92)**[b]
Fill in all trimesters	908	79 (9%)	0.78 (0.60-1.02)	**0.68 (0.52-0.91)**[b]

RR: relative risk; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors
Numbers for specific medications may add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four), and categories are overlapping.
SSRI antidepressants also include escitalopram and fluvoxamine, and other types of antidepressants include mirtazapine and desvenlafaxine, but there were too few births exposed to these medications to present separately here.

[a]Weighted by characteristics included in Variable Set 3 in Supplementary Table 3.3.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 3.3.

[c]Weighted by characteristics included in Variable Set 1 in Supplementary Table 3.3.

Table 3.5. Association of antidepressant continuation in pregnancy with low birthweight (<2500 g)**.**

	No.	No. (%) with low birthweight	Crude RR (95% CI)	Inverse probability of treatment weighted RR (95% CI)
No antidepressant fill in pregnancy	1249	50 (4%)	ref	ref
Any antidepressant fill in pregnancy	1772	87 (5%)	1.23 (0.87-1.72)	1.36 (0.94-1.98)[a]
SSRIs	1536	74 (5%)	1.36 (0.94-1.98)	1.36 (0.94-1.98)[b]
Citalopram	381	17 (4%)	1.12 (0.65-1.92)	1.31 (0.62-2.78)[b]
Fluoxetine	514	21 (4%)	1.02 (0.62-1.68)	1.20 (0.70-2.07)[b]
Sertraline	546	33 (6%)	1.51 (0.99-2.32)	1.56 (0.98-2.50)[b]
Bupropion	242	15 (6%)	1.52 (0.86-2.70)	1.88 (0.89-3.95)[b]
Venlafaxine	110	6 (5%)	1.19 (0.48-2.92)	---
Any first trimester fill	1534	76 (5%)	1.24 (0.87-1.75)	1.35 (0.93-1.96)[b]
Any second trimester fill	1249	66 (5%)	1.32 (0.92-1.89)	**1.48 (1.00-2.17)**[b]
Any third trimester fill	1191	60 (5%)	1.26 (0.87-1.81)	1.41 (0.95-2.10)[b]
Fill in all trimesters	908	47 (5%)	1.29 (0.88-1.91)	1.46 (0.95-2.26)[b]

RR: relative risk; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors
Numbers for specific medications may add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four), and categories are overlapping.
SSRI antidepressants also include escitalopram, fluvoxamine, and paroxetine, and other types of antidepressants include mirtazapine and desvenlafaxine, but there were too few births exposed to these medications to present separately here.
Cells with "---" were too small to run models.

[a]Weighted by characteristics included in Variable Set 3 in Supplementary Table 3.3.

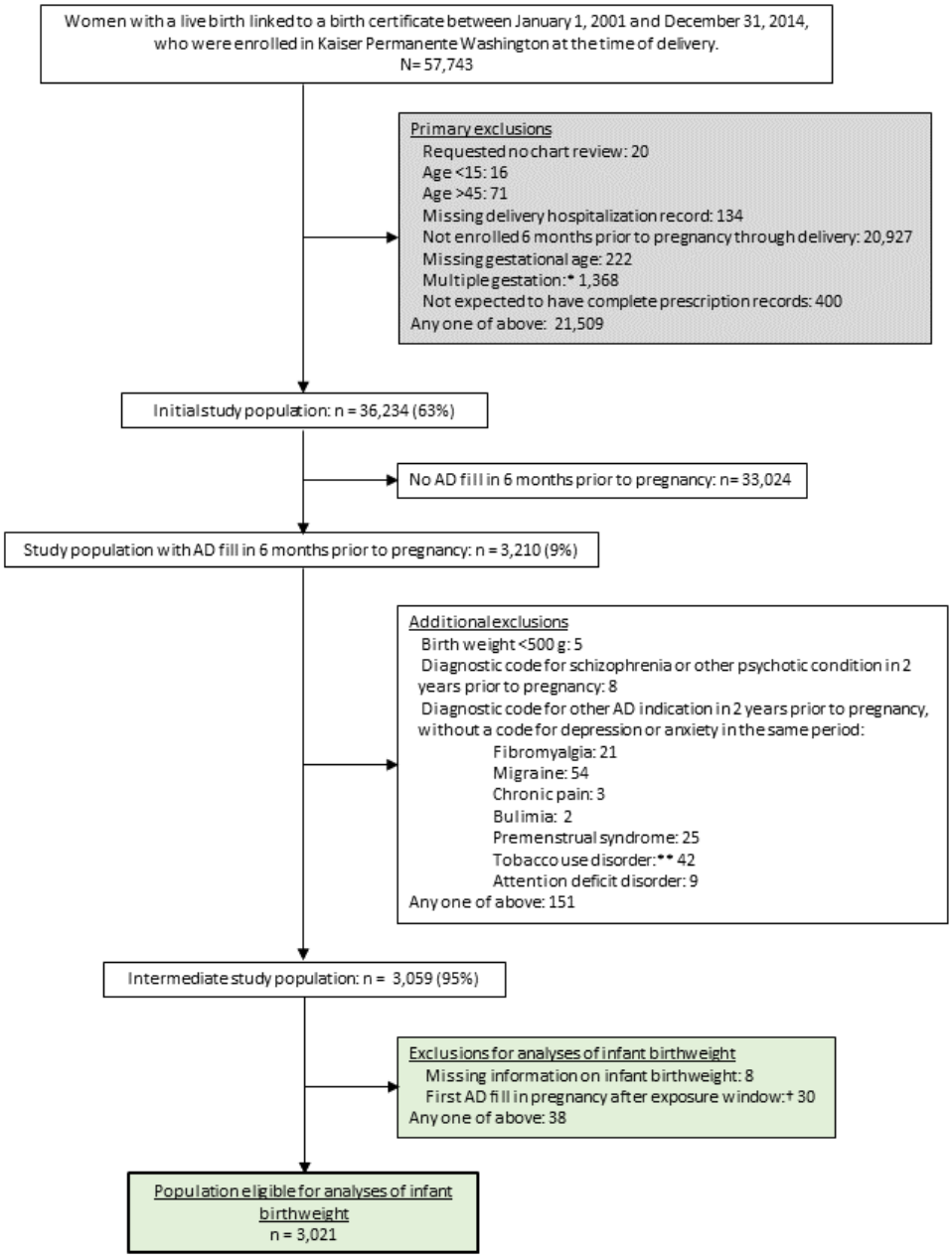
[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 3.3.

