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Ketevan Marr, Charlotte Maguet, Honor Scarlett, Rosemary Dray-Spira, Caroline Dubertret, Florence Gressier, Anne-laure Sutter-Dallay, Maria Melchior, Judith van der Waerden

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SYSTEMATIC REVIEW

Social determinants in prenatal antidepressant use and continuation: Systematic review and meta-analysis

Ketevan Marr[1] | **Charlotte Maguet**[1] | **Honor Scarlett**[1] | **Rosemary Dray-Spira**[1,2] | **Caroline Dubertret**[3,4] | **Florence Gressier**[5] | **Anne-Laure Sutter-Dallay**[6,7] | **Maria Melchior**[1] | **Judith van der Waerden**[1]

[1]Institut Pierre Louis d'Epidémiologie et de Santé Publique, Équipe de Recherche en Épidémiologie Sociale, Paris, France

[2]EPI-PHARE Scientific Interest Group in Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety, French National Health Insurance, Saint-Denis, France

[3]AP-HP, Groupe Hospital-Universitaire AP-HP Nord, DMU ESPRIT, Service de Psychiatrie et Addictologie, Hôpital Louis Mourier, Colombes, France

[4]Faculté de Médecine, Université de Paris, Paris, France

[5]CESP, Inserm UMR1178, Department of Psychiatry, Assistance Publique-Hôpitaux de Paris, Bicêtre University Hospital, Le Kremlin Bicêtre, France

[6]Inserm, Bordeaux Population Health Research Center, U1219, Bordeaux University, Bordeaux, France

[7]University Department of Child and Adolescent Psychiatry, Charles Perrens Hospital, Bordeaux, France

Correspondence
Ketevan Marr, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Équipe de Recherche en Épidémiologie Sociale, INSERM U1136, Sorbonne Université, 75012 Paris, France.
Email: ketevan.marr@inserm.fr

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Abstract

Introduction: Depression is one of the most common co-morbidities during pregnancy; with severe symptoms, antidepressants are sometimes recommended. Social determinants are often linked with antidepressant use in the general population, and it is not known if this is the case for pregnant populations. Our objective was to determine if social determinants are associated with prenatal antidepressant intake via a systematic review and meta-analysis.

Methods: A systematic search of five databases was conducted to identify publications from inception to October 2022 that reported associations with prenatal antidepressant intake (use/continuation) and one or more social determinants: education, race, immigration status, relationship, income, or employment. Eligible studies were included in random effects meta-analyses.

Results: A total of 23 articles describing 22 studies were included. Education was significantly and positively associated with prenatal antidepressant continuation and heterogeneity was moderate. (Odds ratio = 0.83; 95% CI, 0.78 to 0.89; $p < 0.00001$; $I^2 = 53\%$). Meta-analyses of antidepressant use and education, race, and relationship status, and antidepressant continuation and income were not significant with high levels of heterogeneity.

Discussion: While most social determinants in this review were not linked with prenatal antidepressant intake, lower maternal education level does seem to be associated with lower rates of prenatal antidepressant continuation.

Conclusions: Education appears to be linked with prenatal antidepressant intake. The low number of included studies precludes conclusive evidence for other social determinants.

KEYWORDS

antidepressants, mental health, prenatal medication continuation, prenatal medication use, social determinants

1 | INTRODUCTION

Prenatal depression is increasingly recognized as the most common morbidity in pregnancy,[1] with global pooled prevalence rates estimated to be 15%,[2,3] and is associated with sustained poor maternal mental health in the postpartum period,[4] as well as a variety of adverse short- and long-term outcomes in children. First-line treatment options for prenatal mild to moderate depression symptoms include psychotherapy, of which cognitive behavioral therapy and interpersonal therapy are both efficacious among pregnant women,[5–7] Nevertheless, moderate to severe symptoms often require pharmacotherapy such as antidepressants as second-line treatments, especially for those who respond well to these medications.[8] Use of antidepressants during pregnancy, particularly Selective serotonin reuptake inhibitors (SSRIs), is increasing over time.[9] The pooled prevalence of prenatal SSRI use from 15 countries was 3.0% (95%CI 2.3;3.7), although with regional differences, as Australasia and Northern America have pooled prevalence estimates of 1.3%, and 5.5%, respectively.[9] Nevertheless, while specific rates vary, once pregnancy is confirmed, antidepressant discontinuation rates increase from 1.8 to 3.5 fold.[10–13]

Generally, guidelines used to determine if various classifications of antidepressants are appropriate for pregnant patients, recommend that both the medical provider and the patient use a risk–benefit analysis to make individual decisions.[14] During this process, primarily the balance between the severity of mental health symptoms and known risks to the fetus is considered.[15,16] However, other factors aside from fetal exposure concerns are possibly at play.[10] The social determinants of health behavior is an interdisciplinary framework of understanding differences in health behaviors that recognizes the impact of social resource distribution and resulting systemic inequalities on individual decision-making.[17,18] These social determinants (SD) have been researched aiming to elucidate the impact various indicators have on health behaviors, including education, employment, income, relationship status, race/ethnicity, immigration, as well as others. Although links between SD and obstetric outcomes[19] and antidepressant use[20] have been examined, the relationship between antidepressant intake rates and SD is not yet fully understood for pregnant populations. Some studies report that women with disadvantageous SD, particularly low socioeconomic status, diagnosed with mood disorders are less likely to be medicinally treated during pregnancy.[21,22] Other research, however, indicates that they are more likely to use psychotropic medications than women of higher income or educational levels.[23] Likewise, high discontinuation rates for antidepressants have also been reported, especially among low income and ethnic minority women.[24,25]

As antidepressant discontinuation during pregnancy is linked to increased risk of psychiatric emergency[26] and an increased risk of relapse,[27] the potential differentiation of these intake patterns by SD is necessary to explore, particularly as disadvantageous SD are linked with an elevated risk of depression symptoms among pregnant women[25,28,29] and a social gradient of prenatal depression symptoms has also been demonstrated.[30] A fuller understanding of this issue could provide opportunities to understand how best to increase access to high-quality healthcare for pregnant patients with social disadvantages. Additionally, this information is equally important for clinicians, so they are better able to take these factors into account when considering treatment options with their patients, particularly those that are resource-intensive.[31,32]

To our knowledge, no previous reviews have been conducted examining the relationship between prenatal antidepressant use and continuation and social determinants.

Summations

- Most studied social determinants were not associated with frequency of prenatal antidepressant use or continuation.
- Pregnant women having high school or lower levels of education discontinue their antidepressant medication more frequently compared to those with more years of education.
- Perinatal healthcare providers should be aware that educational level may impact antidepressant intake decision-making.

Limitations

- Heterogeneity between included studies precluded substantial conclusions for most social determinants and the small number of included papers limited our ability to explore additional sources of heterogeneity.
- We explored possible sources of heterogeneity and found that antidepressant category, healthcare system, antidepressant data collection methods, and study quality were not sources of heterogeneity.
- We were unable to explicitly explore factors frequently linked with social determinants, such as health literacy and broad social support.

The purpose of this article is to evaluate these associations through a systematic review of the literature and meta-analysis. We provide pooled association measures between prenatal antidepressant intake and various SD.

2 | METHODS

This review was registered with The International Prospective Register of Systematic Reviews PROSPERO (CRD42021243752) and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[33]

2.1 | Data sources

A literature search was conducted across five databases: Medline (OVID), PubMed, Web of Science, PsycINFO, and Cochrane Library, from inception to October 2022. The search was developed around key terms relating to social determinants of health, and prenatal psychotropic medication intake. Though SD can be categorized at the individual, family, or neighborhood levels, this paper will focus on individual measures.[34] Medication classifications in the search strategy were deliberately not limited to antidepressants to ensure that we captured all potential studies on this topic. Social determinant search terms included general terms as well as terms related to education, class, and race/ethnicity, although additional social determinants were identified during the article review (e.g., marital status). No restrictions were made on publication date or language of publication. The full search strategy can be found in Supplementary Table 1. Additional articles were identified through hand-searching reference lists.

