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ORIGINAL RESEARCH

Maternal Depression and Antidepressant Use During Pregnancy and Associations with Depressive Symptoms and Suicidality in Adolescent Children

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Purpose: Children of mothers with prenatal depression have elevated risk for depression later in life. Pregnant women are hesitant to use antidepressants due to fear of adverse fetal effects. To inform prevention, this study examined associations between maternal prenatal depression and antidepressant use, and adolescent depressive symptoms and suicidality.

Patients and Methods: Prospective data from 74,695 mother-adolescent dyads from the Kaiser Permanente Northern California integrated healthcare delivery system were used. Three prenatal exposure groups were examined: maternal depression and antidepressants (Med); depression and no antidepressants (No-Med); neither depression nor antidepressants (NDNM). Adolescent depressive symptoms (Patient Health Questionnaire-2 score ≥3) and suicidality were assessed for 12- to 18-year-olds. Associations were analyzed using mixed effects logistic regression, adjusted for confounders.

Results: Maternal prenatal depression was associated with higher odds of adolescent depressive symptoms (Med odds ratio [OR]: 1.50, 95% confidence interval [CI]: 1.23–1.84; No-Med OR: 1.59, CI: 1.34–1.88) and suicidality (Med OR: 2.36, CI: 1.67–3.34; No-Med OR: 1.54, CI: 1.10–2.14) compared to no prenatal depression (NDNM). Adolescents exposed to prenatal depression and antidepressants were not at greater odds of depressive symptoms (Med OR: 0.95, CI: 0.74–1.21) compared to those not exposed to antidepressants (No-Med). However, they showed non-significant but greater odds of suicidality (Med OR: 1.54, CI: 0.99–2.39).

Conclusion: Our findings suggest that maternal prenatal depression is associated with adolescent depressive symptoms and suicidality, and that exposure to antidepressants in utero does not increase risk of depressive symptoms, specifically. While not statistically significant, the increased odds of suicidality among adolescents exposed to antidepressants suggest a possible association; however, further investigation is needed. After replication, the findings of this study may inform shared clinical decision-making when considering options regarding antidepressant use for the treatment of maternal prenatal depression.

Keywords: prenatal depression, adolescent depression, intergenerational depression, antidepressants, mental health, maternal health

Introduction

Prenatal depression affects approximately 10% to 20% of pregnancies in the United States and other high-income countries[1,2] and appears to be increasing.[3] Prenatal depression is associated with adverse maternal and child health outcomes,[4] including depression in adolescent children.[5–7] The association between in utero exposure to prenatal depression and depression in the child during adolescence remains even when adjusting for maternal depression throughout the child's life.[6]

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The decision to use pharmacotherapy to treat prenatal depression is complicated by fear of adverse fetal effects[8] and the lack of clear clinical guidelines on prenatal antidepressant management.[9] Discontinuation of antidepressants during pregnancy is common. In national cohort studies, approximately 2 out of 3 women with Medicaid and 1 out of 4 women with commercial insurance discontinued antidepressants during the first trimester.[10,11] Additionally, pregnant women may be hesitant to start antidepressants during pregnancy. A convenience sample of 509 women in the third trimester of pregnancy recruited from two obstetric clinics in the Northeastern United States found that only one-third of women self-reported that they would use antidepressants if recommended during pregnancy.[12] Further research on the impact of antidepressant use during pregnancy is needed to inform shared clinical decision-making.

Concerns regarding antidepressant exposure during pregnancy stem from their ability to cross the placenta and blood-brain barriers.[13] Throughout gestation, serotonin regulates numerous aspects of neurodevelopment including the formation of the serotonergic system.[14–16] As the serotonergic system is central to regulating mood, and its disruption is associated with the development of affective disorders, in utero exposure to antidepressants may have long-term consequences including vulnerability or "plasticity" to affective disorders across the life span.

Another possible explanation for associations between prenatal antidepressant exposure and risk of affective disorders in children is residual confounding, particularly confounding by indication. The indication for which antidepressants are prescribed, such as depression versus another psychiatric disorder, may be responsible for this association. Even within depression as an indication for antidepressant use, those who use antidepressants versus those who do not may differ in symptom severity or chronicity of depressive episodes. Maternal psychopathology may impact the child through shared genetic susceptibility or environmental liability, including parenting factors.[17–19] While some studies have found increased risk of internalizing behaviors and affective disorders in children exposed to prenatal antidepressants,[20] the few prospective cohort studies that took maternal mood into account found that prenatal depressive symptoms, but not prenatal antidepressant use, were associated with children's internalizing behavior up to age 7 years.[20–24]

Despite the fact that the prevalence of childhood depression increases with age and is most common among adolescents 12 years and older, only two studies on the association between in utero antidepressant exposure and depression in the child have followed children into adolescence. These include a population-based study in Finland with outcomes in children 2–14 years old and a population-based study in Denmark with outcomes in children up to 18 years old.[20,25,26] These studies found that maternal antidepressant use during pregnancy may increase the risk for depression diagnosis among teens.[20,25,26] However, these studies did not restrict antidepressant use to mothers with a depression diagnosis and did not account for preexisting and new onset depression during pregnancy. These studies were also limited by racially and ethnically homogeneous study populations that were predominantly White, and measurement of adolescent outcomes in secondary and tertiary care sites. The concern regarding measurement at secondary and tertiary care sites is detection bias if mothers receiving treatment for depression are more likely to take their children to specialty care for diagnosis and treatment than mothers who are not participating in treatment.

Additionally, no research has investigated maternal prenatal antidepressant use and adolescent suicidality. This is a critical gap in the literature, particularly in the United States, where nearly 20% of high school students report serious thoughts of suicide, 9% report an attempt, and suicide is the second-leading cause of death among 14- to 18-year-olds.[27]

The current study uses a large, racially and ethnically diverse sample, drawn from a population representative of Northern California, to address these gaps by examining the association between maternal prenatal antidepressant use, restricted to mothers with preexisting or new onset depression diagnoses, and adolescent depressive symptoms and suicidality as measured in a primary care setting. Consistent with prior research in young children which accounted for confounding by indication by limiting the indication for which antidepressants were prescribed to mothers with depression,[20] we hypothesized that maternal prenatal depression, not prenatal antidepressant use, would be associated with depressive symptoms and suicidality in adolescents. While the two prior studies in adolescents found maternal prenatal antidepressant use may increase the risk for depression diagnosis among teens,[20,25,26] in utero antidepressant exposure confers "plasticity" to affective disorders[14–16] which suggests the possibility of a protective or harmful effect. Thus, we explored the association, among adolescents born to mothers with prenatal depression, between those exposed and unexposed to antidepressants in utero and depressive symptoms and suicidality. This information could be influential to clinical practice and may weigh into the shared decision-making process of whether to start or continue antidepressants during pregnancy.

Methods

Setting

Data for this study were obtained from the Kaiser Permanente Northern California (KPNC) electronic health record (EHR) system and research databases. KPNC is an integrated healthcare delivery system serving approximately 4.5 million socioeconomically, and racially and ethnically diverse members who are representative of the Northern California population with the exception of income, as members slightly under represent the very poor and the very wealthy.[28–30] As an integrated healthcare delivery system, once enrolled in a Kaiser health insurance plan via individual coverage, employer-sponsorship, or Medicaid, members may access inpatient and outpatient care as well as pharmacy, behavioral health care, and additional services. Care and services are coordinated through a central EHR.