Table 3.6. Association of antidepressant continuation in pregnancy with macrosomia (≥4500 g).

	No.	No. (%) with macrosomia	Crude RR (95% CI)	Inverse probability of treatment weighted RR (95% CI)
No antidepressant fill in pregnancy	1249	28 (2%)	ref	ref
Any antidepressant fill in pregnancy	1772	38 (2%)	0.96 (0.59-1.55)	0.75 (0.44-1.27)[a]
SSRIs	1536	32 (2%)	0.93 (0.56-1.53)	0.74 (0.44-1.24)[b]
Fluoxetine	514	13 (3%)	1.13 (0.59-2.16)	1.13 (0.58-2.22)[b]
Sertraline	546	12 (2%)	0.98 (0.50-1.92)	0.80 (0.40-1.60)[b]
Bupropion	242	5 (2%)	0.92 (0.36-2.37)	---
Any first trimester fill	1534	34 (2%)	0.99 (0.60-1.62)	0.82 (0.49-1.37)[b]
Any second trimester fill	1249	19 (2%)	0.68 (0.38-1.21)	**0.52 (0.28-0.95)**[b]
Any third trimester fill	1191	18 (2%)	0.67 (0.37-1.21)	**0.50 (0.27-0.93)**[b]
Fill in all trimesters	908	13 (1%)	0.64 (0.33-1.23)	**0.49 (0.25-0.99)**[b]

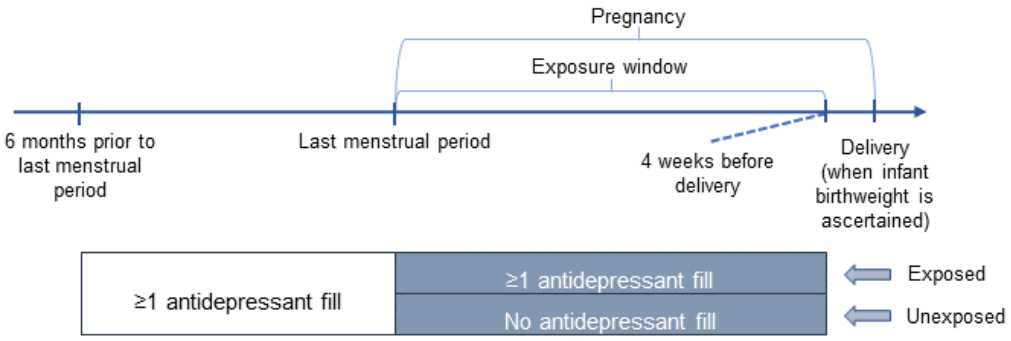
RR: relative risk; CI: confidence interval; SSRIs: selective serotonin reuptake inhibitors
Numbers for specific medications may add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four), and categories are overlapping.
SSRI antidepressants also include escitalopram, fluvoxamine, paroxetine, and citalopram, and other types of antidepressants include mirtazapine and desvenlafaxine, but there were too few births exposed to these medications to present separately here.
Cells with "---" were too small to run models.
[a]Weighted by characteristics included in Variable Set 3 in Supplementary Table 3.3.
[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 3.3.

Figure 3.1. Identification of women with singleton, live births and a fill for an antidepressant in the six months prior to pregnancy for analyses of infant birthweight.



AD: antidepressant; Antidepressants of interest include paroxetine, sertraline, escitalopram, citalopram, fluoxetine, fluvoxamine, desvenlafaxine, venlafaxine, bupropion, mirtazapine.
LBW: low birth weight, LGA: large for gestational age, SGA: small for gestational age
*We excluded twin and higher order births because birthweight is typically very different for these babies.
**We only excluded births to women who had a tobacco use disorder code in the 2 years prior to pregnancy if they also had a prescription fill for bupropion, as that is the only antidepressant indicated to treat tobacco use disorder.
†The exposure window spans the start of pregnancy through 4 weeks prior to delivery.

Figure 3.2. Study design for analyses of infant birthweight.



Supplementary Materials

Supplementary Table 3.1. Disorder diagnostic codes for model covariates.

Characteristic	ICD-9 Code Start of Range	End of Range
Anxiety	300	300.02
	300.2	300.29
	309.21	309.21
	309.24	309.24
Obsessive compulsive disorder	300.3	300.3
Posttraumatic stress disorder	309.81	309.81
Depression	296.2	296.39
	296.82	296.82
	298.0	298.0
	300.4	300.4
	301.12	301.12
	311	311
	309.0	309.1
	309.28	309.28
Bipolar disorders	296	296.19
	296.4	296.81
	296.89	296.89
	301.11	301.11
	301.13	301.13
Alcohol abuse	291	291.9
	303	303.99
	305.0	305.09
Other drug abuse	292	292.99
	304	304.99
	305.2	305.99
Diabetes mellitus		
During the 6 months prior to pregnancy:	249.0	250.99
	357.2	357.2
	362.01	362.07
	366.41	366.41
Or, during pregnancy, prior to 24 weeks gestation:	249.0	250.99
	362.01	362.07
	357.2	357.2
	366.41	366.41
	648.0	648.0
Chronic hypertension	401.0	405.99
Chronic hypertension diagnosis during the 6 months prior to pregnancy through delivery:	642.0	642.29
	642.70	642.79
Or, hypertension, not otherwise specified diagnosis prior to 20 weeks gestation:	642.9	642.99

Definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Table 3.2. Disorder diagnostic codes for exclusion variables.