2.2 | Study selection

Studies included in this review met the following criteria: (1) measurement of prenatal antidepressant intake, that is, comparing women who experienced mental health issues who consumed antidepressants during pregnancy with women who experienced mental health issues and did not consume antidepressants; (2) the comparison between one or more SD such as education, race, relationship status, financial situation, occupation, and immigration status (see Supplementary Table 2 for information on their operationalization); (3) cross-sectional, cohort and randomized controlled trial study designs; and (4) available as full-text. See Supplementary Table 2 for all inclusion/exclusion criteria.

Records were uploaded to Rayyan software[35] and duplicates were removed. Screening of titles and abstracts were conducted by two reviewers (Ketevan Marr, Judith van der Waerden) and a dual-review full-text screening was conducted in parallel by three reviewers (Ketevan Marr and Charlotte Maguet/Honor Scarlett). Discrepancies were resolved through discussion and consensus.

2.3 | Data extraction and quality appraisal

Data extraction was conducted by two reviewers (Ketevan Marr, Charlotte Maguet); any discrepancies were resolved through discussion and consensus with a third reviewer (Judith van der Waerden). The following information was extracted using a standardized form: study characteristics, psychiatric medication use information, SD measures, and the primary data relating to the association of SD and prenatal antidepressant intake, primarily association measures. Dichotomous groupings of various SD indicators were created based on what was presented in the included papers, and our aim in these groupings was to emphasize the differences in social advantages rather than imply any inherent variation. Some SD indicators, such as education or income, are ordinal with a clear gradient and a threshold was chosen and applied to all included papers. Other SD indicators, such as marital status and race/ethnicity, are categorical without a demonstrated social gradient and, similarly, a classification system was created from the categories presented in the included papers and then applied uniformly. For more details, see Supplementary Table 2. If necessary, odds ratios were calculated using sub-group counts. When calculating the totals of each sub-group, numbers of each may vary due to rounding issues. Study authors were contacted for missing information if papers did not present association measures between measured SD and antidepressant intake or other information in which those associations can be calculated.

2.4 | Quality assessment and GRADE

The quality of the studies was assessed by two independent investigators (Ketevan Marr, Charlotte Maguet) with Joanna Briggs Institute (JBI) critical appraisal checklists of eight and 11 items for cross-sectional and cohort studies, respectively.[31,36] This checklist assesses the methodological quality of a study and determines the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. If a study had more than one point deducted from the total score, it was classified

as low quality. Studies that received all points or just had one point deducted were classified as high quality.

Risk of bias was determined using the Grading of Recommendations Assessment, Development and Evaluations (GRADE) approach evaluating the risk of bias, imprecision, inconsistency, indirectness, and publication bias.[37] Each article's quality of evidence was ranked either "high," "moderate," "low," or "very low." "High" rankings indicated effect estimates for which further research is unlikely to change the confidence rating, whereas for "very low" the estimate of the effect is very uncertain. Any disagreements on rated components were discussed until a consensus was reached.

2.5 | Data synthesis and effect measures

To summarize and present the main findings for the relationship between SD and prenatal antidepressant intake, results were first analyzed using a narrative synthesis conducted in accordance with the Cochrane guidance for narrative syntheses[38] and Joanna Briggs' guidelines.[39]

Eligibility criteria for studies to be included in the meta-analysis were (1) unadjusted raw data reporting antidepressant intake for an individual social determinant indicator, (2) total participant numbers or other information to identify the total number of participants using prenatal antidepressant medication for the SD indicator being evaluated. At least four or more odds ratios were required to run a meta-analysis for any given SD indicator. To facilitate comparison across studies' association measures, confidence intervals and standard errors were extracted or calculated independently by two reviewers (Ketevan Marr, Charlotte Maguet) and discrepancies were resolved through discussion and consensus (Judith van der Waerden). Odds ratios were then entered into Review Manager 5.4[40] to run the meta-analyses and generate forest plots. Random effects inverse-variance meta-analyses were performed to access the association between SD and prenatal antidepressant intake. I^2 was calculated to determine the degree of heterogeneity, with an I^2 of >30%, 30%–60%, and >60% as the thresholds of low, moderate, and high heterogeneity, respectively.

A priori hypothesized subgroup analyses were performed according to type of antidepressant (all/multiple subclassifications of antidepressants vs SSRI-only antidepressants), healthcare system study participants were exposed to (guaranteed/comprehensive vs free market systems), medication use data collection method (self-report vs medical records/reimbursement data), and quality score (high vs low risk of bias). Healthcare system was largely determined by the country the study was conducted in, with exceptions if study participants had access to stable healthcare coverage. (Supplementary Table 2) Finally, the potential role of small study and publication bias was examined graphically through funnel plots.

3 | RESULTS

3.1 | Literature search

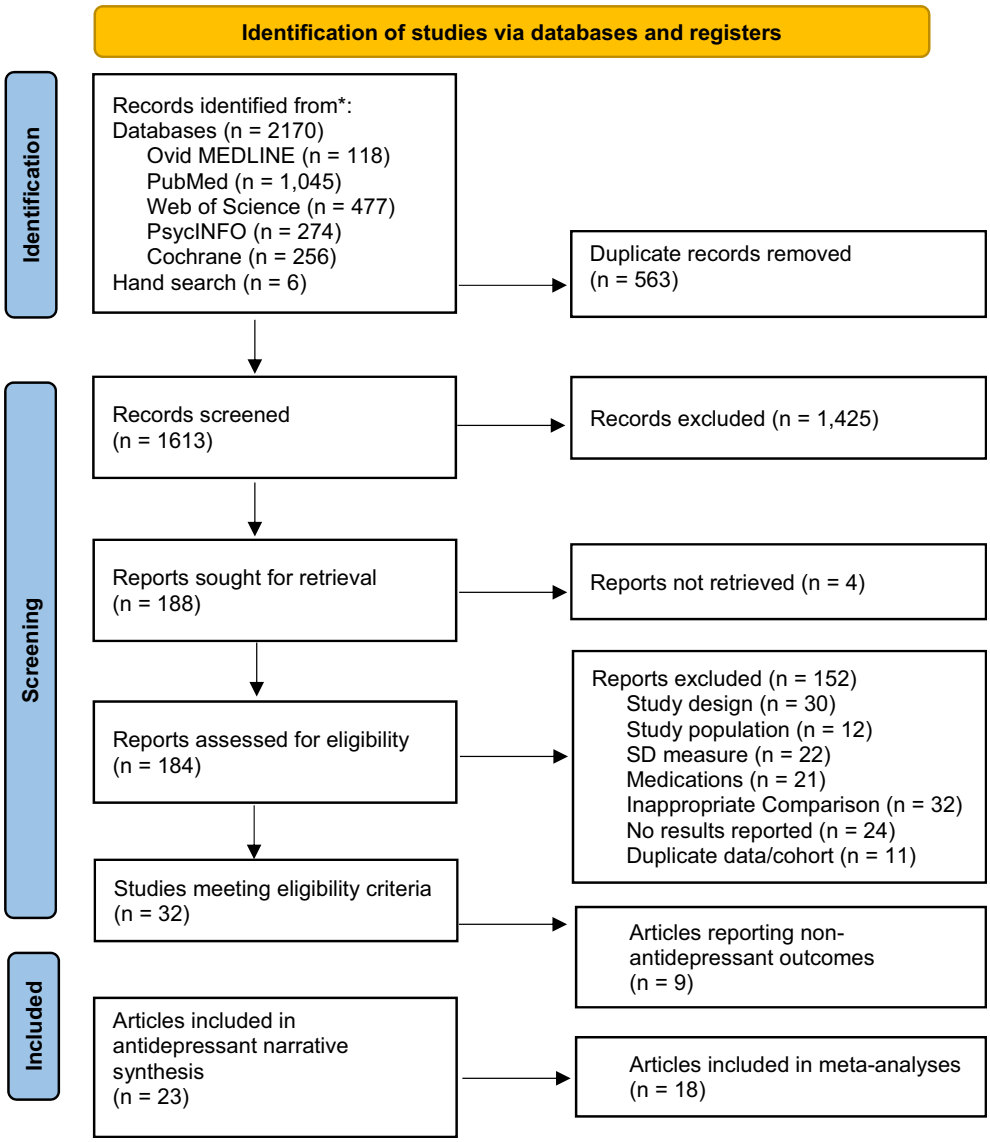
Our database search retrieved 2170 citations. An additional six were found through handsearching reference lists. (Figure 1) After removing duplicates, 1613 articles were screened for eligibility based on title and abstract. The full text of 184 articles were screened, resulting in 32 articles meeting inclusion criteria for the systematic review. A list of papers excluded in the full-text phases and the reason for exclusion are listed in Supplementary Table 4. Nine studies examined medications other than antidepressants; as the number of studies per category is few and results disparate, their synthesis would not be meaningful in the context of this paper. Nevertheless, characteristics of these studies and results are presented in Supplementary Table 5a and 5b.