Participants

Our study sample was a prospective cohort of adolescents who are members of KPNC identified using a birth cohort of all infants born singleton at a KPNC medical facility (or transferred to KPNC within 24 hours of birth) between 2003 and 2011. At KPNC, all adolescents who present for a well-teen primary care appointment are asked to complete a questionnaire that includes questions about mental health. The mental health questions include the Patient Health Questionnaire-2 (PHQ-2) and a question regarding suicidality (described below). There were 81,954 births for whom adolescent PHQ-2 data were available in the EHR. To account for potential confounding, mother-adolescent dyads were excluded for a variety of variables documented in the literature to be associated with both prenatal depression and depression in the child. Dyads were excluded if mothers reported intimate partner violence on a routine prenatal care appointment questionnaire (N = 17) or had a diagnosis of substance use disorder (N = 1491), epilepsy (N = 167), bipolar disorder (N = 188), or schizophrenia (N = 13) during the prenatal period (defined below). Figure 1

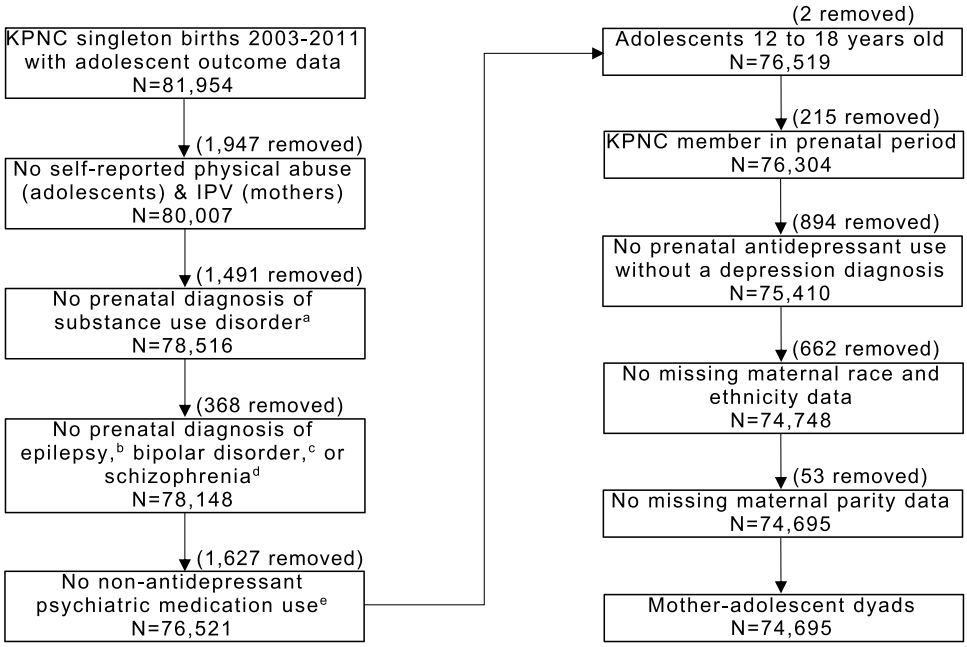


Figure 1 Inclusion criteria.

Notes: International Classification of Disease, 9th edition codes. Depression diagnosis: 296.20-296.25, 296.30-296.35, 300.4, 311. [a]Substance use disorder: 291.0, 291.1, 291.2, 291.3, 291.4, 291.5, 291.81, 291.82, 291.89, 291.9, 292.0, 292.11, 292.12, 292.2, 292.81, 292.82, 292.83, 292.84, 292.85, 292.89, 292.9, 303.00, 303.01, 303.02, 303.90, 303.91, 303.92, 304.00, 304.01, 304.02, 304.10, 304.11, 304.12, 304.20, 304.21, 304.22, 304.30, 304.31, 304.32, 304.40, 304.41, 304.42, 304.50, 304.51, 304.52, 304.60, 304.61, 304.62, 304.70, 304.71, 304.72, 304.80, 304.81, 304.82, 304.90, 304.91, 304.92, 305.00, 305.01, 305.02, 305.20, 305.21, 305.22, 305.30, 305.31, 305.32, 305.40, 305.41, 305.42, 305.50, 305.51, 305.52, 305.60, 305.61, 305.62, 305.70, 305.71, 305.72, 305.80, 305.81, 305.82, 305.90, 305.91, 305.92, 648.33. [b]Epilepsy: 333.2, 345.00, 345.01, 345.10, 345.11, 345.2, 345.3, 345.40, 345.41, 345.50, 345.51, 345.70, 345.71, 345.80, 345.81, 345.90, 345.91, 649.43. [c]Bipolar disorder: 296.00, 296.01, 296.02, 296.03, 296.04, 296.05, 296.06, 296.10, 296.11, 296.12, 296.13, 296.14, 296.15, 296.16, 296.40, 296.41, 296.42, 296.43, 296.44, 296.45, 296.46, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.7, 296.80, 296.81, 296.89, 301.13. [d]Schizophrenia: 295.00, 295.01, 295.02, 295.03, 295.04, 295.05, 295.10, 295.11, 295.12, 295.13, 295.14, 295.15, 295.20, 295.21, 295.22, 295.23, 295.24, 295.25, 295.30, 295.31, 295.32, 295.33, 295.34, 295.35, 295.40, 295.41, 295.42, 295.43, 295.44, 295.45, 295.50, 295.51, 295.52, 295.53, 295.54, 295.55, 295.60, 295.61, 295.62, 295.63, 295.64, 295.65, 295.70, 295.71, 295.72, 295.73, 295.74, 295.75, 295.80, 295.81, 295.82, 295.83, 295.84, 295.85, 295.90, 295.91, 295.92, 295.93, 295.94, 295.95. [e]Non-antidepressant psychiatric medications: Anxiolytics and hypnotic (benzodiazepines and non-benzodiazepines), antiepileptic and mood stabilizer, antipsychotic, stimulant, and non-stimulant medications.

Abbreviations: KPNC, Kaiser Permanente Northern California; IPV, Intimate Partner Violence.

displays International Classification of Disease, 9th edition codes [ICD-9] for these diagnoses. To focus on prenatal antidepressant exposure, dyads were excluded if mothers made one or more purchases of non-antidepressant psychiatric medications from a KPNC pharmacy during the prenatal period (N = 1627). Dyads were excluded if adolescents reported histories of physical abuse (N = 1930) with a response of "Yes" to the question, "Have you ever been physically abused (hit, slapped, kicked, shoved) by an adult?" on the same questionnaire that asks about mental health at well-teen primary care appointments. Additionally, dyads were excluded if adolescents were younger than 12 years old when they completed the PHQ-2 (N = 2) as this screening measure is rarely given to patients younger than 12-years-old, in alignment with the United States Preventive Services Task Force guidelines recommending screening for major depressive disorder in adolescents 12- to 18-years-old.[31] Dyads were also excluded if mothers were not members of KPNC anytime during the prenatal period (N = 215) to minimize exposure misclassification, and if mothers were taking antidepressant medications during the prenatal period but did not have a depression diagnosis (N = 894) as this group was too heterogeneous, particularly in regard to indication, to be clinically meaningful. Finally, dyads were excluded if covariate data were missing (maternal race and ethnicity, N = 662; maternal parity, N = 53). This resulted in an analytic sample of 74,695 mother-adolescent dyads (Figure 1). This study was approved by the KPNC Institutional Review Board (ID: 1387130).

