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Associations Between Maternal Depression, Antidepressant Use During Pregnancy, and Adverse Pregnancy Outcomes: An Individual Participant Data Meta-analysis

Richelle Vlenterie, PhD,[a] Marleen M.H.J. van Gelder, PhD,[a,b] H. Ross Anderson, MD,[c] Liselott Andersson, PhD,[d] Birit F.P. Broekman, PhD,[e] Gal Dubnov-Raz, PhD,[f] Hanan El Marroun, PhD,[g,h] Ema Ferreira, MSc,[i] Emma Fransson, PhD,[j,k] Frank M.M.A. van der Heijden, PhD,[l] Claudia B. Holzman, PhD,[m] J. Jo Kim, PhD,[n] Ali S. Khashan, PhD,[o] Betty R. Kirkwood, PhD,[p] Harold J.H. Kuijpers, MD,[q] Marius Lahti-Pulkkinen, PhD,[r] Dan Mason, PhD,[s] Dawn Misra, PhD,[t] Maria Niemi, PhD,[u] Hedvig M.E. Nordeng, PhD,[v] Janet L. Peacock, PhD,[w] Kate E. Pickett, PhD,[x] Stephanie L. Prady, PhD,[x] Shahirose S. Premji, PhD,[y] Katri Räikkönen, PhD,[r] Christine Rubertsson, PhD,[k] Mine Sahingoz, MD,[z] Kiran Shaikh, PhD,[aa] Richard K. Silver, MD,[n] Jaime Slaughter-Acey, PhD,[ab] Seyi Soremekun, PhD,[p] Dan J Stein, PhD,[ac] Inger Sundström-Poromaa, PhD,[k] Anne-Laure Sutter-Dallay, PhD,[ad] Henning Tiemeier, PhD,[g,ae] Faruk Uguz, MD,[z] Pinelopi Varela, MSc,[af] Tanja G.M. Vrijkotte, PhD,[ag] Ursula Winterfeld, PhD,[ah] Heather J. Zar, PhD,[ac] Iannis M. Zervas, PhD,[af] Judith B. Prins, PhD,[ai] Monica Pop-Purceleanu, PhD,[aj] and Nel Roeleveld, PhD[a]

[a] Department for Health Evidence, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, The Netherlands
[b] Radboud REshape Innovation Center, Radboud university medical center, Nijmegen, The Netherlands
[c] Environmental Research Group, King's College, London, United Kingdom
[d] Department of Clinical Science, Obstetrics and Gynecology, Umeå University, Umeå, Sweden
[e] Singapore Institute for Clinical Sciences, Singapore
[f] Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel
[g] Department of Child and Adolescent Psychiatry, Erasmus University Rotterdam, Rotterdam, The Netherlands
[h] Department of Psychology, Education and Child Studies, Erasmus School of Social and Behavioral Sciences, Erasmus University Rotterdam, Rotterdam, The Netherlands; Department of Pediatrics, Erasmus, University Rotterda, Rotterdam, The Netherlands
[i] Departments of Pharmacy (Centre IMAGe), Centre Hospitalier Universitaire Sainte-Justine and Faculté de Pharmacie, Université de Montréal, Montreal, Canada