3.2 | Study characteristics

Of the 23 studies that looked at prenatal antidepressant intake,[26,41–62] 14 measured antidepressant use (ADU),[42–46,48–50,53–55,59,61,62] defined as any prenatal antidepressant use compared to no antidepressant use among women who experienced mental health issues; this includes pregnant women who continued their medication intake throughout pregnancy, women who began antidepressant treatment during pregnancy, and women who started/stopped at various intervals during their pregnancy. Ten measured antidepressant continuation (ADC),[26,41,42,47,51,52,56–58,60] defined as women who were using antidepressants prior to/during pregnancy and continued throughout compared to those who discontinued use during the pregnancy.

The 23 included papers used a wide variety of measures to assess SD. Fourteen studies reported on education,[26,44–47,50,52–54,56–59,62] 11 studies on race,[43,45,48,49,55–57,59–62] and nine studies on relationship status.[26,44,45,48,50,52,54,56,59] Ten papers reported on income/insurance,[41,42,44,47,51–53,56,57,61] three on employment,[48,50,53] and one on immigration.[58] Studies ranged in sample size from 28 to 33,773 and were conducted in a wide range of countries: Australia,[43,49,50] Canada,[46] Denmark,[26,47] France,[41] New Zealand,[55] Norway,[44] South Korea,[51] Spain,[52] Sweden,[58] and Turkey.[53] Most studies were

FIGURE 1 Flow-chart.



conducted in the United States.[42,45,48,54,56,57,59–62] Full descriptions of study characteristics can be found in Table 1. According to JBI evaluations, 17 of the 23 studies were found to be high quality, while the remaining six were rated as low quality. The GRADE evaluations were mostly low (13%) and very low (87%). (Table 1).

3.3 | Narrative review

The main findings regarding the association of SD and antidepressant use are presented in Table 2 and for continuation in Table 3.

3.4 | Education

Eight papers looked at pregnant women's education levels and ADU. The majority of these reported that lower education levels (completion of high school only or less) were associated with lower prenatal ADU rates,[45,50,53,54,59,62] although results were statistically significant for only two papers,[45,59] both from the United States. Two papers found this association in the opposite direction: lower education levels were associated with higher prenatal ADU rates; one was statistically significant[46] and the other was not.[44]

Six papers reported positive associations between lower education levels and lower rates of ADC; four were statistically significant[26,47,57,58] and two were not.[52,56]

3.5 | Race

The seven papers which looked at race and prenatal ADU, were all from the United States, Australia, and New Zealand. Six found an association between non-white race and lower ADU rates compared to women

TABLE 1 Study characteristics.

Author, year	Study type	Country	Cohort	Study n	Use/Continuation	SD category	Quality score	GRADE
Cabaillot et al., 2020	Cohort	France	General Sample of Beneficiaries (EGB) database affiliated with the French Health Insurance System, from 2009 to 2014	760	(Dis)continuation	Insurance	High	Very low
Copeland et al., 2022	Cohort	United States	The Center for Maternal and Infant Outcomes Research in Translation (COMFORT) study	501	(Dis)continuation	Income	High	Very low
Grzeskowiak et al., 2012	Cohort	Australia	Women's and Children's Health Network	1787	Use	Income	High	Very low
Grzeskowiak et al., 2022	Cohort	Norway	Norwegian mother, father, and child cohort study	80,882	Use	Education, relationship, income	High	Very low
Hayes et al., 2012	Cohort	United States	Tennessee Medicaid	23,280	Use	Education, race, relationship	High	Very low
Hutchison et al., 2019	Cohort	Canada	Longitudinal cohort study examining the effects of prenatal exposure to SRIs and maternal mood disturbances in mothers	139	Use	Education	High	Very low
Johansen et al., 2014	Cohort	Denmark	Danish National Patient Register/ Danish National Birth Cohort	1,191,164	(Dis)continuation	Education, income	High	Very low
Kroll-Desrosiers et al., 2020	Cohort	United States	The Center for Maternal and Infant Outcomes Research in Translation (COMFORT) study	142	Use	Race, relationship, employment	Low	Very low
Leggett et al., 2016	Cohort	Australia	Women's and Children's Health Network	32,662	Use	Race	High	Very low
Lewis et al., 2012	Cohort	Australia	Longitudinal Study of Australian Children	1686	Use	Education, relationship, employment	Low	Very low
Liu et al., 2022	Cohort	Denmark	Danish Medical Birth Registry and the Danish National Prescription Registry	21,189	(Dis)continuation	Education, relationship	High	Very low
Noh et al., 2022	Cohort	South Korea	Health Insurance Review and Assessment (HIRA) database of South Korea	5207	(Dis)continuation	Insurance	High	Low
Roca et al., 2013	Cohort	Spain	Perinatal Psychiatry Service of a university general hospital	132	(Dis)continuation	Education, relationship, income	High	Very low

TABLE 1 (Continued)

Author, year	Study type	Country	Cohort	Study n	Use/Continuation	SD category	Quality score	GRADE
Sahingoz et al., 2014	Cross-sectional	Turkey	Three psychiatric outpatient clinics	89	Use	Education, income, employment	Low	Very low
Suri et al., 2007	Cohort	United States	Cohort recruited from community clinics, advertisements, and psychiatric practices in Los Angeles	71	Use	Education, relationship	Low	Very low
Svardal et al., 2022	Cohort	New Zealand	Growing Up in New Zealand	6822	Use	Race	Low	Very low
Toh et al., 2009	Cohort	United States	Slone Epidemiology Center Birth Defects Study (BDS)	192	(Dis)continuation	Education, income, race, relationship	Low	Very low
Wartko et al., 2020	Cohort	United States	Kaiser Permanente Washington	2635	(Dis)continuation	Education, insurance, race	High	Very low
Wikman et al., 2020	Cohort	Sweden	Five national longitudinal population-based health registers in Sweden	38,595	(Dis)continuation	Education, immigration	High	Low
Wisner et al., 2009	Cohort	United States	Recruitment was by self-referral, physician referral, advertising, and screening in obstetrical ultrasound suites in Cleveland and Pittsburgh	238	Use	Education, race, relationship	High	Very low
Wu & Davis-Ajami, 2014	Cohort	United States	South Carolina Medicaid claims data	804	(Dis)continuation	Race	High	Very low
Yamamoto et al., 2014	Cohort	United States	National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Medical Care Survey (NHAMCS)	37.8 million patient visits	Use	Race, insurance	High	Low
Yazdy et al., 2014	Case control	United States	Birth defect registries in Massachusetts, North Carolina, and New York	2683	Use	Education, race	High	Very low

TABLE 2 Associations between prenatal antidepressant use and social determinant indicators.