Measures

Exposure Variables

The exposure variables were maternal depression diagnosis and antidepressant use during the prenatal period ("pregnancy"). Consistent with prior studies, we defined the prenatal period as 30 days prior to pregnancy until delivery,[25,26] which was calculated based on gestational age (complete weeks) at birth. Where gestational age was missing, 39 weeks was used as a substitute. Depression diagnosis was defined using ICD-9 codes (296.20-296.25, 296.30-296.35, 300.4, 311).[32]

Consistent with prior literature, we defined prenatal antidepressant use as one or more purchases of antidepressants from a KPNC outpatient pharmacy during the prenatal period.[25,26] We considered total exposure across the prenatal period based on prior literature indicating that duration of gestational exposure to antidepressants, not timing or dosage, is associated with adverse outcomes in offspring.[26,33] Antidepressants included selective serotonin reuptake inhibitors (SSRI; Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline), selective norepinephrine reuptake inhibitors (SNRI; Desvenlafaxine, Duloxetine, Venlafaxine), tricyclic antidepressants (TCA; Amitriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline, Protriptyline), atypical antidepressants (Bupropion, Mirtazapine), and serotonin modulators (Nefazodone, Trazodone). The median length of supply of one prescription purchase was 90 days.

Exposure variables were categorized into three groups: both prenatal depression diagnosis and prenatal antidepressant use (Medication Use, Med); prenatal depression diagnosis and no prenatal antidepressant use (No Medication Use, No-Med); and neither prenatal depression diagnosis nor prenatal antidepressant use (Neither Depression Nor Medication, NDNM).

Outcome Variables

The outcome variables were adolescents' self-report of depressive symptoms and suicidality on their most recent well-teen health questionnaire. Depressive symptoms were assessed using the PHQ-2, a standard two-question screener that asks about frequency of depressed mood and anhedonia in the prior two weeks. Response options were "Not at all", "Several days", "More than half the days", and "Nearly every day", scored from 0 to 3, respectively.[34] The final score was determined by summing responses from both questions and ranged from 0 to 6. From this total score, a binary variable was calculated for which a score greater than or equal to 3 indicates depressive symptoms. A validation study of the PHQ-2 in adolescents found that this cutoff has a sensitivity of 74% and a specificity of 75% for major depression, and is associated with greater functional impairment and internalizing problems.[35] The PHQ-2 using this cut-point is included in the Guidelines for Adolescent Depression in Primary Care (supported by the American Academy of Pediatrics, American Academy of Child and Adolescent Psychiatry, and the American Psychiatric Association) as one possible instrument recommended for use in screening for adolescent depression.[36] Clinically, this cut-point also indicates which adolescent patients should receive further evaluation for the diagnosis of depression.[35,36]

Not all adolescents who are suicidal will screen positive for depressive symptoms; thus, it is recommended to also screen adolescents for suicidality.[35–37] Suicidality was assessed by asking adolescents, within the past two weeks, "Have

you thought seriously about killing yourself, made a plan, or tried to kill yourself?" The response options were "Yes" or "No."

Covariates

The following maternal factors were selected as covariates, using a directed acyclic graph, a priori: maternal age at delivery, anxiety diagnosis during pregnancy (Y/N) (see Table 1 for ICD-9 codes), depression diagnosis in the year before pregnancy (pregravid depression) (Y/N), maternal race and ethnicity, parity, and Medicaid insurance status during

Table 1 Selected Characteristics by Exposure to Maternal Depression and Antidepressant Use During the Prenatal Period, N (%)

	Med	No-Med	p-value (Med vs No-Med)	NDNM	p-value (Med vs NDNM)	Total	p-value (all 3 groups)[a]
Characteristic	**1290 (1.73)[b]**	**1721 (2.30)[c]**		**71,684 (95.97)[d]**		**74,695 (100)[e]**	
Maternal age at delivery (years)			<0.001		<0.001		<0.001
≤19	31 (2.40)	86 (5.00)		2347 (3.27)		2464 (3.30)	
20–24	132 (10.23)	251 (14.58)		9736 (13.58)		10,119 (13.55)	
25–29	303 (23.49)	472 (27.43)		20,041 (27.96)		20,816 (27.87)	
30–34	403 (31.24)	483 (28.07)		23,269 (32.46)		24,155 (32.34)	
35–39	319 (24.73)	337 (19.58)		13,104 (18.28)		13,760 (18.42)	
≥40	102 (7.91)	92 (5.35)		3187 (4.45)		3381 (4.53)	
Prenatal Medicaid insurance			0.506		<0.001		<0.001
No	1228 (95.19)	1629 (94.65)		69,611 (97.11)		72,468 (97.02)	
Yes	62 (4.81)	92 (5.35)		2073 (2.89)		2227 (2.98)	
Parity (live births)			0.903		<0.001		<0.001
0	501 (38.84)	682 (39.63)		31,066 (43.34)		32,249 (43.17)	
1	437 (33.88)	578 (33.59)		25,153 (35.09)		26,168 (35.03)	
≥2	352 (27.29)	461 (26.79)		15,465 (21.57)		16,278 (21.79)	
Maternal race and ethnicity			<0.001		<0.001		<0.001
Hispanic	288 (22.33)	563 (32.71)		20,675 (28.84)		21,526 (28.82)	
NH Asian, Native Hawaiian, Pacific Islander	82 (6.36)	222 (12.90)		18,603 (25.95)		18,907 (25.31)	
NH Black	76 (5.89)	196 (11.39)		5070 (7.07)		5342 (7.15)	
NH Indigenous	6 (0.47)	12 (0.70)		304 (0.42)		322 (0.43)	
NH Multiracial	68 (5.27)	73 (4.24)		2584 (3.60)		2725 (3.65)	
NH White	770 (59.69)	655 (38.06)		24,448 (34.11)		25,873 (34.64)	
Maternal prenatal anxiety diagnosis[f]			<0.001		<0.001		<0.001
No	879 (68.14)	1292 (75.07)		69,478 (96.92)		71,649 (95.92)	
Yes	411 (31.86)	429 (24.93)		2206 (3.08)		3046 (4.08)	
Maternal pregravid depression diagnosis			<0.001		<0.001		<0.001
No	629 (48.76)	1231 (71.53)		69,695 (97.23)		71,555 (95.80)	
Yes	661 (51.24)	490 (28.47)		1989 (2.77)		3140 (4.20)	
Sex assigned at birth of adolescent			0.717		0.852		0.737
Female	630 (48.84)	829 (48.17)		35,196 (49.10)		36,655 (49.07)	
Male	660 (51.16)	892 (51.83)		36,488 (50.90)		38,040 (50.93)	
Gestational age of adolescent (weeks)			0.078		0.001		0.006
<28	2 (0.16)	4 (0.23)		130 (0.18)		136 (0.18)	
28–32	5 (0.39)	10 (0.58)		384 (0.54)		399 (0.54)	
32–37	106 (8.29)	102 (5.96)		3980 (5.61)		4188 (5.67)	
≥37	1165 (91.16)	1595 (93.22)		66,443 (93.66)		69,203 (93.61)	
Adolescent age at most recent PHQ-2 (years)			0.133		0.255		0.001
12	16 (1.24)	16 (0.93)		686 (0.96)		718 (0.96)	
13	315 (24.42)	439 (25.51)		15,606 (21.77)		16,360 (21.90)	
14	313 (24.26)	460 (26.73)		18,663 (26.04)		19,436 (26.02)	
15	261 (20.23)	374 (21.73)		15,084 (21.04)		15,719 (21.04)	
16	241 (18.68)	272 (15.80)		13,181 (18.39)		13,694 (18.33)	
17	138 (10.70)	152 (8.83)		8037 (11.21)		8327 (11.15)	
18	6 (0.47)	8 (0.46)		427 (0.60)		441 (0.59)	

(*Continued*)

Table 1 (Continued).