Characteristic	ICD-9 Code	
	Start of Range	**End of Range**
Schizophrenic disorders	295	295.99
Other psychoses	297.1	297.1
	297.3	297.9
	301.22	301.22
Other indications for antidepressant use		
Fibromyalgia	729.1	729.1
Migraine	346	346.99
Chronic pain	338.2	338.29
	338.4	338.4
Bulimia	307.51	307.51
Tobacco use	305.1	305.1
	649.0	649.09
Attention deficit disorder	314.0	314.01

Definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Table 3.3. Sets of characteristics included in models.

Covariates	Variable Set 1[a]	Variable Set 2[b]	Variable Set 3[c]
Year of delivery, continuous (years)	0	X	X
Maternal age at delivery, continuous (years)	X	X	X
Male infant, yes/no	0	X[d]	X[d]
Number of prior pregnancies (parity): Zero One Two or more	0	X	X
Maternal race/ethnicity: Hispanic Non-Hispanic Asian Non-Hispanic black Non-Hispanic Native American Non-Hispanic Native Hawaiian or Other Pacific Islander Non-Hispanic white	X[e]	X[f]	X
Maternal education level: High school diploma/general equivalency degree or less Some college Bachelor's degree or more	X	X	X
Medicaid, yes/no	0	X	X
Integrated Group Practice, yes/no	0	X	X
Chronic hypertension, yes/no	0	0	X
Established diabetes, yes/no	0	0	X
Pre-pregnancy weight, continuous (lbs)	X[g]	X[g]	X[g]
Alcohol abuse disorder diagnostic code during the two years prior to pregnancy	0	0	X
Tobacco use disorder diagnostic code during the two years prior to pregnancy	0	X	X
Drug abuse disorder diagnostic code during the two years prior to pregnancy	0	0	X
Depression disorder diagnostic code during the two years prior to pregnancy	0	X	X
Anxiety disorder diagnostic code during the two years prior to pregnancy	0	X	X
Obsessive compulsive disorder diagnostic code during the two years prior to pregnancy	0	0	X
Post-traumatic stress disorder diagnostic code during the two years prior to pregnancy	0	0	X
Bipolar disorder diagnostic code during the two years prior to pregnancy	0	X	X
Any fill of antipsychotic medication during the year prior to pregnancy	0	X	X
Any fill of benzodiazepine medication during the year prior to pregnancy	0	X	X
Any fill for hypnotic sleep medication during the year prior to pregnancy	0	X	X
Any fill for mood stabilizer medication during the year prior to pregnancy	0	X	X
Any fill for trazodone during the year prior to pregnancy	0	X	X
Any fill for tricyclic antidepressant medication during the year prior to pregnancy	0	X	X

Any fill for other anxiety medication during the year prior to pregnancy	0	X	X
Any fill for medication associated with weight gain during the year prior to pregnancy	0	X	X
Any fill for diabetes medication during the year prior to pregnancy	0	X	X
Any psychotherapy visit during the year prior to pregnancy	0	X	X
Any psychiatry visit during the year prior to pregnancy	0	X	X
Any inpatient psychiatric hospitalization during the year prior to pregnancy	0	0	X
Any fill of antipsychotic medication more than one year prior to pregnancy	0	0	X
Any fill of benzodiazepine medication more than one year prior to pregnancy	0	0	X
Any fill for hypnotic sleep medication more than one year prior to pregnancy	0	0	X
Any fill for mood stabilizer medication more than one year prior to pregnancy	0	0	X
Any fill for trazodone more than one year prior to pregnancy	0	0	X
Any fill for tricyclic antidepressant medication more than one year prior to pregnancy	0	0	X
Any fill for other anxiety medication more than one year prior to pregnancy	0	0	X
Any fill for medication associated with weight gain more than one year prior to pregnancy	0	0	X
Any fill for diabetes medication more than one year prior to pregnancy	0	0	X
Any fill for antidepressant medication more than one year prior to pregnancy	0	0	X
Any psychotherapy visit more than one year prior to pregnancy	0	0	X
Any psychiatry visit more than one year prior to pregnancy	X	0	X
Any inpatient psychiatric hospitalization more than one year prior to pregnancy	0	0	X

Categorical characteristics are included in models as categorized, unless otherwise stated.

Diagnostic codes for conditions are listed in Supplementary Table 3.1. Specific medications in medication categories are listed in Supplementary Table 3.12. Definitions of mental health care utilization are described in Supplementary Table 3.13.

[a]Variable Set 1 is used for analyses of paroxetine and venlafaxine only, where the small number of exposed women limited how many variables we could include in the models.

[b]Variable Set 2 is used for sub- and sensitivity analyses (including the multivariable-adjusted analyses) for all outcomes, other than for analyses of paroxetine and venlafaxine.

[c]Variable Set 3 is only used for the overall analyses.

[d]Infant sex is not adjusted for in the analyses of small and large for gestational age, as the definitions of these outcomes already accounts for infant sex. In sensitivity analyses for all outcomes that stratify by infant sex, we did not adjust for infant sex.

[e]We combined Hispanic, non-Hispanic black, non-Hispanic Asian, non-Hispanic Native American, non-Hispanic Native Hawaiian or Other Pacific Islander, and into one group (“Other”) for these analyses due to small numbers.