[j] Division of Reproductive and Perinatal Health, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
[k] Department of Health Science, Medical Faculty, Lund university, Lund, Sweden
[l] Vincent van Gogh Institute for Psychiatry, Venlo, The Netherlands
[m] Michigan State University, Department of Epidemiology and Biostatistics, East Lansing, MI, USA
[n] Department of Obstetrics & Gynecology, NorthShore University HealthSystem, Chicago; University of Chicago Pritzker School of Medicine, Chicago, IL, USA
[o] School of Public Health, University College Cork; Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Cork, Ireland
[p] London School of Hygiene and Tropical Medicine, London, United Kingdom
[q] Elisabeth TweeSteden Hospital (ETZ), Tilburg, The Netherlands
[r] Department of Psychology and Logopedics, University of Helsinki, Helsinki, Finland
[s] Bradford Teaching Hospitals NHS Foundation Trust, Bradford, United Kingdom
[t] Wayne State University, Detroit, MI, USA
[u]Karolinska Institutet, Department of Public Health Science, Stockholm, Sweden
[v] PharmacoEpidemiology & Drug Safety Research Group, School of Pharmacy, University of Oslo, ; Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway
[w] Department of Epidemiology, Geisel School of Medicine at Dartmouth, Hanover, NH, US
[x] University of York, York, United Kingdom
[y] York University, Faculty of Health, School of Nursing, Toronto, Canada
[z] Department of Psychiatry, University of Necmettin Erbakan, Meram Faculty of Medicine, Konya, Turkey
[aa] Aga Khan University, School of Nursing and Midwifery, Karachi, Pakistan
[ab] Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, MN, USA
[ac] Department of Psychiatry and Mental Health, University of Cape Town; South African Medical Research Council, Unit on Risk and Resilience in Mental Disorders, Cape Town, South Africa
[ad] Charles Perrens Hospital, Bordeaux; Bordeaux Population Health Center, INSERM 1219, Bordeaux University, Bordeaux, France
[ae] Department of Social and Behavioral Sciences, Harvard TH Chan School of Public Health, Boston, MA, USA
[af] "Alexandra" General Hospital of Athens, Greece
[ag] Department of Public and Occupational Health, Amsterdam Public Health Research Institute, Academic Medical Center - University of Amsterdam, Amsterdam, The Netherlands
[ah] STIS and Clinical Pharmacology Service, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[ai] Department of Medical Psychology, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, The Netherlands
[aj] Department of Psychiatry, Radboud university medical center, Nijmegen, The Netherlands

Corresponding author: Dr. Marleen van Gelder, Department for Health Evidence (HP 133), Radboud university medical center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Telephone: +31-24-3666126. E-mail: Marleen.vanGelder@radboudumc.nl.

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PRÉCIS:

Depressive symptoms or a clinical diagnosis of depression during pregnancy are associated with preterm birth and low Apgar scores, even without exposure to antidepressants.

ABSTRACT

Objective: To evaluate the associations of depressive symptoms and antidepressant use during pregnancy with the risks of preterm birth, low birth weight, small-for-gestational age (SGA), and low Apgar scores.

Data Sources: MEDLINE, EMBASE, ClinicalTrials.gov, and PsycINFO up to June 2016.

Methods of Study Selection: Data were sought from studies examining associations of depression, depressive symptoms, or use of antidepressants during pregnancy with gestational age, birth weight, SGA, or Apgar scores. Authors shared the raw data of their studies for incorporation into this individual participant data meta-analysis.

Tabulation, Integration, and Results: We performed one-stage random-effects meta-analyses to estimate odds ratios (ORs) with 95% confidence intervals (CI). The 215 eligible articles resulted in 402,375 women derived from 27 study databases. Increased risks were observed for preterm birth among women with a clinical diagnosis of depression during pregnancy irrespective of antidepressant use (OR 1.6, 95% CI 1.2-2.1) and among women with depression who did not use antidepressants (2.2, 1.7-3.0), as well as for low Apgar scores in the former (1.5, 1.3-1.7), but not the latter group. Selective serotonin-reuptake inhibitor use was associated with preterm birth among women who used antidepressants with or without restriction to women with depressive symptoms or a diagnosis of depression (1.6, 1.0-2.5 and 1.9, 1.2-2.8, respectively), as well as with low Apgar scores among women in the latter group (1.7, 1.1-2.8).

Conclusion: Depressive symptoms or a clinical diagnosis of depression during pregnancy are associated with preterm birth and low Apgar scores, even without exposure to antidepressants. However, selective serotonin-reuptake inhibitors may be independently associated with preterm birth and low Apgar scores.

Systematic review registration: PROSPERO, CRD42016035711.