	Med	No-Med	p-value (Med vs No-Med)	NDNM	p-value (Med vs NDNM)	Total	p-value (all 3 groups)[a]
Characteristic	**1290 (1.73)[b]**	**1721 (2.30)[c]**		**71,684 (95.97)[d]**		**74,695 (100)[e]**	
Antidepressant medication[g]							
Atypical antidepressant	133 (10.31)						
Serotonin modulator	63 (4.88)						
SNRI	47 (3.64)						
SSRI	1154 (89.46)						
TCA	29 (2.25)						
More than one type (Not monotherapy)	132 (10.23)						

Notes: [a]p-values refer to chi square tests. [b]Column total for Med is 1290 with following exception: gestational age of adolescent (N= 1278). [c]Column total for No-Med is 1721 with following exception: gestational age of adolescent (N= 1711). [d]Column total for NDNM is 71,684 with following exception: gestational age of adolescent (N= 70,937). [e]Column total for Total is 74,695 with following exception: gestational age of adolescent (N= 73,926). [f]Birthing parent prenatal anxiety diagnosis: (ICD-9) 293.84, 300.00, 300.01, 300.02, 300.09, 300.20, 300.21, 300.22, 300.23, 300.29, 300.3, 300.7, 309.21, 309.24, 309.81. [g]Antidepressant medication: Atypical antidepressant (Bupropion, Mirtazapine), serotonin modulator (Nefazodone, Trazodone), serotonin norepinephrine reuptake inhibitor (SNRI; Desvenlafaxine, Duloxetine, Venlafaxine), selective serotonin reuptake inhibitor (SSRI; Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline), tricyclic antidepressant (TCA; Amitriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline, Protriptyline).

Abbreviations: Med, Adolescents with mothers who had depression and used antidepressants during the prenatal period; No-Med, Adolescents with mothers who had depression and did not use antidepressants during the prenatal period; NDNM, Adolescents with mothers who neither had depression nor used antidepressants during the prenatal period; NH, Non-Hispanic; PHQ-2, Patient Health Questionnaire-2.

pregnancy (Y/N). Maternal age at delivery was treated categorically (19 or younger, 20 to 24, 25 to 29, 30 to 34, 35 to 39, 40 or older) because the relationship between maternal age and prenatal depression is non-linear with younger and older ages being associated with higher rates of depression. Parity was categorized as 0, 1, or ≥2 prior live births. Medicaid insurance status was used as a proxy for socioeconomic status.

Maternal race and ethnicity were categorized as: Hispanic; non-Hispanic (NH) Asian, Native Hawaiian, Pacific Islander; NH Black; NH Indigenous; NH Multiracial; and NH White. Race and ethnicity data were also extracted from the EHR and research databases. This was included as a covariate as some studies have found racial and ethnic minority groups to have higher prevalence of prenatal depression[38] as well as depressive symptoms in adolescence.[39] Race is likely a proxy for the experience of racism, such as through chronic life stress (secondary to similar socioeconomically disadvantaged environments or internalization as low self-esteem for both mother and child) which has been associated with higher rates of depression.[38,39]

Adolescents' characteristics, including gestational age (continuous) and sex assigned at birth (male/female), were also considered as covariates. Gestational age at birth was ultimately not included in analyses because it was not associated with both outcomes.

Statistical Analysis

Descriptive analyses were conducted using chi-square tests. Multivariable logistic regression models were used to analyze associations between maternal prenatal depression, antidepressant use, and adolescent depressive symptoms and suicidality. Adolescent depressive symptoms and suicidality were analyzed as separate outcomes. To account for non-independence between siblings, adolescents were clustered at the level of the mother. Mixed effects logistic regression models output odds ratios (OR) and their associated 95% confidence intervals (CI). To investigate the odds of intergenerational depression (depressive symptoms in adolescents whose mothers had prenatal depression), NDNM was used as the reference group. To investigate the odds associated with maternal prenatal antidepressant use, we restricted the analyses to dyads exposed to prenatal depression and used No-Med as the reference group. We also evaluated the role of adolescent sex as a potential effect modifier by including a cross-product term between prenatal exposure and adolescent sex. All models were adjusted for covariates.

We conducted two sensitivity analyses. First, to limit misclassification of prenatal antidepressant use, we redefined exposure to antidepressants as two or more antidepressant purchases during the prenatal period, as opposed to just one purchase. This would remove any mother who purchased an initial prescription but ultimately decided not to take

antidepressants. Second, to reduce confounding by indication (as it has been suggested that monotherapy partially accounts for confounding by depression severity)[25] and for consistency with prior studies, we redefined exposure to antidepressants as SSRI monotherapy (one or more purchases of SSRIs and no other classes of antidepressants) during the prenatal period and excluded mothers who had taken any other class of antidepressants (eg, SNRI, TCA, atypical antidepressants, or serotonin modulators).[20–23,25,26] All analyses were performed using Stata/BE 17.0.

Results

Participant Characteristics

Table 1 displays demographic characteristics of the 74,695 mother-adolescent dyads included in our sample, overall and stratified by prenatal exposure: both prenatal depression diagnosis and prenatal antidepressant use (Med; N = 1290); prenatal depression diagnosis and no prenatal antidepressant use (No-Med; N = 1721); and neither prenatal depression diagnosis nor prenatal antidepressant use (NDNM; N = 71,684). Mothers with prenatal depression were more likely than those without prenatal depression to have more than one child and Medicaid insurance. Of mothers with prenatal depression, those who took antidepressants were more likely to be older and NH White than those who did not take antidepressants.

Table 2 presents demographic characteristics stratified by adolescents' depressive symptoms and suicidality. Approximately 9% (N = 6384) of adolescents reported depressive symptoms and 2% (N = 1314) endorsed suicidality. Adolescents with depressive symptoms or suicidality were more likely to be female and born to mothers who had pregravid depression, were <19 or ≥40 years old at delivery, had more than one child, were NH Black, or had Medicaid

Table 2 Selected Characteristics by Depressive Symptoms and Suicidality in Adolescents, N (%)

	Depressive Symptoms in Adolescents			**Suicidality in Adolescents**		
	N= 67,741[a]			**N= 66,801**		
	<3, No	**≥3, Yes**		**No**	**Yes**	
Characteristic	**68,311 (91.45)**	**6384 (8.55)**	***p*-value[b]**	**72,331 (98.22)**	**1314 (1.78)**	***p*-value[b]**
Maternal age at delivery (years)			<0.001			0.014
≤19	2188 (3.20)	276 (4.32)		2369 (3.28)	59 (4.49)	
20–24	8159 (13.41)	960 (15.04)		9780 (13.52)	196 (14.92)	
25–29	19,194 (28.10)	1622 (25.41)		20,183 (27.90)	343 (26.10)	
30–34	22,223 (32.53)	1932 (30.26)		23,430 (32.39)	390 (29.68)	
35–39	12,498 (18.30)	1262 (19.77)		13,304 (18.39)	259 (19.71)	
≥40	3049 (4.46)	332 (5.20)		3265 (4.51)	67 (5.10)	
Prenatal Medicaid insurance			<0.001			<0.001
No	66,359 (97.14)	6109 (95.69)		70,210 (97.07)	1238 (94.22)	
Yes	1952 (2.86)	275 (4.31)		2121 (2.93)	76 (5.78)	
Parity (live births)			<0.001			0.001
0	29,518 (43.21)	2731 (42.78)		31,232 (43.18)	555 (42.24)	
1	24,024 (35.17)	2144 (33.58)		25,398 (35.11)	418 (31.81)	
≥2	14,769 (21.62)	1509 (23.64)		15,701 (21.71)	341 (25.95)	
Maternal race and ethnicity			<0.001			<0.001
Hispanic	19,392 (28.39)	2134 (33.43)		20,824 (28.79)	379 (28.84)	
NH Asian, Native Hawaiian, Pacific Islander	17,618 (25.79)	1289 (20.19)		18,383 (25.42)	286 (21.77)	
NH Black	4791 (7.01)	551 (8.63)		5112 (7.07)	138 (10.50)	
NH Indigenous	287 (0.42)	35 (0.55)		311 (0.43)	7 (0.53)	
NH Multiracial	2495 (3.65)	230 (3.60)		2635 (3.64)	45 (3.42)	
NH White	23,728 (34.74)	2145 (33.60)		25,066 (34.65)	459 (34.93)	

(*Continued*)

Table 2 (Continued).