[f]We combined Non-Hispanic Asian, Non-Hispanic Native American, and Non-Hispanic Native Hawaiian or Other Pacific Islander into one group ("Other") for these analyses due to small numbers.

[g]Pre-pregnancy weight is not adjusted for in sensitivity analyses that instead adjust for body mass index.

Supplementary Table 3.4. Full set of characteristics of women and births.

Covariates	No antidepressant fill in pregnancy (n=1249)	Antidepressant fill in pregnancy (n=1772)	Unweighted SMD	Inverse probability of treatment weighted SMD
Year of delivery, mean (SD)	2008 (3.8)	2008 (3.8)	0.034	0.001
Maternal age at delivery, mean (SD)	29.7 (5.8)	31.4 (5.4)	0.305	0.007
Male infant, n (%)	628 (50.3%)	915 (51.6%)	0.027	0.005
Number of prior pregnancies (parity), n (%)				
Zero	556 (44.9%)	656 (37.3%)	0.155	<0.001
One	426 (34.4%)	617 (35.0%)	0.014	0.004
Two or more	257 (20.7%)	488 (27.7%)	0.133	0.019
Maternal race/ethnicity, n (%)				
Hispanic	87 (7.0%)	107 (6.1%)	0.038	0.004
Non-Hispanic Asian	35 (2.8%)	27 (1.5%)	0.088	0.001
Non-Hispanic black	50 (4.0%)	38 (2.2%)	0.108	0.003
Non-Hispanic Native American	15 (1.2%)	26 (1.5%)	0.023	0.003
Non-Hispanic Native Hawaiian or Other Pacific Islander	21 (1.7%)	23 (1.3%)	0.032	0.002
Non-Hispanic white	1033 (83.2%)	1543 (87.5%)	0.120	<0.001
Maternal education level, n (%)				
High school diploma/general equivalency degree or less	273 (22.0%)	326 (18.5%)	0.087	<0.001
Some college	492 (39.7%)	653 (37.1%)	0.053	0.004
Bachelor's degree or more	474 (38.3%)	780 (44.3%)	0.124	0.003
Medicaid, n (%)	48 (3.8%)	61 (3.4%)	0.021	0.001
Integrated Group Practice, n (%)	773 (61.9%)	1064 (60.0%)	0.038	0.003
Established diabetes, n (%)	35 (2.8%)	51 (2.9%)	0.005	0.006
Chronic hypertension, n (%)	44 (3.5%)	87 (4.9%)	0.069	0.007
Pre-pregnancy weight in lbs, mean (SD)	167.2 (46.2)	170.2 (45.4)	0.066	0.009
During the year prior to pregnancy, n (%)				
Any fill of antipsychotic medication	23 (1.8%)	40 (2.3%)	0.029	0.011
Any fill of benzodiazepine medication	279 (22.3%)	425 (24.0%)	0.039	0.025
Any fill for hypnotic sleep medication	51 (4.1%)	80 (4.5%)	0.021	0.012
Any fill for mood stabilizer medication	59 (4.7%)	95 (5.4%)	0.029	0.047
Any fill for trazodone	111 (8.9%)	181 (10.2%)	0.045	0.023
Any fill for tricyclic antidepressant medication	72 (5.8%)	90 (5.1%)	0.030	0.064
Any fill for other anxiety medication	82 (6.6%)	125 (7.1%)	0.019	0.003
Any fill for medication associated with weight gain	178 (14.3%)	270 (15.2%)	0.028	0.023
Any fill for diabetes medication	38 (3.0%)	65 (3.7%)	0.035	0.015
Any psychotherapy visit	231 (18.5%)	302 (17.0%)	0.038	0.010
Any psychiatry visit	177 (14.2%)	281 (15.9%)	0.047	0.018

Any inpatient psychiatric hospitalization	9 (0.7%)	17 (1.0%)	0.026	0.011
During the two years prior to pregnancy, n (%)				
Alcohol abuse disorder	53 (4.2%)	76 (4.3%)	0.002	0.016
Tobacco use disorder	165 (13.2%)	250 (14.1%)	0.026	0.005
Drug abuse disorder	49 (3.9%)	63 (3.6%)	0.019	0.008
Depression disorder	906 (72.5%)	1300 (73.4%)	0.019	0.003
Anxiety disorder	482 (38.6%)	742 (41.9%)	0.067	0.002
Obsessive compulsive disorder	22 (1.8%)	57 (3.2%)	0.094	0.012
Post-traumatic stress disorder	41 (3.3%)	57 (3.2%)	0.004	0.001
Bipolar disorder	58 (4.6%)	78 (4.4%)	0.012	0.001
More than one year prior to pregnancy, n (%)				
Any fill of antipsychotic medication	22 (1.8%)	42 (2.4%)	0.043	0.007
Any fill of benzodiazepine medication	255 (20.4%)	421 (23.8%)	0.081	0.048
Any fill for hypnotic sleep medication	54 (4.3%)	85 (4.8%)	0.023	0.043
Any fill for mood stabilizer medication	58 (4.6%)	90 (5.1%)	0.020	0.070
Any fill for trazodone	126 (10.1%)	169 (9.5%)	0.019	0.073
Any fill for tricyclic antidepressant medication	107 (8.6%)	167 (9.4%)	0.030	0.017
Any fill for other anxiety medication	120 (9.6%)	202 (11.4%)	0.058	0.010
Any fill for medication associated with weight gain	291 (23.3%)	443 (25.0%)	0.040	0.046
Any fill for diabetes medication	30 (2.4%)	63 (3.6%)	0.068	0.012
Any fill for antidepressant medication	586 (46.9%)	1099 (62.0%)	0.307	0.003
Any psychotherapy visit	336 (26.9%)	533 (30.1%)	0.070	0.011
Any psychiatry visit	155 (12.4%)	308 (17.4%)	0.140	0.030
Any inpatient psychiatric hospitalization	16 (1.3%)	18 (1.0%)	0.025	0.016

SD: Standard deviation; SMD: Standardized mean difference

3% of observations were missing prenatal weight, and <1% of observations were missing race/ethnicity, parity, and education. All other observations did not have missing values.