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INTRODUCTION

Depression is a prevalent medical conditions during pregnancy with average prevalence rates around 10%.[1,2] As it has been associated with decreased quality of life,[3] postpartum depression,[4] and adverse pregnancy outcomes,[5-7] pharmacological treatment might be recommended.[8] Consequently, antidepressant use among pregnant women increased substantially with prevalence estimates of 1-8%.[9-12] This increase led to concerns about safety of antidepressant use for pregnant women and unborn children, as some systematic reviews and meta-analyses showed associations with adverse pregnancy outcomes, including preterm birth, low birth weight, and low Apgar scores.[13-15] Most results remain inconclusive,[16-22] however, as methodological shortcomings, including retrospective designs, small sample sizes, poor exposure assessment, and lack of adjustment for the underlying disorder, may hamper interpretation. Meta-analyses of individual participant data (IPD) can overcome some of these shortcomings and have been recognized as gold standard approach.[23,24] The main advantage is that individual participant data enable standardisation of analyses across studies independent of presentation of the data in the original publications. Thus, IPD meta-analyses are potentially more reliable than aggregate data meta-analyses, and the two approaches may lead to different conclusions.[24]

The aim of this IPD meta-analysis is to provide insight into the independent effects of non-pharmacologically managed depression and antidepressant use during pregnancy on the risks of preterm birth, low birth weight, small-for-gestational age (SGA), and low Apgar scores. It was performed according to a protocol designed a priori and registered prospectively with the PROSPERO International Prospective Register of Systematic Reviews number CRD42016035711 following the PRISMA guidelines for protocols (PRISMA-P).[25] Reporting follows all aspects recommended in the PRISMA-IPD guidelines.[26]

SOURCES

Studies were identified through a systematic literature search of MEDLINE, EMBASE, ClinicalTrials.gov, and PsycINFO from database inception until June 4, 2016, and systematic reviews were hand-searched for additional articles.[5-7,13-22] The complete search strategy is provided in Appendix 1, available online at http://links.lww.com/xxx.

STUDY SELECTION

Two authors (RV and MvG) independently screened titles and abstracts obtained from the literature search (Figure 1). No language or publication year restrictions were applied. Studies were included if they examined associations of depression, depressive symptoms, or use of antidepressants during pregnancy with gestational age, birth weight, SGA, or Apgar scores. The full texts of all potentially eligible studies were examined independently by the same authors. Articles not written in English were translated online. Discrepancies were resolved by discussion with a third reviewer (NR).

The corresponding authors or principal investigators of all eligible studies were invited to share their raw data according to the study protocol. When published studies used the same database, only the most recent study was included to prevent duplicate data. All databases obtained were checked for inconsistencies, formatted and recoded into the same data format, and entered into one common database.

We requested continuous exposure data on depressive symptoms collected via self-completed questionnaires, including the Center for Epidemiological Studies Depression Scale,[27] Edinburgh Postpartum Depression Scale also called Edinburgh Depression Scale,[28] General Health Questionnaire,[29] Patient Health Questionnaire-9,[30] Primary Care Evaluation of Mental Disorders Patient Questionnaire,[31] Brief Symptom Inventory,[32] and Hopkins Symptoms Check list.[33] Standardized instrument-specific cut-off values were used to dichotomize these data for presence or absence of depressive symptoms. Although not synonymous with a diagnosis of depression, these

questionnaires were validated worldwide to signal a state with relevant clinical symptoms. Data on clinical diagnoses of depression and antidepressant use were delivered dichotomously. The exposure time windows were divided into trimesters of pregnancy and the types of antidepressants into: selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and mirtazapine.

Preterm birth was defined as delivery before 37 weeks of gestation, low birth weight as <2500 grams, and low Apgar score as <7 at 5 minutes. SGA was dichotomized conform the national standards of the country of origin for sex and gestational age. Data on multiple potential confounders were obtained, including race/ethnicity retaining the classifications used in the original studies (Table 1). Multiple pregnancies were excluded as these are known to have increased risks of the selected pregnancy outcomes.