	Depressive Symptoms in Adolescents			Suicidality in Adolescents		
	N= 67,741[a]			N= 66,801		
	<3, No	≥3, Yes		No	Yes	
Characteristic	**68,311 (91.45)**	**6384 (8.55)**	***p*-value[b]**	**72,331 (98.22)**	**1314 (1.78)**	***p*-value[b]**
Maternal prenatal anxiety diagnosis			<0.001			0.515
No	65,600 (96.03)	6049 (94.75)		69,397 (95.94)	1256 (95.59)	
Yes	2711 (3.97)	335 (5.25)		2934 (4.06)	58 (4.41)	
Maternal pregravid depression diagnosis			<0.001			0.002
No	65,556 (95.97)	5999 (93.97)		69,309 (95.82)	1236 (94.06)	
Yes	2755 (4.03)	385 (6.03)		3022 (4.18)	78 (5.94)	
Sex assigned at birth of adolescent			<0.001			<0.001
Female	32,350 (47.36)	4305 (67.43)		35,116 (48.55)	1001 (76.18)	
Male	35,961 (52.64)	2079 (32.57)		37,215 (51.45)	313 (23.82)	
Gestational age of adolescent (weeks)			0.030			0.628
<28	127 (0.19)	9 (0.14)		128 (0.18)	3 (0.23)	
28–32	360 (0.53)	39 (0.62)		388 (0.54)	4 (0.31)	
32–37	3878 (5.74)	310 (4.90)		4058 (5.67)	70 (5.37)	
≥37	63,237 (93.54)	5966 (94.34)		67,013 (93.61)	1227 (94.10)	
Adolescent age at most recent PHQ-2 (years)			<0.001			0.058
12	679 (0.99)	39 (0.61)		692 (0.96)	10 (0.76)	
13	15,155 (22.19)	1205 (18.88)		15,838 (21.90)	280 (21.31)	
14	17,825 (26.09)	1611 (25.23)		18,804 (26.00)	364 (27.70)	
15	14,315 (20.96)	1404 (21.99)		15,206 (21.02)	303 (23.06)	
16	12,401 (18.15)	1293 (20.25)		13,278 (18.36)	227 (17.28)	
17	7536 (11.03)	791 (12.39)		8084 (11.18)	128 (9.74)	
18	400 (0.59)	41 (0.64)		429 (0.59)	2 (0.15)	

Notes: [a]Numbers are marginally lower for gestational age of adolescent (N= 73,926) due to missing data. [b]p-values refer to chi square tests of independence.
Abbreviations: NH, Non-Hispanic; PHQ-2, Patient Health Questionnaire-2.

insurance. Older adolescents (16 to 18 years old) were more likely to endorse depressive symptoms, whereas younger adolescents (14 to 15 years old) were more likely to endorse suicidality.

Primary Analyses

We found no significant interaction between prenatal exposure and adolescent sex in models with either depressive symptoms or suicidality as the outcome, thus we do not present sex-stratified results.

Prenatal Depression and Depressive Symptoms in Adolescents

Adjusting for covariates, adolescents exposed to mothers' prenatal depression had higher odds of depressive symptoms than those whose mothers neither experienced prenatal depression nor took antidepressants. The associations were almost identical among adolescents whose mother used antidepressants (Med OR: 1.50, CI: 1.23–1.84) and those who did not use antidepressants (No-Med OR: 1.59, CI: 1.34–1.88) (Table 3 and Figure 2).

Prenatal Antidepressant Use and Depressive Symptoms in Adolescents

Among adolescents exposed to prenatal depression, prenatal antidepressant exposure was not associated with increased odds of depressive symptoms (Med OR: 0.95, CI: 0.74–1.21) compared to those who were not exposed to antidepressants (Table 3 and Figure 2).

Table 3 Association of Maternal Depression and Antidepressant Use During the Prenatal Period with Depressive Symptoms and Suicidality in Adolescent Children

	Depressive Symptoms in Adolescents	Suicidality in Adolescents
	Adjusted Model[a]	Adjusted Model[a]
	OR (95% CI)	OR (95% CI)
Main Model: Med = Any antidepressants, ≥ 1 purchase		
	N= 74,695	N= 73,645
Med vs NDNM (Ref)	1.50 (1.23, 1.84)***	2.36 (1.67, 3.34)***
No-Med vs NDNM (Ref)	1.59 (1.34, 1.88)***	1.54 (1.10, 2.14)**
Med vs No-Med (Ref)	0.95 (0.74, 1.21)	1.54 (0.99, 2.39)
Sensitivity Analysis 1: Med = Any antidepressants, ≥ 2 purchases		
	N= 74,135	N= 73,095
Med vs NDNM (Ref)	1.59 (1.23, 2.06)***	2.29 (1.44, 3.63)***
No-Med vs NDNM (Ref)	1.60 (1.35, 1.89)***	1.54 (1.11, 2.15)**
Med vs No-Med (Ref)	0.99 (0.74, 1.33)	1.48 (0.87, 2.52)
Sensitivity Analysis 2: Med = SSRI monotherapy, ≥ 1 purchase		
	N= 74,440	N= 73,392
Med vs NDNM (Ref)	1.44 (1.15, 1.80)***	2.43 (1.66, 3.55)***
No-Med vs NDNM (Ref)	1.58 (1.34, 1.87)***	1.56 (1.12, 2.18)**
Med vs No-Med (Ref)	0.91 (0.70, 1.18)	1.55 (0.97, 2.48)

Notes: [a]All models were clustered by mother and adjusted for birth sex of adolescent, maternal age at delivery, maternal race and ethnicity, pregravid depression diagnosis, prenatal anxiety diagnosis, parity, and prenatal Medicaid insurance. **p-value ≤0.01. ***p-value ≤0.001.

Abbreviations: OR, adjusted odds ratio; 95% CI, 95% confidence interval; Med, Antidepressant exposure group; Med, Adolescents with mothers who had depression and used antidepressants during the prenatal period; No-Med, Adolescents with mothers who had depression and did not use antidepressants during the prenatal period; NDNM, Adolescents with mothers who neither had depression nor used antidepressants during the prenatal period; SSRI, selective serotonin reuptake inhibitor.

Prenatal Depression and Suicidality in Adolescents

Among adolescents, both prenatal depression exposure groups (Med OR: 2.36, CI: 1.67–3.34; No-Med OR: 1.54, CI: 1.10–2.14) had higher odds of suicidality compared to those whose mothers neither experienced prenatal depression nor took antidepressants (NDNM) (Table 3 and Figure 3).

Prenatal Antidepressant Use and Suicidality in Adolescents

Among adolescents exposed to prenatal depression, prenatal antidepressant exposure was not significantly associated with increased odds of suicidality; however, this association was marginal (Med OR: 1.54, CI: 0.99–2.39) (Table 3 and Figure 3).