If the SMD was ≥0.10, a standard cut point,[28] we considered the two groups to be substantially different. Weighted SMDs <0.10 indicate that we had achieved good balance in terms of measured baseline characteristics between births to exposed and unexposed women.

This table includes all covariates used to create the inverse probability of treatment weights for the overall regression models.

Diagnostic codes for conditions are listed in Supplementary Table 3.1. Specific medications in medication categories are listed in Supplementary Table 3.12. Definitions of mental health care utilization are described in Supplementary Table 3.13.

Supplementary Table 3.5. Counts and proportions of births to women with fills for specific antidepressants in pregnancy.

Antidepressant class or specific name	Antidepressant continuers N=1772 No. (%) during pregnancy
SSRIs	1536 (87%)
Citalopram	381 (22%)
Escitalopram	43 (2%)
Fluvoxamine	4 (<1%)
Fluoxetine	514 (29%)
Paroxetine	162 (9%)
Sertraline	546 (30%)
SNRIs	111 (6%)
Desvenlafaxine	1 (<1%)
Venlafaxine	110 (6%)
Bupropion	242 (14%)
Mirtazapine	11 (<1%)

SSRIs: serotonin reuptake inhibitors; SNRIs: serotonin norepinephrine reuptake inhibitors

Numbers for specific medications add to >100% due to some women having used multiple antidepressants (89% of deliveries were to women who used one medication, 10% used 2, and 1% used three or four). This includes women who switched antidepressants or were using multiple antidepressants simultaneously.

Supplementary Table 3.6. Extent of antidepressant exposure for women continuing antidepressants: Number of antidepressant medication fills and days covered[a] during the exposure window.[b]

	Overall n (%)	Single antidepressant[c] n (%)	Two different antidepressants[c,d] n (%)
	n= 1772	n=1573[c]	n=182[c]
Number of fills, median (IQR)	3 (1-5)	2 (1-4)	5 (3-7)
1 fill	547 (31%)	547 (35%)	NA
2 fills	325 (18%)	293 (19%)	32 (18%)
3 fills	267 (15%)	236 (15%)	28 (15%)
4 or more fills	633 (36%)	497 (32%)	122 (67%)
	n=1772	n= 1491	n=255
Days covered in exposure window, median (IQR)	143.5 (65.0-219.0)	132.0 (60.0-211.5)	185.0 (104.5-257.5)
<30	22 (1%)	22 (1%)	NA
≥30 to 89	550 (31%)	498 (33%)	51 (20%)
≥90 to 179	511 (29%)	432 (29%)	73 (29%)
≥180 to 239	392 (22%)	332 (22%)	51 (20%)
≥240	297 (17%)	207 (14%)	80 (31%)
Proportion of days covered in exposure window, median (IQR)	59% (27-91%)	55% (24-88%)	76% (41-108%)
<20%	292 (16%)	284 (19%)	8 (3%)
20 to 49%	474 (27%)	400 (27%)	71 (28%)
50 to 79%	380 (21%)	317 (21%)	57 (22%)
≥80%	603 (34%)	471 (32%)	115 (45%)

IQR: interquartile range

Values represent n (%) unless otherwise noted.

Antidepressants are commonly filled in 30, 60, or 90 days' supply at Kaiser Permanente Washington.

15 women had fills of 3 different antidepressants in pregnancy, and 2 had fills of 4 different antidepressants in pregnancy. They are only included in the "Overall" column of the table.

[a]"Days covered" was defined as number of days supplied with an antidepressant within the exposure window[b]. This is available in the prescription fill records as a different variable from the number of pills because some patients are prescribed more than one pill of a given medication per day. For fills that only partially overlapped with pregnancy, we prorated the days covered. "Proportion of days covered" is defined as the number of days covered in the exposure window divided by the number of days in the exposure window.

[b]We defined the exposure window as the start of pregnancy through four weeks prior to delivery. The median length of the exposure window in our study was 245 days (~35 weeks), with an interquartile range of 238 to 252 days.

[c]The number of deliveries exposed to 1 specific antidepressant versus 2 different antidepressants in the exposure window is different when considering fills versus days covered. When describing number of fills, we only considered women with *fills* of two different antidepressants in the exposure window to be exposed to 2 different antidepressants. When describing days covered, we allowed fills prior to pregnancy that overlapped into pregnancy to contribute to the total days supplied (prorated), which increased the number of women we considered to have exposure to 2 different antidepressants in pregnancy.

[d]For women taking 2 antidepressants, we calculated the total number of days covered by adding the number of days covered for each antidepressant (we did not attempt to account for overlap, even though some of these women may have been taking the 2 antidepressants simultaneously.) This made it possible for a woman to have more than 100% of days covered according to our calculations.

Supplementary Table 3.7. Sensitivity analyses for association of antidepressant continuation in pregnancy with mean infant birthweight.