Author, year	Description of comparison	Comparison *N*	Type of association measure	Result	Direction of result
Educational level					
Grzeskowiak et al., 2022	High school or less vs university or higher	5514	Calculated OR	1.14 (0.99–1.31)	Negative
Hayes et al., 2012	Less than 12 years of education vs more	16,526	Calculated OR	**0.87 (0.82–0.92)**	Positive
Hutchison et al., 2019	Mean years of education in non-exposed vs exposed	139	T-test	**17.90 in non-exposed vs 16.59 in exposed (p = 0.02)**	Negative
Lewis et al., 2012	Non-completion of highschool vs highschool completers	658	Calculated OR	0.94 (0.62–1.41)	Positive
Suri et al., 2007	High school or less vs university or higher	28	Calculated OR	0.47 (0.13–1.76)	Positive
Sahingoz et al., 2014	High school or less vs university or higher	55	Calculated OR	0.59 (0.13–2.65)	Positive
Wisner et al., 2009	High school or less vs university or higher	248	Calculated OR	**0.28 (0.16–0.50)**	Positive
Yazdy et al., 2014	High school or less vs university or higher	1071	Calculated OR	0.86 (0.63–1.17)	Positive
Employment					
Kroll-Desrosiers et al., 2020	Non-fulltime employment vs fulltime employment	77	Calculated OR	1.26 (0.50–3.18)	Negative
Lewis et al., 2013	Non-fulltime employment vs fulltime employment	859	Calculated OR	**0.28 (0.20–0.38)**	Positive
Sahingoz et al., 2015	Non-fulltime employment vs fulltime employment	56	Calculated OR	1.61 (0.37–6.98)	Negative
Income					
Copeland et al., 2022	Low income vs not low income	501	Relative Risk Ratios	0.86 (0.50–1.47)	Positive
Grzeskowiak et al., 2012	Low vs high income	1668	Calculated OR	1.18 (0.89–1.56)	Negative
Grzeskowiak et al., 2023	Low income vs average/high	5181	Calculated OR	1.17 (0.99–1.37)	Negative
Sahingoz et al., 2016	Low income vs moderate/high	43	Calculated OR	1.31 (0.41–4.21)	Negative
Yamamoto et al., 2014	Medicaid vs private insurance	37.8 million patient visits	Reported OR	1.00 (0.50–2.00)	No Association
Race					
Hayes et al., 2013	Non-white vs White	19,862	Calculated OR	**1.20 (1.14–1.27)**	Negative
Kroll-Desrosiers et al., 2021	Non-white vs White	36	Calculated OR	0.75 (0.17–3.39)	Positive
Leggett et al., 2016	Non-white vs White	1537	Calculated OR	**0.66 (0.48–0.92)**	Positive
Svardal et al., 2022	Non-white vs White	7830	Calculated OR	**0.30 (0.22–0.40)**	Positive
Wisner et al., 2010	Non-white vs White	42	Calculated OR	**0.12 (0.04–0.33)**	Positive
Yamamoto et al., 2014	Non-white vs White	37.8 million patient visits	Reported OR	**0.50 (0.30, 0.90)**	Positive
Yazdy et al., 2014	Non-white vs White	317	Calculated OR	**1.85 (1.15–2.96)**	Negative

TABLE 2 (Continued)

Author, year	Description of comparison	Comparison *N*	Type of association measure	Result	Direction of result
Relationship status					
Grzeskowiak et al., 2024	Not married/cohabiting vs Married/cohabiting	5209	Calculated OR	**1.44 (1.14–1.82)**	Negative
Hayes et al., 2014	Not married/cohabiting vs Married/cohabiting	26,619	Calculated OR	**0.90 (0.86–0.94)**	Positive
Kroll-Desrosiers et al., 2022	Not married/cohabiting vs Married/cohabiting	50	Calculated OR	0.64 (0.24–1.73)	Positive
Lewis et al., 2014	Not married/cohabiting vs Married/cohabiting	643	Calculated OR	0.68 (0.45–1.02)	Positive
Suri et al., 2008	Not married/cohabiting vs Married/cohabiting	28	Calculated OR	0.88 (0.20–3.91)	Positive
Wisner et al., 2011	Not married/cohabiting vs Married/cohabiting	50	Calculated OR	**0.31 (0.13–0.74)**	Positive

Note: Bolded results indicate a statistically significant result.
Abbreviation: OR, odds ratio.

labeled as white. Two of these papers were based on the same study population (Women's and Children's Health Network), but one reported on all antidepressants,[49] while the other reported on SSRI-only.[43] The association for all antidepressants was significant; but when looking at SSRI-only the association with race was no longer significant. For the remaining studies, one of the reported associations was not statistically significant,[48] while four were.[49,55,59,61] Two papers from the United States found an inverse relationship, with a statistically significant association between non-white women and increased ADU.[45,62]

All three papers reporting on race and ADC reported that non-white participants had lower rates of antidepressant medication continuation during pregnancy. Two were statistically significant[57,60] and one was not.[56]

3.6 | Relationship status

Six papers looked at relationship status and ADU, five of which found an association between being unmarried/not cohabiting with a partner and lower rates of ADU; two were statistically significant, both from the United States[45,59] and three were not.[48,50,54] One study reported a statistically significant association in the opposite direction: being unmarried/not cohabiting with a partner was associated with increased ADU.[44]

Three papers examined relationship status and ADC during pregnancy, two of which found that being unmarried/not cohabiting was associated with lower rates of ADC, although these associations were not statistically significant.[52,56] One paper reported a statistically significant association that found being unmarried/not cohabiting was associated with higher rates of ADC.[26]

3.7 | Immigration

One paper based on Swedish data looked at immigration and compared three groups of women by countries of origin: Nordic countries, EU countries, and non-EU countries.[58] Both EU and non-EU country of origin showed less continuation of antidepressants during pregnancy compared to Nordic countries of origin, but only the non-EU country association was statistically significant.

3.8 | Income/Insurance

As all papers reporting insurance types indicated that study participants were only eligible for these insurance schemes due to very low income, the insurance and

TABLE 3 Associations between antidepressant continuation and social determinants.