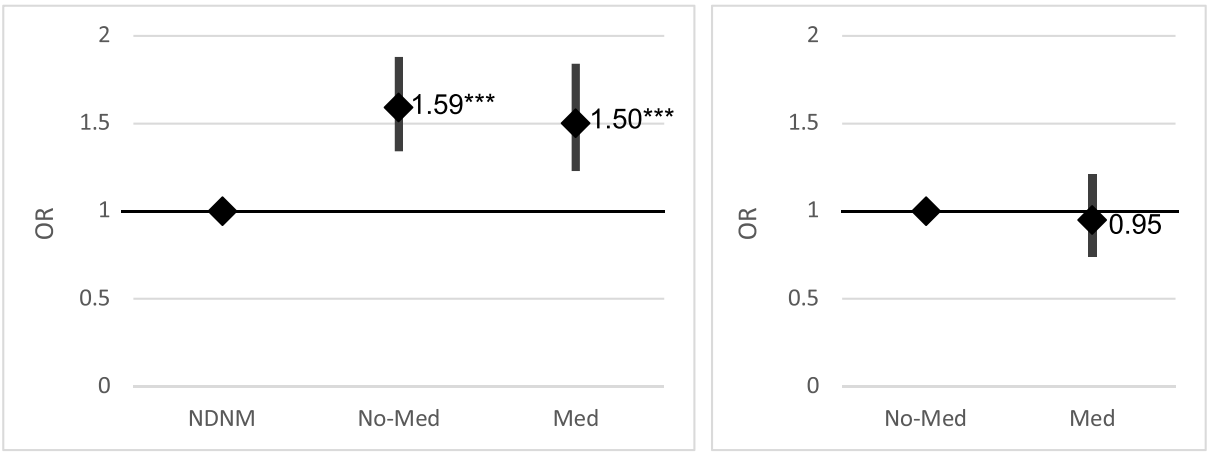
Sensitivity Analysis 1: Two or More Purchases of Any Antidepressant

Depressive Symptoms

Redefining antidepressant use as two or more purchases yielded findings consistent with our primary analyses (main model), ie, adolescents whose mothers had prenatal depression (Med OR: 1.59, CI: 1.23–2.06 and No-Med OR: 1.60, CI: 1.35–1.89) had higher odds of depressive symptoms in comparison to those whose mothers did not have prenatal depression (NDNM). Among those whose mothers had prenatal depression, antidepressant use (Med OR: 0.99, CI: 0.74–1.33) was not associated with greater odds of depressive symptoms compared to those whose mothers did not use antidepressants (No-Med) (Table 3 and Figure 2).

Suicidality

Consistent with the main model, Med (OR: 2.29, CI: 1.44–3.63) and No-Med (OR: 1.54, CI: 1.11–2.15) were associated with significantly higher odds of suicidality in adolescents compared to NDNM. Similarly, Med (OR: 1.48, CI: 0.87–2.52) did not have greater odds of suicidality in adolescents compared to No-Med (Table 3 and Figure 3).



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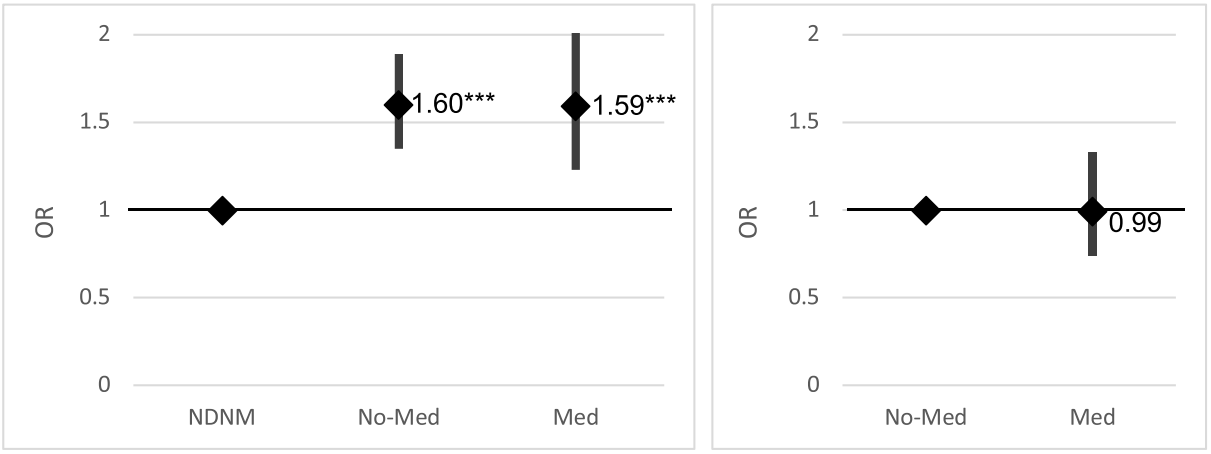

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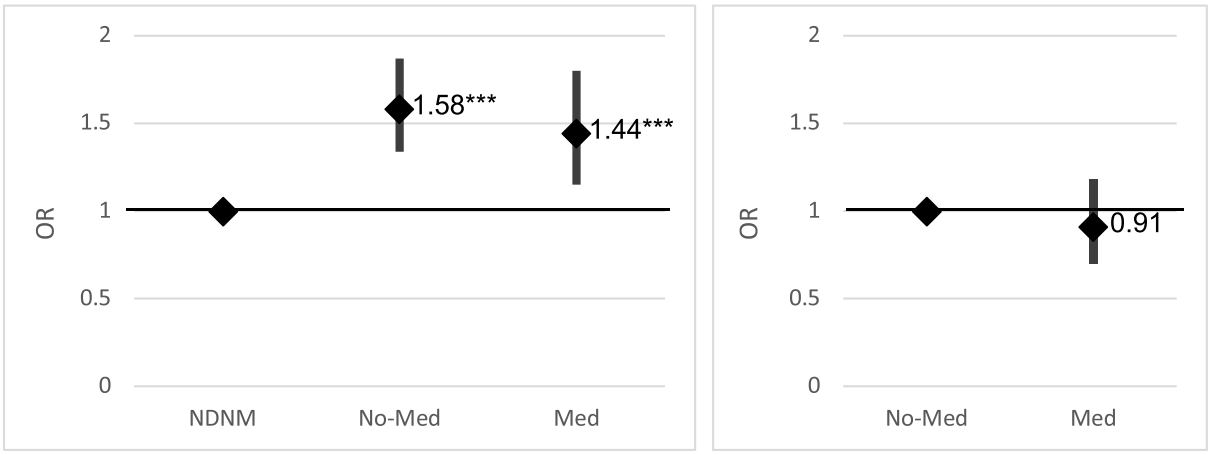