	No. of continuers Total n = 1772	Infant birthweight (g) for continuers Mean (SD)	No. of discontinuers Total n = 1249	Infant birthweight (g) for discontinuers Mean (SD)	Mean difference (g) (95% CI)
Inverse probability of treatment weighted models					
Overall model from primary analysis[a]	1772	3406 (566)	1249	3461 (546)	-75.7 (-118.9 to -32.6)
Exposure defined as ≥2 antidepressant fills[b]	1265	3378 (549)	1249	3461 (546)	-110.2 (-155.4 to -65.1)
Including pre-pregnancy BMI in model[b]	1557	3405 (556)	1107	3458 (535)	-79.8 (-122.9 to -36.8)
Adjusting for gestational age[b]	1772	3406 (566)	1249	3460 (546)	-31.5 (-75.5 to 12.4)
Less than 50% of days covered with fills[b,c]	614	3460 (580)	1249	3461 (546)	-17.6 (-73.2 to 38.1)
Greater than 50% of days covered with fills[b,c]	691	3372 (555)	1249	3461 (546)	-110.5 (-166.6 to -54.5)
Births to women with fills overlapping pregnancy re-categorized as exposed[b]	2174	3415 (563)	847	3463 (546)	-76.9 (-123.4 to -30.4)
Anxiety or depression diagnosis[d] in 2 years prior to pregnancy[b]	1522	3405 (572)	1055	3467 (542)	-78.4 (-123.7 to -33.0)
Female infant[b]	857	3320 (572)	621	3405 (545)	-105.4 (-163.0 to -47.7)
Male infant[b]	915	3485 (549)	628	3516 (541)	-50.8 (-108.6 to 7.1)
Multivariable-adjusted model					
Overall[e]	1772	3406 (566)	1249	3461 (546)	-69.0 (-108.7 to -29.2)

g: grams; SD: standard deviation, CI: confidence interval; BMI: body mass index

[a]Repeated from Table 3.2 for comparison. Weighted by characteristics included in Variable Set 3 in Supplementary Table 3.3.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 3.3.

[c]Only includes women who had a fill for one specific antidepressant during the exposure window.

[d]Anxiety and depression disorders defined in Supplementary Table 3.1.

[e]Adjusted for characteristics included in Variable Set 2 in Supplementary Table 3.3.

Supplementary Table 3.8. Sensitivity analyses for association of antidepressant continuation in pregnancy with large for gestational age.

	No. of continuers Total n = 1772	No. (%) of continuers with large for gestational age	No. of discontinuers Total n = 1249	No. (%) of discontinuers with large for gestational age	RR (95% CI)
Inverse probability of treatment weighted models					
Overall model from primary analysis[a]	1772	180 (10%)	1249	139 (11%)	0.82 (0.66-1.03)
Exposure defined as ≥2 antidepressant fills[b]	1265	113 (9%)	1249	139 (11%)	**0.71 (0.55-0.91)**
Including pre-pregnancy BMI in model[b]	1557	155 (10%)	1107	121 (11%)	0.82 (0.65-1.04)
Less than 50% of days covered with fills[b,c]	614	64 (10%)	1249	139 (11%)	0.88 (0.66-1.18)
Greater than 50% of days covered with fills[b,c]	691	69 (10%)	1249	139 (11%)	0.84 (0.63-1.12)
Women with fills overlapping pregnancy re-categorized as exposed[b]	2174	224 (10%)	847	95 (11%)	**0.78 (0.61-0.99)**
Anxiety or depression diagnosis[d] in 2 years prior to pregnancy[b]	1522	155 (10%)	1055	121 (11%)	0.81 (0.64-1.03)
Female infant[b]	857	88 (10%)	621	77 (12%)	0.74 (0.55-1.00)
Male infant[b]	915	92 (10%)	628	62 (10%)	0.91 (0.66-1.26)
Multivariable-adjusted model					
Overall[e]	1772	180 (10%)	1249	139 (11%)	0.84 (0.67-1.04)

CI: confidence interval; RR: relative risk

[a]Repeated from Table 3.4 for comparison. Weighted by characteristics included in Variable Set 3 in Supplementary Table 3.3.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 3.3.

[c]Only includes women who had a fill for one specific antidepressant during the exposure window.

[d]Anxiety and depression disorders defined in Supplementary Table 3.1.

[e]Adjusted for characteristics included in Variable Set 2 in Supplementary Table 3.3.

Supplementary Table 3.9. Sensitivity analyses for association of antidepressant continuation in pregnancy with macrosomia.

	No. of continuers Total n = 1772	No. (%) of continuers with macrosomia	No. of discontinuers Total n = 1249	No. (%) of discontinuers with macrosomia	RR (95% CI)
Inverse probability of treatment weighted models					
Overall model from primary analysis[a]	1772	38 (2%)	1249	28 (2%)	0.75 (0.44-1.27)
Exposure defined as ≥2 antidepressant fills [b]	1265	19 (2%)	1249	28 (2%)	**0.53 (0.29-0.97)**
Including pre-pregnancy BMI in model[b]	1557	30 (2%)	1107	25 (2%)	0.67 (0.39-1.16)
Including gestational age in model[b]	1772	38 (2%)	1249	28 (2%)	0.81 (0.49-1.35)
Less than 50% of days covered with fills[b,c]	614	21 (3%)	1249	28 (2%)	1.38 (0.78-2.45)
Greater than 50% of days covered with fills[b,c]	691	10 (1%)	1249	28 (2%)	0.55 (0.26-1.16)
Women with fills overlapping pregnancy re-categorized as exposed[b]	2174	43 (2%)	847	23 (3%)	**0.56 (0.33-0.95)**
Anxiety or depression diagnosis[d] in 2 years prior to pregnancy[b]	1522	31 (2%)	1055	23 (2%)	0.77 (0.44-1.35)
Female infant[b]	857	13 (2%)	621	12 (2%)	0.68 (0.29-1.59)
Male infant[b]	915	25 (3%)	628	6 (1%)	0.82 (0.43-1.56)
Multivariable-adjusted model					
Overall[e]	1772	38 (2%)	1249	28 (2%)	0.89 (0.53-1.49)

CI: confidence interval; RR: relative risk

[a]Repeated from Table 3.6 for comparison. Weighted by characteristics included in Variable Set 3 in Supplementary Table 3.3.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 3.3.