The study population was divided into four partly overlapping cohorts: 1) depression cohort – all women with information on the presence of depressive symptoms or a clinical diagnosis of depression; 2) restricted depression cohort – depression cohort, excluding women who used antidepressants during pregnancy and those for whom no information was available about antidepressant use; 3) antidepressant use cohort – all women with information on antidepressant use; and 4) restricted antidepressant use cohort – antidepressant use cohort, excluding women without depressive symptoms or a clinical diagnosis of depression (Figure 2). Descriptive statistics were performed for maternal characteristics and absolute risks were calculated for the three exposures of interest separately for all four adverse pregnancy outcomes.

One-stage random-effects logistic regression analyses were performed for the depression and antidepressant use cohorts to estimate odds ratios with 95% confidence intervals. Clustering of participants within studies was preserved and presence of clinical and statistical heterogeneity among studies was taken into account. Adjusted odds ratios were estimated from multivariable

models initially including all relevant potential confounders for which data were available from most studies, using manual backward elimination to retain only confounders that changed the effect estimate >10% upon removal. The same method of analysis was used to study the secondary outcomes: effects of timing of exposure and individual antidepressants with >40 exposures. As these data were not available for all women, the secondary analyses were based on smaller numbers. To account for confounding-by-indication, similar analyses were performed in the depression cohort restricted to women without use of antidepressants and in the antidepressant use cohort restricted to women with depressive symptoms or a clinical diagnosis of depression. As we used complete case analyses, the number of women included in each meta-analysis differed due to variation in data availability. All statistical analyses were performed using Stata Version 13 (Stata Corporation, College Station, TX, USA).

RESULTS

The 215 eligible studies led to a total study population of 402,375 women with singleton pregnancies derived from 27 different databases (Figure 1).[34-60] In Appendices 2 and 3, available online at http://links.lww.com/xxx, cohort-specific data of the studies included are provided. The median population size was 872 pregnant women per database, with large variety in study size and country.

Of the 375,269 pregnant women with data available on mental health in the depression cohort, 28,395 (7.6%) women had depressive symptoms or a clinical diagnosis of depression. Of the 118,097 women with data available on antidepressant use, 2,624 (2.2%) women reported antidepressant use during pregnancy. Among the restricted depression cohort of pregnant women not using antidepressants (N = 99,459), 10,817 (10.9%) women had depressive symptoms or a clinical diagnosis of depression, while 2,624 out of 13,441 (19.5%) women reported antidepressant use in the cohort restricted to women with depressive symptoms or a clinically diagnosed depression (Table

1).

Among women without depressive symptoms or a clinical diagnosis of depression, the risks were 9.4% for preterm birth, 6.9% for low birth weight, 6.2% for SGA, and 1.6% for low 5 minute Apgar score, based on the largest numbers of participants from 26, 25, 11, and 22 studies, respectively. Higher absolute risks for preterm birth (10.4%), low birth weight (8.2%), SGA (7.8%), and low 5 minute Apgar scores (2.3%) were observed among women with depressive symptoms or a clinically diagnosed depression in the depression cohort. These risks varied among the four cohorts and different subgroups studied (Tables 2 and 3).

Having depressive symptoms during pregnancy (adjusted odds ratio 1.2, 95% confidence interval 1.1-1.4) or a clinical diagnosis of depression (1.6, 1.2-2.1) were both associated with preterm birth in the depression cohort (Table 2). When restricting the analyses to women without antidepressant use, the adjusted odds ratio for a clinical diagnosis of depression increased to 2.2 (1.7-3.0). A similar odds ratio was observed for low birth weight in the restricted cohort, but with a much wider confidence interval (1.9, 0.8-4.7). No substantially increased odds ratios were seen for SGA, whereas having a clinically diagnosed depression was associated with a low 5 minute Apgar score (1.5, 1.3-1.7). However, this association disappeared when restricting the analyses to women without antidepressant use (1.0, 0.2-4.5).