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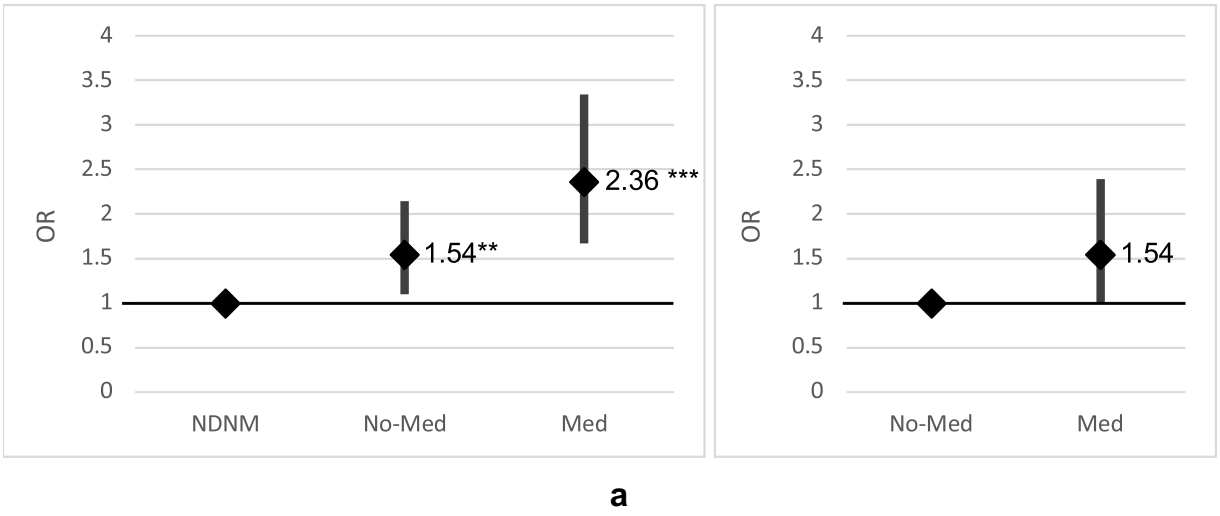
Figure 2 Association of maternal depression and antidepressant use during the prenatal period with depressive symptoms in adolescent children. (**a**) Main Model: Med = Any antidepressants, ≥ 1 purchase. (**b**) Sensitivity Analysis 1: Med = Any antidepressants, ≥ 2 purchases. (**c**) Sensitivity Analysis 2: Med = SSRI monotherapy, ≥ 1 purchase.
Notes: All models were clustered by mother and adjusted for birth sex of adolescent, maternal age at delivery, maternal race and ethnicity, pregravid depression diagnosis, prenatal anxiety diagnosis, parity, and prenatal Medicaid insurance. ***p-value ≤0.001.
Abbreviations: OR, adjusted odds ratio; Med, Antidepressant exposure group; Med, Adolescents with mothers who had depression and used antidepressants during the prenatal period; No-Med, Adolescents with mothers who had depression and did not use antidepressants during the prenatal period; NDNM, Adolescents with mothers who neither had depression nor used antidepressants during the prenatal period; SSRI, selective serotonin reuptake inhibitor.



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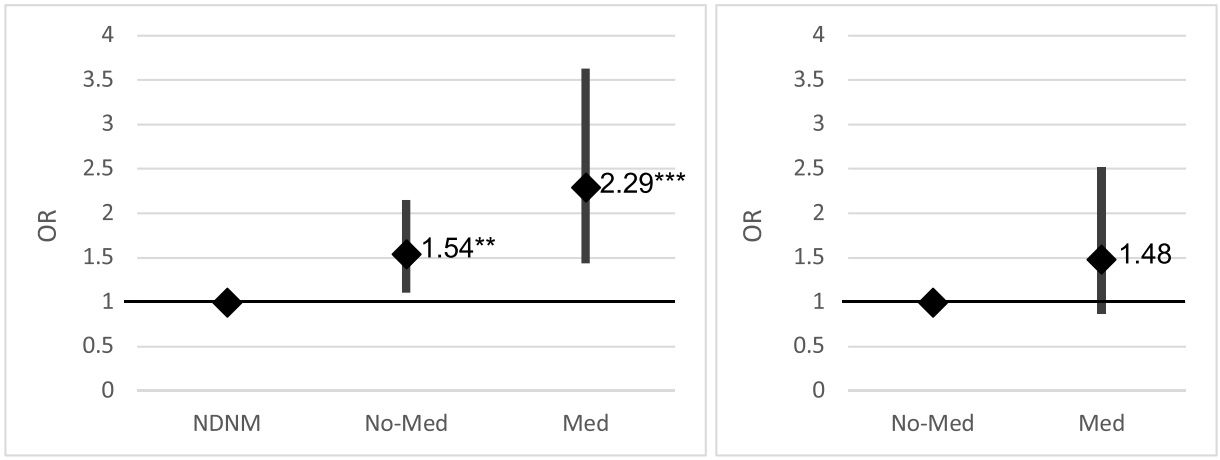

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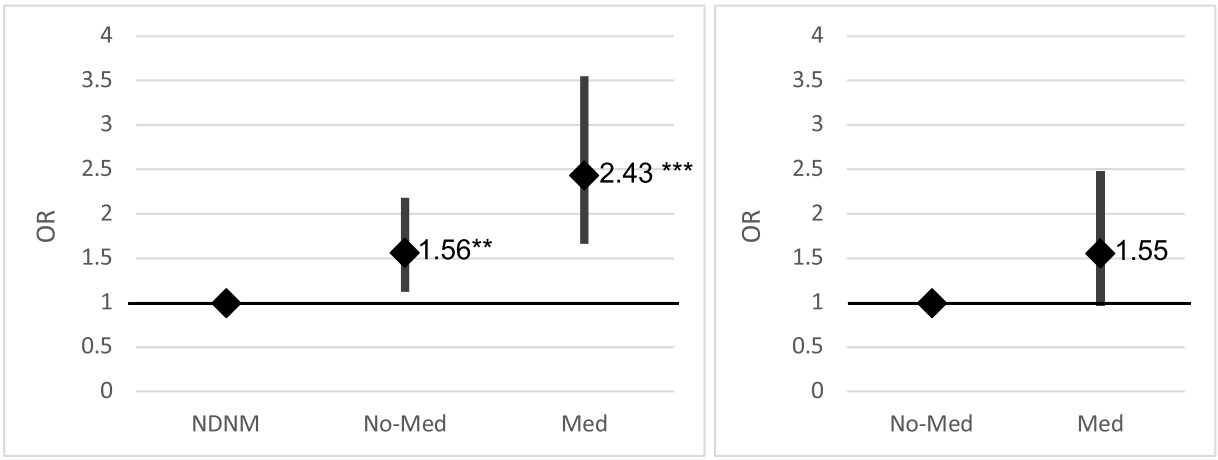

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Figure 3 Association of maternal depression and antidepressant use during the prenatal period with suicidality in adolescent children. (**a**) Main Model: Med = Any antidepressants, ≥ 1 purchase. (**b**) Sensitivity Analysis 1: Med = Any antidepressants, ≥ 2 purchases. (**c**) Sensitivity Analysis 2: Med = SSRI monotherapy, ≥ 1 purchase.
Notes: All models were clustered by mother and adjusted for birth sex of adolescent, maternal age at delivery, maternal race and ethnicity, pregravid depression diagnosis, prenatal anxiety diagnosis, parity, and prenatal Medicaid insurance. ** p-value ≤0.01. *** p-value ≤0.001.
Abbreviations: OR, adjusted odds ratio; Med, Antidepressant exposure group; Med, Adolescents with mothers who had depression and used antidepressants during the prenatal period; No-Med, Adolescents with mothers who had depression and did not use antidepressants during the prenatal period; NDNM, Adolescents with mothers who neither had depression nor used antidepressants during the prenatal period; SSRI, selective serotonin reuptake inhibitor.

Sensitivity Analysis 2: One or More Purchases of SSRI Monotherapy

Depressive Symptoms

For adolescent depressive symptoms, the second sensitivity analysis limited antidepressant use to SSRI monotherapy and yielded findings consistent with results from the primary and first sensitivity analyses (Table 3 and Figure 2).