[c]Only includes women who had a fill for one specific antidepressant during the exposure window.

[d]Anxiety and depression disorders defined in Supplementary Table 3.1.

[e]Adjusted for characteristics included in Variable Set 2 in Supplementary Table 3.3.

Supplementary Table 3.10. Sensitivity analyses for association of antidepressant continuation in pregnancy with low birthweight.

	No. of continuers Total n = 1772	No. (%) of continuers with low birthweight	No. of discontinuers Total n = 1249	No. (%) of discontinuers with low birthweight	RR (95% CI)
Inverse probability of treatment weighted models					
Overall model from primary analysis[a]	1772	87 (5%)	1249	50 (4%)	1.36 (0.94-1.98)
Exposure defined as ≥2 antidepressant fills[b]	1265	63 (5%)	1249	50 (4%)	1.38 (0.93-2.04)
Including pre-pregnancy BMI in model[b]	1557	76 (5%)	1107	41 (4%)	1.47 (1.00-2.16)
Including gestational age in model[b]	1772	87 (5%)	1249	50 (4%)	0.93 (0.64-1.34)
Less than 50% of days covered with fills[b,c]	614	28 (5%)	1249	50 (4%)	1.17 (0.73-1.87)
Greater than 50% of days covered with fills[b,c]	691	37 (5%)	1249	50 (4%)	1.54 (1.00-2.38)
Women with fills overlapping pregnancy re-categorized as exposed[b]	2174	100 (5%)	847	37 (4%)	1.18 (0.79-1.77)
Anxiety or depression diagnosis[d] in 2 years prior to pregnancy[b]	1522	75 (5%)	1055	40 (4%)	1.36 (0.92-2.02)
Female infant[b]	857	50 (6%)	621	28 (5%)	1.46 (0.90-2.35)
Male infant[b]	915	37 (4%)	628	22 (4%)	1.26 (0.72-2.23)
Multivariable-adjusted model					
Overall[e]	1772	87 (5%)	1249	50 (4%)	1.29 (0.91-1.83)

CI: confidence interval; RR: relative risk

[a]Repeated from Table 3.5 for comparison. Weighted by characteristics included in Variable Set 3 in Supplementary Table 3.3.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 3.3.

[c]Only includes women who had a fill for one specific antidepressant during the exposure window.

[d]Anxiety and depression disorders defined in Supplementary Table 3.1.

[e]Adjusted for characteristics included in Variable Set 2 in Supplementary Table 3.3.

Supplementary Table 3.11. Sensitivity analyses for association of antidepressant continuation in pregnancy with small for gestational age.

	No. of continuers Total n = 1772	No. (%) of continuers with small for gestational age	No. of discontinuers Total n = 1249	No. (%) of discontinuers with small for gestational age	RR (95% CI)
Inverse probability of treatment weighted models					
Overall model from primary analysis[a]	1772	130 (7%)	1249	82 (7%)	1.19 (0.89-1.58)
Exposure defined as ≥2 antidepressant fills[b]	1265	86 (7%)	1249	82 (7%)	1.09 (0.80-1.48)
Including pre-pregnancy BMI in model[b]	1557	112 (7%)	1107	72 (7%)	1.16 (0.87-1.56)
Less than 50% of days covered with fills[b,c]	614	42 (7%)	1249	82 (7%)	1.04 (0.72-1.50)
Greater than 50% of days covered with fills[b,c]	691	44 (6%)	1249	82 (7%)	1.07 (0.74-1.56)
Women with fills overlapping pregnancy re-categorized as exposed[b]	2174	151 (7%)	847	61 (7%)	1.02 (0.75-1.38)
Anxiety or depression diagnosis[d] in 2 years prior to pregnancy[b]	1522	113 (7%)	1055	72 (7%)	1.11 (0.82-1.50)
Female infant[b]	857	70 (8%)	621	34 (5%)	**1.65 (1.09-2.50)**
Male infant[b]	915	60 (7%)	628	48 (8%)	0.86 (0.58-1.27)
Multivariable-adjusted model					
Overall[e]	1772	130 (7%)	1249	82 (7%)	1.11 (0.84-1.46)

CI: confidence interval; RR: relative risk

[a]Repeated from Table 3.3 for comparison. Weighted by characteristics included in Variable Set 3 in Supplementary Table 3.3.

[b]Weighted by characteristics included in Variable Set 2 in Supplementary Table 3.3.

[c]Only includes women who had a fill for one specific antidepressant during the exposure window.

[d]Anxiety and depression disorders defined in Supplementary Table 3.1.

[e]Adjusted for characteristics included in Variable Set 2 in Supplementary Table 3.3.

Supplementary Table 3.12. Specific medications included in medication categories for model covaria

Medication category	Specific medications included
Tricyclics and tetracyclics	amitriptyline
	amoxapine
	clomipramine
	desipramine
	imipramine
	doxepin
	nortriptyline
	protriptyline
	trimipramine
	maprotiline
Benzodiazepines	alprazolam
	chlordiazepoxide
	clonazepam
	clorazepate
	diazepam
	estazolam
	flurazepam
	halazepam
	lorazepam
	oxazepam
	prazepam
	quazepam
	temazepam
	triazolam
	midazolam
	bromazepam
Hypnotic sleep medication	zolpidem
	eszopiclone
	zaleplon
	ramelteon
Mood stabilizers	lithium
	valproic acid
	valproate
	divalproex
	carbamazepine
	lamotrigine
	oxcarbazepine
	gabapentin
	topiramate
	tiagabine