Author, Year	Description of comparison	Result *N*	Type of association measure	Result	Direction of the result
Educational level					
Johansen et al., 2014	Highschool or less vs university or higher	16,190	Calculated OR	**0.87 (0.81–0.93)**	Positive
Liu et al., 2022	Highschool or less vs university or higher	6684	Calculated OR	**0.75 (0.69–0.81)**	Positive
Roca et al., 2013	Highschool or less vs university or higher	111	Calculated OR	0.89 (0.43–1.85)	Positive
Toh et al., 2009	Highschool or less vs university or higher	128	Calculated OR	0.79 (0.42–1.50)	Positive
Wartko et al., 2020	Highschool or less vs university or higher	1495	Calculated OR	**0.82 (0.68–0.98)**	Positive
Wikman et al., 2020	Highschool or less vs university or higher	33,773	Calculated OR	**0.87 (0.83–0.91)**	Positive
Migrant status					
Wikman et al., 2021	EU nationals vs Nordic nationals	30,139	Calculated OR	0.90 (0.77–1.06)	Positive
	Non-EU nationals vs Nordic nationals	30,139	Calculated OR	**0.69 (0.64–0.75)**	Positive
	Non-Nordic nationals vs Nordic nationals	30,139	Calculated OR	**0.72 (0.67–0.78)**	Positive
Income					
Cabaillot et al., 2020	Low-income insurance vs not	608	Calculated OR	0.86 (0.50–1.47)	Positive
Copeland et al., 2022	Low income vs not	501	Relative risk ratios	1.01 (0.48–2.12)	No Association
Johansen et al., 2014	Low income vs high	13,619	Calculated OR	**0.93 (0.88–0.99)**	Positive
Noh et al., 2022	Low-income insurance vs not	829	Calculated OR	**0.25 (0.19–0.31)**	Positive
Roca et al., 2014	Financial problems vs no financial problems	82	Calculated OR	0.49 (0.22–1.10)	Positive
Toh et al., 2010	<$45,000 annual income vs >$45,000	136	Calculated OR	1.39 (0.77–2.50)	Negative
Wartko et al., 2021	Medicaid vs private insurance	1252	Calculated OR	0.81 (0.54–1.20)	Positive
Race					
Toh et al., 2011	Non-white vs White	117	Calculated OR	0.67 (0.30–1.50)	Positive
Wartko et al., 2022	Non-white vs White	887	Calculated OR	**0.51 (0.40–0.63)**	Positive
Wu & Davis-Ajami, 2014	Non-white vs White	804	Proportional hazards models	**1.36 (1.10–1.57)**	Negative
Relationship status					
Liu et al., 2022	Not married/cohabiting vs Married/cohabiting	7044	Calculated OR	**1.22 (1.12–1.33)**	Negative
Roca et al., 2015	Not married/cohabiting vs Married/cohabiting	72	Calculated OR	0.36 (0.07–1.83)	Positive
Toh et al., 2012	Not married/cohabiting vs Married/cohabiting	114	Calculated OR	0.58 (0.23–1.42)	Positive

Note: Bolded results indicate a statistically significant result.
Abbreviation: OR, odds ratio.

income results are presented concurrently. Three papers looked at income and ADU; two found an association between low income and increased ADU[44,53] and one reported the opposite with low income associated with decreased ADU among US veterans.[42] One paper looking at insurance and ADU in the US found no differences between Medicaid users and those with private insurance.[61] None of the results were statistically significant.

Four papers examined income and ADC; two reported associations between low income and decreased ADC,[47,52] and one found an association between low income and increased ADC rates,[56] while the fourth found that income was not associated at all.[42] None of the reported association measures for income were statistically significant. Two papers found low-income medical aid recipients had lower ADC rates compared to high-income, non-medical aid recipients; one was statistically significant[51] and the other was not.[41]

3.9 | Employment

Three papers looked at ADU and women's employment status; two found a negative statistically insignificant association between non-full-time employment and increased ADU based on medical records data in the US[48] and Turkey.[53] These studies had small sample sizes ($n = 77$ and $n = 56$, respectively). One Australian study ($n = 660$) found the inverse: non-full-time employment was statistically significantly associated with less ADU rates.[50]

3.10 | Meta-analysis results

SD which were reported by at least four studies were included in a meta-analysis, which we were able to perform for education, relationship status, race, and income.

3.11 | Social determinants and prenatal antidepressant use

In seven pooled studies, lower *educational levels* were associated with lower prenatal antidepressant use, although this was not significant (odds ratio [OR] = 0.81; 95% CI, 0.65 to 1.03; $p = 0.08$; Figure 2). Heterogeneity across studies was significant ($Tau^2 = 0.05$; $Chi^2 = 28.81$, $df = 6$ ($p < 0.0001$); $I^2 = 79\%$).

Six studies investigating the association between *race* and antidepressant use were included, and non-white women had a non-statistically significant lower chance of using antidepressants, giving a pooled OR of 0.51 (95% CI, 0.25 to 1.03; $p = 0.06$; Figure 2). Heterogeneity across studies was significant ($Tau^2 = 0.64$; $Chi^2 = 128.96$, $df = 5$ ($p < 0.00001$); $I^2 = 96\%$).

Concerning *relationship status*, six studies were eligible for meta-analysis and women not in a relationship had a non-statistically significantly lower chance of using antidepressants, with a pooled OR of 0.84 (95% CI, 0.61 to 1.17; $p = 0.59$; Figure 2), with significant heterogeneity across studies ($Tau^2 = 0.09$; $Chi^2 = 23.24$, $df = 5$ ($p = 0.0003$); $I^2 = 76\%$).

3.12 | Social determinants and prenatal antidepressant continuation

Seven studies investigated the association between *educational level* and antidepressant continuation and were eligible for meta-analysis. This resulted in a statistically significant pooled OR, indicating lower education level is associated with less prenatal antidepressant continuation (odds ratio [OR] = 0.83; 95% CI, 0.78 to 0.89; $p < 0.00001$; Figure 3). Heterogeneity across studies was moderate. (0.00; $Chi^2 = 10.57$, $df = 6$ ($p = 0.10$); $I^2 = 53\%$).

Eight studies investigated the association between *income* and antidepressant continuation, revealing a non-significant association between low-income and lower rates of antidepressant continuation. Meta-analysis gives a pooled OR of 0.75 (95% CI, 0.51 to 1.11; $p = 0.15$; Figure 3). Heterogeneity across studies was significant ($Tau^2 = 0.44$; $Chi^2 = 120.72$, $df = 7$ ($p < 0.00001$); $I^2 = 95\%$).

3.13 | Sub-group analyses

To explore potential sources explaining the overall high heterogeneity of our results, we conducted subgroup analyses of antidepressant classification, type of healthcare system, medication reporting, and quality score. (Table 4) Due to insufficient number of studies per category, four could not be computed. Most of the explored sub-group analyses were not significant, apart from the stratification of the race and ADU result by quality score, with four high quality studies having a pooled OR of 0.66 (95% CI, 0.37 to 1.16; $p = 0.15$; Table 5)/($Tau^2 = 0.27$; $Chi^2 = 32.13$, $df = 3$ ($p < 0.00001$); $I^2 = 91\%$) and two low quality studies having a pooled OR of 0. 27 (95% CI, 0.19 to 0.39; $p < 0.00001$; Table 5)/($Tau^2 = 0.01$; $Chi^2 = 1.05$, $df = 1$ ($p = 0.31$); $I^2 = 4\%$), which may indicate that results were partly driven by low quality studies.

Publication bias and small study bias was explored via funnel plots which showed that our study outcomes were not notably impacted by the relatively small number of studies that could be included in the meta-analysis. (Figure 4.)