Suicidality

For adolescent suicidality, the second sensitivity analysis limited antidepressant use to SSRI monotherapy and yielded findings consistent with results from the primary and first sensitivity analyses (Table 3 and Figure 3).

Discussion

In this large prospective cohort, maternal prenatal depression was associated with greater depressive symptoms and suicidality in adolescent children. Among adolescents exposed to prenatal depression, we found no difference in depressive symptoms between those whose mothers used and did not use antidepressants during the prenatal period. Prenatal antidepressant exposure was marginally associated with greater suicidality among adolescents; however, this association was not statistically significant.

Prior research on prenatal antidepressant use and depression in the child during adolescence is limited, with most research focusing on early childhood (up to age 7).[20] Prospective cohort studies in young children have found associations between maternal depressive symptoms, but not prenatal antidepressant use, and children's internalizing behaviors and affective disorders.[21–24] While other studies in young children have reported associations between prenatal antidepressant use and higher levels of depressive behavior and affective disorders, these studies failed to account for confounding by indication as they did not restrict their participants to those with depression.[20] Only two studies have explored this association in adolescent children.[25,26] A population-based study in Finland found higher rates of depression among children (2–14 years old) whose mothers took SSRIs during pregnancy for a variety of indications (approximately 30% of mothers had depression, anxiety, or bipolar disorder) compared to children whose mothers discontinued antidepressant use prior to pregnancy and children whose mothers had a psychiatric disorder but did not take antidepressants during pregnancy.[25] The second study, a population-based study in Denmark, found increased rates of depression diagnosis in children up to 18 years old whose mothers continued antidepressants during pregnancy as compared to children of mothers who discontinued antidepressant use prior to pregnancy.[26] This study did not report mothers' psychiatric diagnoses. Thus, our study is the first to our knowledge to account for confounding by indication, by restricting to mothers with a depression diagnosis, using an adolescent cohort.

One way in which this study accounted for confounding by the indication for which antidepressants were prescribed was in defining exposure groups. This study limited maternal prenatal antidepressant use to mothers with a depression diagnosis and included the comparison group of mothers with depression who did not use antidepressants during the prenatal period. As antidepressants are also prescribed for sleep disorders, neuropathic pain, anxiety, and other psychiatric disorders,[40,41] the two prior studies in adolescents,[25,26] which did not restrict by indication, are less informative for clinical decision-making when mothers are specifically weighing whether or not to treat their depression during the prenatal period. Furthermore, because depression is the primary indication for which antidepressants are prescribed,[40,41] we excluded maternal psychiatric diagnoses that have been associated with both prenatal depression and depression in children, included by these prior studies,[25,26] to better inform clinical decision-making on less complex cases of prenatal depression, specifically.

A second way in which this study accounted for confounding by indication in defining exposure groups, and built upon limitations of the two prior studies in adolescents, was by considering chronicity of maternal depression. The population-based study in Denmark used the exposure groups of mothers who continued or discontinued antidepressants during pregnancy, which limits the study population (and generalizability) to only mothers with prenatal depression who had preexisting depression prior to pregnancy.[26] We accounted for differences in chronicity of maternal depression by including preexisting and new onset prenatal depression diagnoses in both our Med and No-Med groups and controlling for pregravid depression diagnosis.

Another strength of the current study was the evaluation of the association between prenatal antidepressant exposure and adolescent suicidality, which had not been included in prior studies. We found that prenatal antidepressant exposure was marginally associated with increased odds of suicidality; however, this association was not statistically significant. One possible explanation for the marginal association may be that mothers with more severe depression may be more likely to use antidepressants and have children with suicidal ideation. It is also possible that children of mothers who take antidepressants feel more comfortable disclosing suicidal ideation. While our findings suggest a possible association between maternal prenatal antidepressant use and adolescent suicidality, further investigation is needed.

Consistent with the population-based study in Finland,[25] we did not find an interaction between prenatal antidepressant exposure and child sex at birth on adolescent depressive symptoms nor suicidality. There are several proposed mechanisms suggesting male fetuses have greater vulnerability to prenatal adversity, such as maternal depression. These include prolonged periods of vulnerability due to slower fetal maturation, reduced uterine hospitability due to immune system response to the unfamiliar Y chromosome, sex steroids for fetal sex organ development influence the intrauterine environment, and different coping strategies when faced with prenatal adversity based on an evolutionary biology framework.[42] Male fetuses are also more susceptible to prenatal adversity introduced through maternal behavior such as medication use.[42] Thus, it is notable that we found no significant difference between males and females in odds of depressive symptoms nor suicidality among those exposed and unexposed to prenatal depression and/or antidepressants.

This study has several limitations. First, we could not control for alcohol or drug use during pregnancy (although we excluded mothers with a substance use disorder diagnosis). Second, while we accounted for chronicity of depression by including preexisting and new onset prenatal depression and controlling for pregravid depression diagnosis, we could not account for the timing or duration of maternal episodes of depression during pregnancy or throughout the child's life. Additionally, prior studies have identified prenatal depression as an independent risk factor for depression in adolescent children, even after adjusting for maternal depression throughout the child's life,[5–7] however, this does not mean that environmental liability to depression could not be a confounding factor. Third, we could not control for severity of prenatal depression, although it has been suggested that restricting antidepressant use to monotherapy partially accounts for confounding by depression severity.[25] Fourth, we were unable to confirm medication adherence, although we accounted for this with a sensitivity analysis redefining antidepressant use as two purchases rather than one, nor medication treatment effectiveness in symptom reduction or remission. Lastly, we were unable to account for exact duration, timing, or dosage of prenatal antidepressant use. While prior studies have suggested duration of gestational exposure to antidepressants, not timing or dosage, is associated with adverse outcomes in offspring,[26,33] replication of these studies is needed.

Despite these limitations, to our knowledge this is the first large, racially and ethnically diverse study to examine the relationship between prenatal depression (preexisting and new onset) and antidepressant use, and depressive symptoms and suicidality in adolescents. By measuring self-reported depressive symptoms and suicidality at well-teen appointments, we overcame prior studies' problem of detection bias.[25,26] Prior studies were concerned that mothers receiving treatment for their depression may be more likely to bring in their children for diagnosis and treatment to specialty care.[25,26] Additional strengths include the use of EHR data for exposure assessment, reducing the potential of non-response and recall bias. Moreover, prescription purchase records are considered the strongest approach for pharmacotherapy exposure over self-report and medical records.[43,44]

Conclusion

Additional research is needed to guide clinical decision-making.[9] Future studies should monitor severity of maternal prenatal depressive symptoms throughout pregnancy to control for initial severity and as a proxy for treatment efficacy. This is an important future area of research as the majority of women with prenatal depression are undertreated[10,45] and it can be challenging to optimize pharmacotherapy dosage across pregnancy. Thus, current studies are more representative of real-world experience in which the child is likely experiencing the dual exposure of undertreated prenatal depression and antidepressants in utero. Future studies should explore the impact of antidepressants in the setting of prenatal depression symptom reduction or remission.

This study adds to the limited literature on long-term outcomes associated with antidepressant use during pregnancy. In contrast to prior studies,[25,26] our results suggest no additional risk of adolescent depressive symptoms when exposed to antidepressants in utero. While our findings suggest a possible association between maternal antidepressant use in the setting of prenatal depression and adolescent suicidality, further investigation is needed. These findings may inform shared clinical decision-making when deciding whether to start, continue, or discontinue antidepressants to treat maternal depression during pregnancy.

Additional Information

While we recognize not all birthing people identify as maternal, mothers, or women, we chose to use this language for consistency with prior literature.

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Disclosure

The authors report no conflicts of interest in this work.

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