	zonisamide
First generation antipsychotics	chlorpromazine
	fluphenazine
	haloperidol
	loxapine
	molindone
	thiothixene
	perphenazine
	pimozide
	thioridazine
	thiothixene
	trifluoperazine
Second generation antipsychotics	aripiprazole
	asenapine
	clozapine
	iloperidone
	olanzapine
	paliperidone
	quetiapine
	risperidone
	ziprasidone
Other anti-anxiety	hydroxyzine
	meprobamate
	meprobamate
	pregabalin
	buspirone
Diabetes medications	regular insulin
	insulin aspart
	insulin glulisine
	insulin lispro
	insulin isophane
	insulin degludec
	insulin detemir
	insulin glargine
	insulin glargine
	NovoLog Mix 70/30 (insulin aspart protamine-insulin aspart)
	Humalog Mix 75/25 (insulin lispro protamine-insulin lispro)
	Humalog Mix 50/50 (insulin lispro protamine-insulin lispro)
	Humulin 70/30 (human insulin NPH-human insulin regular)
	Novolin 70/30 (human insulin NPH-

human insulin regular)
Ryzodeg (insulin degludec-insulin aspart)
pramlintide
acarbose
miglitol
metformin
metformin-alogliptin
metformin-canagliflozin
metformin-dapagliflozin
metformin-empagliflozin
metformin-glipizide
metformin-glyburide
metformin-linagliptin
metformin-pioglitazone
metformin-repaglinide
metformin-rosiglitazone
metformin-saxagliptin
metformin-sitagliptin
alogliptin
alogliptin-metformin
alogliptin-pioglitazone
linagliptin
linagliptin-empagliflozin
linagliptin-metformin
saxagliptin
saxagliptin-metformin
sitagliptin
sitagliptin-metformin
sitagliptin and simvastatin
albiglutide
dulaglutide
exenatide
exenatide extended-release
liraglutide
nateglinide
repaglinide
repaglinide-metformin
dapagliflozin
dapagliflozin-metformin
canagliflozin
canagliflozin-metformin
empagliflozin
empagliflozin-linagliptin
empagliflozin-metformin

	glimepiride glimepiride-pioglitazone glimeperide-rosiglitazone gliclazide glipizide glipizide-metformin glyburide glyburide-metformin chlorpropamide tolazamide tolbutamide rosiglitazone rosiglitazone-glimepiride rosiglitizone-metformin pioglitazone pioglitazone-alogliptin pioglitazone-glimepiride pioglitazone-metformin
Drugs that may cause weight gain[35,36]	Metoprolol Atenolol Propranolol Amlodipine Clonidine Pioglitazone Rosiglitazone fexofenadine cetirizine diphenhydramine prednisone (oral) methylprednisolone (oral) cortisone (oral)

Some definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Table 3.13. Definitions of mental healthcare utilization variables

Mental health utilization type	Definition
Psychotherapy	Includes individual and group therapy. Any of the following CPT codes: 90801, 90802, 90806-9, 90812-15, 90847, 90849, 90853, or 90857, and for 2013 and 2014: 90791, 90832, 90833, 90834, or 90836-9 Does not include: 90804, 90805, 90810, 90811, 90862, and for 2013 and 2014: 90792
Psychiatry	A record of an outpatient visit that meets the two following conditions: 1. Visit is with a provider who is licensed to prescribe medication (MD, DO, ARNP, PA, or PA-C). 2. Visit is with a provider whose specialty is Mental Health or Psychiatry, *or* the encounter takes places in a Mental Health, Behavioral Health Services, or Psychiatry Department.
Inpatient psychiatric hospitalization	Any inpatient encounter with a mental health diagnosis as the principle diagnosis.

Some definitions were based on resources from the Mental Health Research Network (http://hcsrn.org/mhrn/).

Supplementary Figure 3.1. Unweighted and weighted standardized mean differences (SMDs) comparing characteristics between births to women who continued or discontinued antidepressants in pregnancy.

Methods Appendix 3.1. Description of inverse probability of treatment weighting methods.
Propensity scores were estimated using a logistic regression model in which antidepressant use in pregnancy was regressed on potential confounders. We generated a likelihood of exposure for each birth, conditional on confounders, which was used to weight the population by the inverse probability of exposure. To avoid lowering precision, we did not include variables expected to be associated with exposure but not outcome.[37] For the exposed group, we created stabilized IPTWs by dividing the prevalence of exposure in the study population by the propensity score for each observation. For the unexposed group, we calculated stabilized IPTWs as *(1–prevalence of exposure)/(1–propensity score)*.[28] These weights were applied to the primary regression model without adjusting for any covariates. This up-weighted the "unexpected" combinations of confounders and exposure and down-weighted the "expected" combinations of confounders and exposure, in attempt to create a pseudo-population in which exposure is not associated with confounders. To assess balance on baseline covariates, we qualitatively compared exposed and unexposed groups' overlap in propensity scores using cumulative distribution functions and histograms, and checked for SMDs between groups ≥0.10.[28]

Methods Appendix 3.2. Sub-population available for chart review.
We only had access to charts for review among women in the Integrated Group Practice from 2007–2014, when the electronic medical record was implemented. Because this chart review was also used to inform other studies, we additionally excluded women with pregestational diabetes, women who were missing a record of gestational diabetes screening and delivered prior to 29 weeks gestation, and women who were missing information on gestational weight gain. Out of the 197 women with prescription fills before pregnancy with days supplied that overlapped into pregnancy who were originally eligible for our chart review, after these additional exclusions, 185 (94%) were used as the sub-population from which we randomly chose 50. Out of the 116 women with prescriptions in the first 30 days of pregnancy who were originally eligible for our chart review, after these additional exclusions, 114 (98%) were used as the sub-population from which we randomly chose 50.

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VITA

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