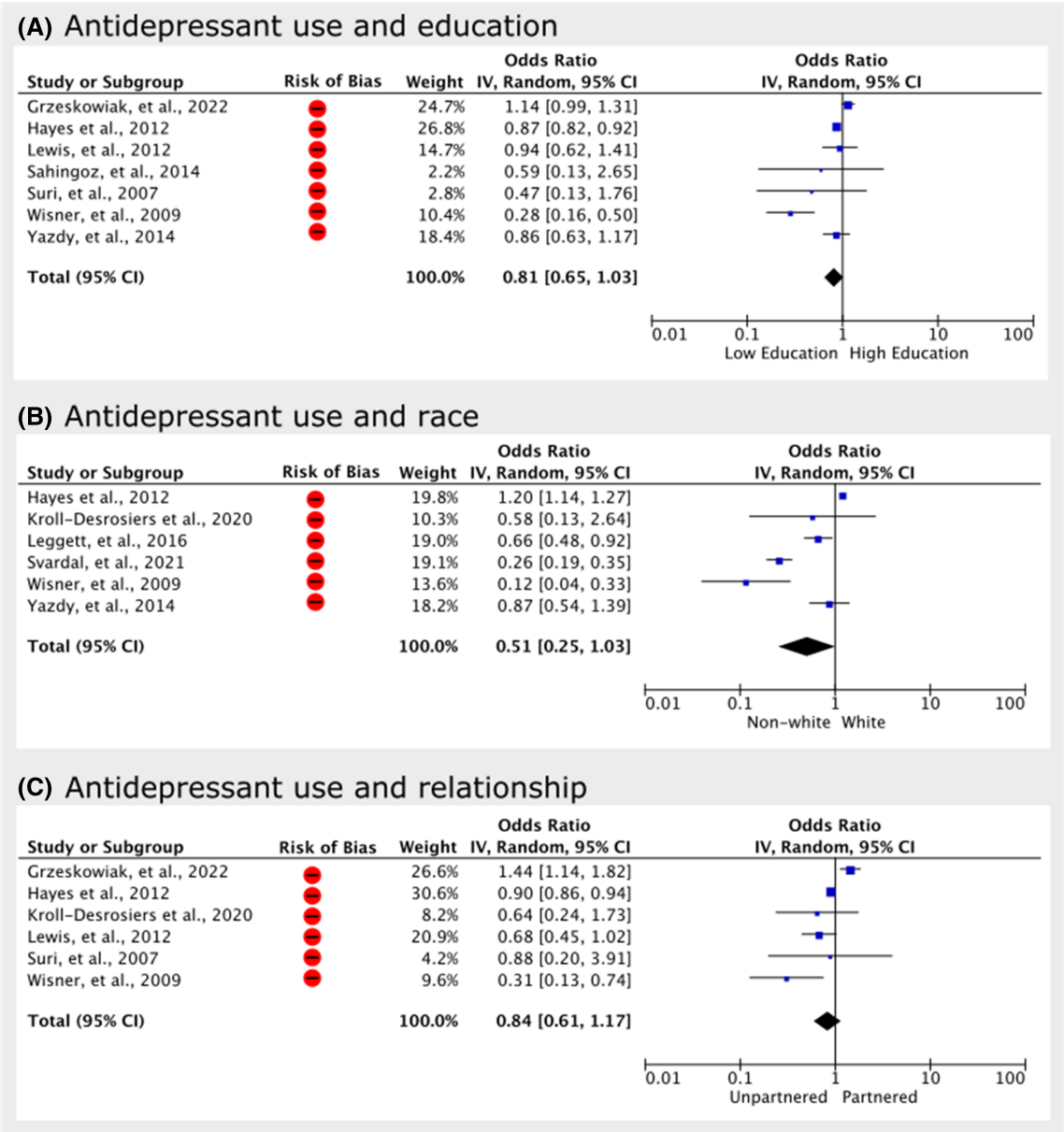


FIGURE 2 Meta-analyses antidepressant use.

4 | DISCUSSION

4.1 | Main findings

To our knowledge, this is the first systematic review and meta-analysis to explore whether social determinants are associated with prenatal intake of antidepressant medications in a cross-cultural context. Outcomes of the narrative review and meta-analysis indicate that none of the explored SD indicators (education, race, relationship status, income, employment, composite socioeconomic scores) are consistently associated with either higher or lower rates of prenatal antidepressant use (ADU). Similarly, our results show that relationship status and income are not consistently associated with either higher or lower rates of prenatal antidepressant continuation (ADC), while for race this association remained inconclusive. However, some indications for social disparities according to educational level and migration status were shown in the narrative review. Of these, the association between low education level and lower rates of prenatal antidepressant continuation was statistically significant with moderate heterogeneity in the meta-analysis. During pregnancy, women who have high school or lower levels of education discontinue their antidepressant medication more frequently compared to those with more years of education.

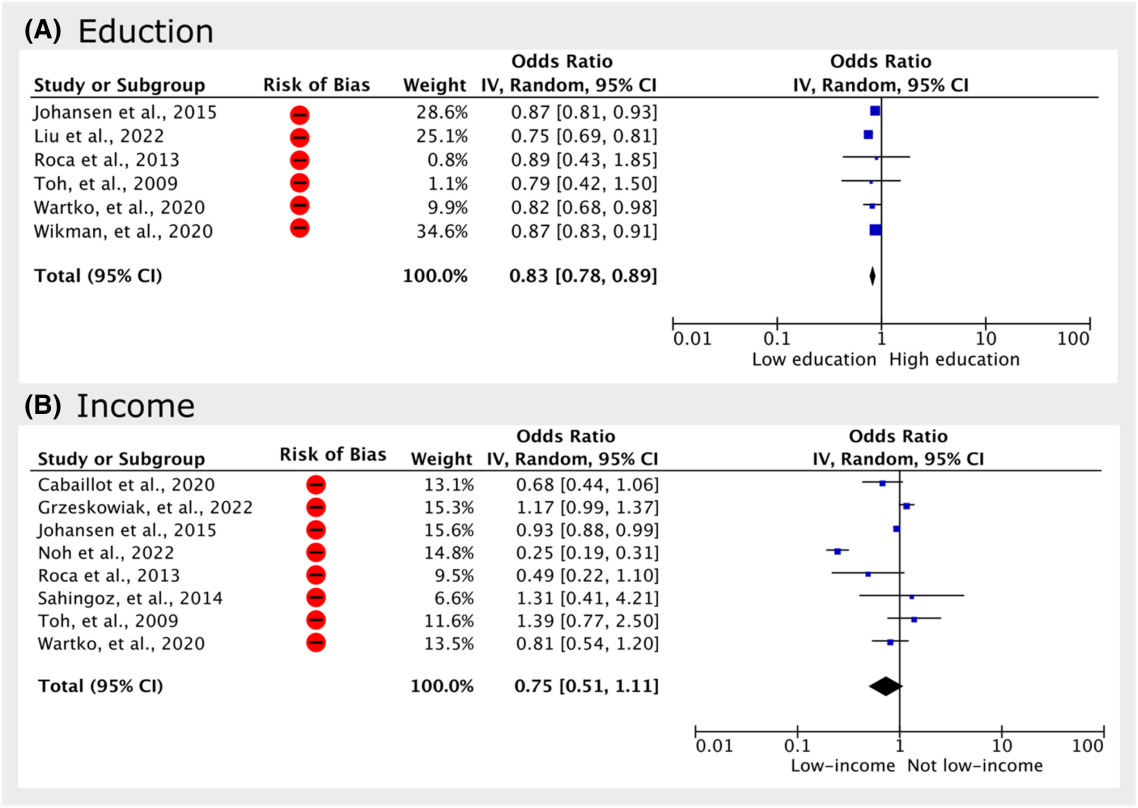


FIGURE 3 Meta analyses antidepressant continuation.

4.2 | Social determinants and antidepressant intake

Among the different SD explored, higher educational levels appear to have the strongest association with higher prenatal antidepressant intake rates, in particular ADC. One potential explanation for this relationship is that individuals with higher education might be more comfortable asking their provider questions, engaging with safety data, and have more confidence in their own research on the subject. Education is also linked with healthcare access and quality of provided information, which remains an important barrier for disadvantaged women receiving adequate treatment. Yet, even for women that can access mental health care services, there might be gaps in information quality. An Australian study found that only 55% of study participants were satisfied that they had all their questions answered by their medical provider before they decided about their prenatal antidepressant use[63] and a lack of information is cited by pregnant women as a feature of accessing care for mental health problems.[64] This is especially important as not only health care practitioners, but also community members, and both traditional and social media are the most influential sources of information about antidepressant medication use during pregnancy.[65] As social media can be unreliable and overestimates risk of antidepressants,[66] clear information from medical providers is key. However, in qualitative studies, clinicians report a lack of knowledge and skill in managing perinatal depression.[67,68] In a review of patient and healthcare provider perspectives on this topic, healthcare providers overestimate the risks of psychoactive medications, with many reporting that they need increased education about the use of antidepressants in pregnancy.[65] Further, in terms of treatment decision-making, the majority of healthcare providers report being influenced by patient preference, who also tend to overestimate the risks of psychoactive medications.[65] Thus it could be that associations between educational level and decreased antidepressant intake can be explained by an overestimation of risks by some population groups, especially in contexts which rely on patient-led decision-making, although this has not been explored in the literature yet.

Our narrative analysis and meta-analyses looking at race and ADU found an association between non-white race and lower rates of ADU that approached significance. All three of the studies not included in the meta-analysis[56,57,60] reported results with the same direction, with two of them being statistically significant.[57,60] These studies originated exclusively in the United States, Australia, and New Zealand, so results are likely not

TABLE 4 Sub-group analyses for antidepressant use meta-analyses.

	Subgroup category	*N*	Odds ratios	I^2	*p*-value
Education					
Overall		***7***	***0.81 (0.65–1.03)***	***79%***	**0.08**
Medication category	All antidepressants	4	0.96 (0.77–1.19)	76%	0.19
	SSRI-only	3	0.53 (0.22–1.26)	82%	
Healthcare system	Comprehensive	4	0.97 (0.78–1.19)	75%	0.15
	Free market	3	0.50 (0.21–1.19	83%	
Medication data source	Self-report	5	0.74 (0.48–1.12)	84%	0.45
	Medical records	2	0.87 (0.81–0.92)	0%	
Quality score	High quality	4	0.81 (0.61–1.06)	89%	0.79
	Low quality	3	0.86 (0.59–1.26)	0%	
Race					
Overall		***6***	**0.51 (0.25–1.03)**	***96%***	**0.06**
Medication category	All antidepressants	4	0.59 (0.25–1.43)	97%	0.67
	SSRI-only	2	0.73 (0.55–0.95)	0%	
Healthcare system	Comprehensive	4	0.59 (0.25–1.43)	97%	0.61
	Free market	2	0.34 (0.05–2.43)	91%	
Medication reporting	Self-report	4	0.32 (0.12–0.88)	91%	0.09
	Medical records	2	0.51 (0.25–1.03)	85%	
Quality score	High quality	4	0.66 (0.37–1.16)	91%	0.01*
	Low quality	2	0.27 (0.19–0.39)	4%	
Relationship					
Overall		***6***	***0.84 (0.61–1.17)***	***78%***	***0.59***
Medication category	All antidepressants	5	n/a		
	SSRI-only	1	n/a		
Healthcare system	Comprehensive	4	0.95 (0.68–1.32)	84%	0.14
	Free market	2	0.44 (0.16–1.16)	30%	
Medication data source	Self-report	4	0.76 (0.38–1.50)	84%	0.62
	Medical records	2	0.90 (0.86–0.94)	0%	
Quality score	High quality	3	0.68 (0.47–0.98)	0%	0.36
	Low quality	3	0.90 (0.56–1.44)	90%	

*p significant at 0.01.

generalizable outside of these regions. Nonetheless, there is some indication that it might be possible that racialized individuals in these countries have different experiences in terms of antidepressant intake decision-making. Our concatenation of all non-white races aimed to clarify that the social constructs and meanings assigned to race are what we aim to measure, rather than imply any potential genetic or biological causation.[69]

The literature indicates that non-white women are less likely to initiate prenatal antidepressant medication compared to white women.[70] Similarly, racial/ethnic minorities and foreign-born mothers are less likely to consult doctors or think they needed consultation for their emotional problems compared to white mothers.[68,69,71] Because similar trends exist outside of pregnancy, both prior and into motherhood, it is possible that there are additional factors outside of fearing harm to the fetus in the studies included in this paper, although that has not been directly evaluated. As cultural incompetencies and language barriers are often cited as issues by clinicians and patients alike, these structural inequalities might further impact non-white women's ability to access mental healthcare.[67,68,72]

The three studies examining employment and ADU had disparate results, possibly because it is not a robust SD indicator for pregnant women due to gender-based discrimination and that many women of childbearing age

TABLE 5 Sub-group analyses for antidepressant continuation meta-analyses.

	Subgroup category	*N*	Odds ratios	I^2	*p*-value
Education					
Overall		***6***	***0.83 (0.78–0.89)***	***53%***	***<0.0001***
Medication category	All antidepressants	3	0.81 (0.71–0.93)	79%	0.41
	SSRI-only	3	0.86 (0.81–0.92)	0%	
Healthcare system	Comprehensive	5	n/a		
	Free market	1	n/a		
Medication data source	Self-report	2	0.84 (0.52–1.35)	0%	0.98
	Medical records	4	0.83 (0.77–0.90)	71%	
Quality score	High quality	5	n/a		
	Low quality	1	n/a		
Income					
Overall		***7***	**0.75 (0.51–1.11)**	***95%***	*0.15*
Medication category	All antidepressants	3	0.60 (0.22–1.66)	95%	0.42
	SSRI-only	4	0.91 (0.80–1.03)	7%	
Healthcare system	Comprehensive	6	n/a		
	Free market	1	n/a		
Medication data source	Self-report	2	0.86 (0.31, 2.36)	76%	0.68
	Medical records	5	0.66 (0.34–1.29)	96%	
Quality score	High quality	5	0.58 (0.30–1.11)	96%	0.04*
	Low quality	2	1.37 (0.81–2.32)	95%	

**p* significant at 0.05.

are often out of the work force for various reasons and time periods.[73] Two social determinants of health were associated with lower antidepressant intake rates: unmarried/not cohabiting with a partner and low-income/insurance, but as none of the results were statistically significant, cautious interpretation is needed. A single study indicated that immigration status appears to be associated with ADU, with mothers from non-EU countries being less likely to continue antidepressants compared to other groups. It is possible that this question might be too culturally specific and context-dependent to fully explore in a meta-analysis or with global data. Key variables must first be fully evaluated to determine if they mediate SD, namely disease severity, fears of risk to the fetus, and more robust social support measures.

Although our sub-group analyses did not demonstrate this, we hypothesized that links to antidepressant intake would be stronger in settings with free market healthcare systems[74] because co-payments of any size can reduce access to medications[75,76] and employment-dependent insurance systems rely on individual employment in order to access healthcare coverage.

None of the sub-group analyses we conducted were significant, apart from the quality score stratification of the ADU and race estimate. As each meta-analysis had few studies included to begin with, it is most likely that the numbers per subcategory were insufficient to compute meaningful group differences. Aside from these factors, it is likely that others are contributing to the relationship between SD and prenatal antidepressant intake. Disease severity is one option, as it begins to impact these trends via initial healthcare access. In one register study, low-income pregnant women were less likely to see a psychiatrist despite having indicators of more severe disease.[73] A general population meta-analysis found no association with educational status, income level, marital status and antidepressant adherence, but did find an association with polypharmacy (three or more psychotropic medications), indicating that disease severity might be a predicting factor.[77] Previously it has been reported that low-income women are more likely to fill three or more psychotropic medications during pregnancy[22] and more likely to end up admitted to a hospital for mental illness.[73] In one study, women with moderate/severe depression symptoms were seven-fold times more likely to prefer antidepressant use over no medical intervention, even after taking race/ethnicity, age, education, and relationship status into account.[78] This pattern also seems to apply to antidepressant continuation, with pregnant women more likely to continue antidepressants if they had a depression inpatient

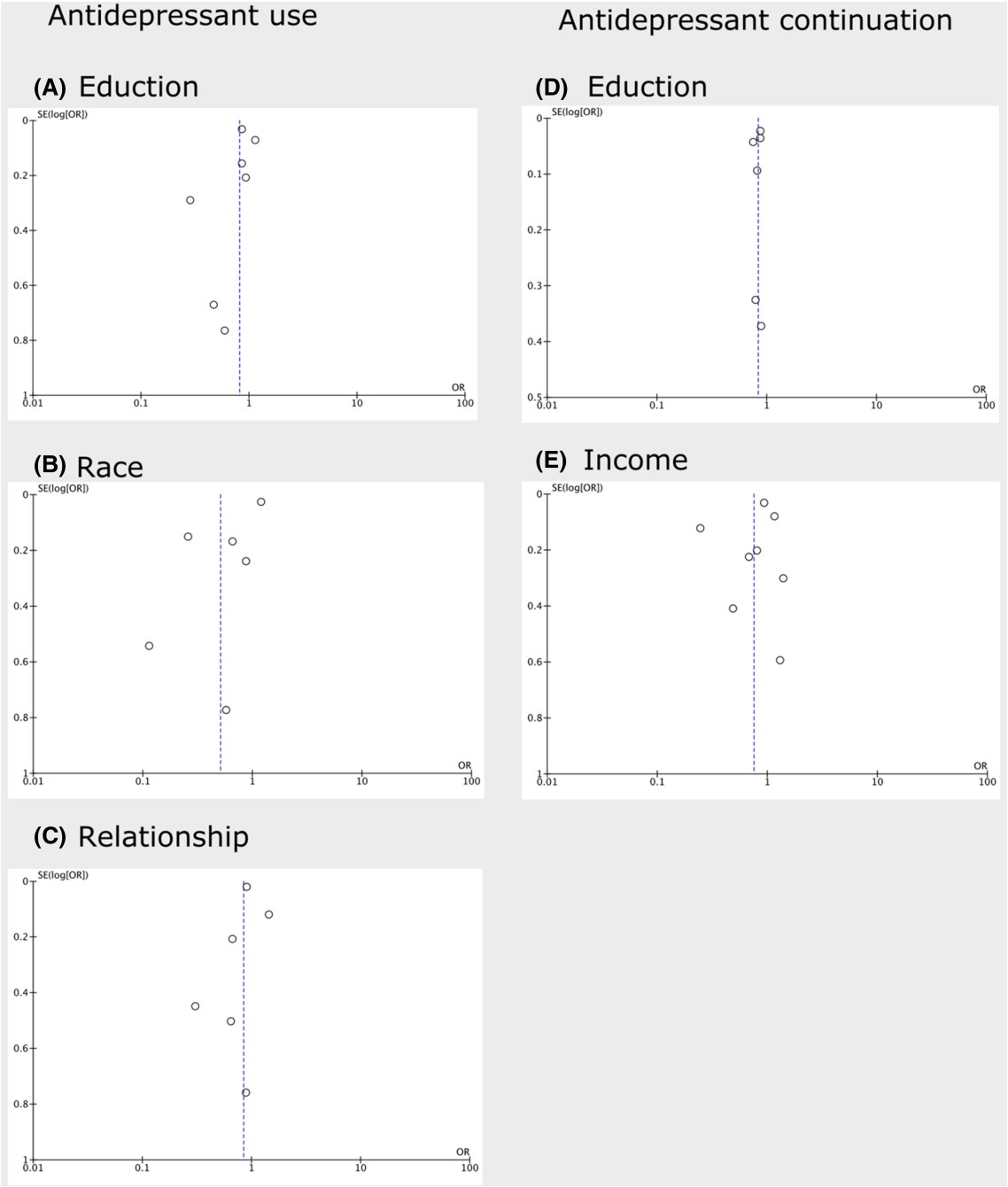


FIGURE 4 Funnel Plots of antidepressant intake and social determinants meta-analyses.

stay in their medical records.[77] Disease severity, education and health literacy together might interact with each other, and further impact interactions pregnant women might have with healthcare providers.

Measuring social capital, or the capacity to obtain resources or information from personal connections, might also be necessary to explore underlying mechanisms, as this positively impacts the health of individuals with low SES.[79] There is a very real possibility that patient empowerment might be an underlying factor. In one study of non-pregnant populations, patients who both disagreed with their diagnosis and felt uninvolved in treatment decisions were 7-fold as likely to discontinue their SSRI, after controlling for SES.[80] Qualitative studies emphasize the importance of non-judgmental support and patient involvement in treatment decisions.[64]

4.3 | Strengths and limitations

This is the first study to make a comprehensive review of SD and antidepressant intake during pregnancy and pool

measures in a meta-analysis, utilizing a rigorous approach to both screening and data extraction and incorporating assessments of study quality, risk of bias and certainty of evidence. We were able to look at both use and continuation and explored possible sources of heterogeneity via sub-group analyses looking at medication classification, healthcare system, antidepressant data collection methods, and the quality scores of the included studies. Despite these strengths, this review has several limitations, the first being a limited quantity of papers published on this subject, preventing meta-analyses from being conducted on several SD. For most of the included papers, the primary research question did not specifically focus on SD and prenatal psychotropic medication intake, and the data extracted for this review were often presented as descriptive variables. To be able to make comparisons across studies, several variables were dichotomized. A drawback to this approach is that it might over simplify complex relations and limits conclusions that can be drawn, specifically the non-white group in our race indicator. Secondly, the heterogeneity of most of the meta-analyses limit our ability to interpret these results with certainty. While we attempted to explore various sources of heterogeneity via sub-group analyses, these sometimes had few observations per category and yielded non-significant subgroup differences. Disease severity was not examined in any of the included studies, so we were unable to account for this key variable, particularly as groups with different SD indicators might have differing levels of disease severity. Additionally, factors such as cultural attitudes toward antidepressant use or country specific practices were sources of heterogeneity that we were unable to explore via subgroup analysis, although this might be expected with global data. Finally, we were unable to address medication uptake during pregnancy and were only able to focus on antidepressants as there were too few papers reporting other medication patterns or types.

4.4 | Implications for future research

SD and other variables are often unavailable for analysis, leaving a gap in our understanding of potential trends among specific population groups of pregnant patients.[81] As various SD cannot be used interchangeably, they should be chosen on explicit conceptual grounds[82] and multiple indicators should be selected as relying on one risks measurement error and residual confounding.[69] These should be collected in addition to other factors that might be also related to psychotropic intake, such as health literacy, social support, social capital, disease severity, concerns about medication risks, patient empowerment in decision-making, or access to both antidepressant and psychotherapy treatment options. Further, if the aim of a study is to explore *social determinants of* health inequities in-depth, descriptive results will not be adequate nor appropriate.[69] Sophisticated statistical methods, that can explore the relationships of multiple SD and other factors synergistically, such as structural equational modeling or network analyses, will prove necessary, as it is most likely that these factors have complicated interrelationships.[20]

4.5 | Implications for clinical practice

As both antidepressants and cognitive behavioral therapy have been found to be efficacious in pregnant populations,[83] every effort should be made to ensure pregnant women have both options available to them, alongside other interventions, both clinically and structurally. Decision-making around prenatal psychotropic medication use is often difficult and would benefit from support, especially to ensure that the impact of low health literacy is minimized as much as possible. Ideally, preconception consultations with specialized perinatal psychiatry teams might be useful to reduce barriers to high-quality care as we know that women prioritize tailored, perinatal-specific care and professional empathy.[71] Patient decision aids have been developed specifically for prenatal antidepressant use[84] and initial evaluations have shown that these tools can potentially be helpful in navigating these conversations with providers.[85] Clinicians must prioritize these conversations and this must be supported by the education of clinicians and the training of perinatal mental health specialists, improved referral systems, and specialized treatment centers.[86,87] To conclude, while most SD in this review were not linked with prenatal antidepressant intake, lower maternal education level does seem to be associated with lower rates of antidepressant continuation during pregnancy. Continued investigation into SD remains a research venue to disentangle the complex web of how SD and other decision-making factors interrelate during this pivotal time for both expectant mothers and their offspring.

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13647.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Ketevan Marr https://orcid.org/0000-0001-7755-7382

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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