In the antidepressant use cohort, any antidepressant use during pregnancy was associated with preterm birth (1.4, 1.1-1.8), particularly the use of SSRIs (1.9, 1.2-2.8) (Table 3). When we restricted the cohort to women with depressive symptoms or a clinical diagnosis of depression, the effect for any antidepressant use all but disappeared, while the odds ratio for SSRI use was slightly lower (1.6, 1.0-2.5). Antidepressant use during pregnancy was neither associated with low birth weight nor with SGA, but associations with a low 5 minute Apgar score were observed for any

antidepressant use during pregnancy (1.6, 1.1-2.5), particularly the use of SSRIs (1.7, 1.1-2.8), in the antidepressant use cohort. We observed similar associations in the antidepressant use cohort restricted to women with depressive symptoms or a clinically diagnosed depression, but with wider confidence intervals (1.6, 0.9-2.8 and 1.4, 0.8-2.4, respectively)

Depressive symptoms in the first trimester (1.4, 1.0-1.8), second trimester (1.3, 1.1-1.4), and third trimester of pregnancy (1.5, 1.2-1.8) all seemed to be associated with preterm birth in the depression cohort. In the restricted depression cohort , however, these effects disappeared for the most part, except for third trimester exposure (1.5, 1.1-2.2) (Appendix 4, available online at http://links.lww.com/xxx). First trimester depressive symptoms were not associated with low birth weight, SGA, or a low 5 minute Apgar score in either of the two cohorts, but depressive symptoms in the second trimester seemed to be associated with low birth weight and SGA in the depression cohort, whereas third trimester depressive symptoms were associated with low birth weight in the restricted cohort (1.6, 1.0-2.6) and with a low Apgar score in the depression cohort (1.8, 1.2-2.7) and possibly in the restricted depression cohort (1.4, 0.9-2.1).

We did not observe increased risks of preterm birth, low birth weight, SGA, or low 5 minute Apgar scores for exposure to antidepressants in specific parts of pregnancy (Appendix 5, available online at http://links.lww.com/xxx). When we analyzed individual antidepressants (Appendix 6, available online at http://links.lww.com/xxx), increased risks of preterm birth were found for the use of fluoxetine (1.9, 1.1-3.3) and sertraline (2.2, 1.2-4.3) in the antidepressant use cohort. When restricting the antidepressant use cohort to women with depressive symptoms or a clinical diagnosis of depression, the odds ratios for fluoxetine (1.6, 1.0-2.7) and sertraline use (2.0, 0.9-4.3) were slightly lower with unity included in the 95% confidence interval. The odds ratios for tricyclic antidepressant use were in the same order of magnitude, but with wider confidence intervals, as only 4 studies could be included. Possibly increased risks of low 5 minute Apgar scores were also

observed for fluoxetine (2.4, 1.0-5.5) and paroxetine use (2.4, 0.7-7.8) in the antidepressant use cohort.

DISCUSSION

In this IPD meta-analysis, we observed increased risks of preterm birth and low Apgar scores for women with depressive symptoms or a clinical diagnosis of depression during pregnancy. In the restricted analyses, excluding women with confirmed or unknown antidepressant use from the depression cohort, increased risks were observed for preterm birth only. Women with depressive symptoms in the third trimester seemed to have the highest risk of preterm birth and low birth weight in this restricted cohort. Antidepressant use during pregnancy was also associated with preterm birth and low Apgar scores, with the highest risks observed for fluoxetine and sertraline. These findings indicate that depressive symptoms, especially in the third trimester, and a clinical diagnosis of depression are associated with preterm birth and low Apgar scores and possibly with low birth weight, while the use of SSRIs during pregnancy, especially fluoxetine and sertraline, is associated with preterm birth and low Apgar scores as well. Depressive symptoms, a clinical diagnosis of depression, and antidepressant use during pregnancy are at best weakly associated with low birth weight and SGA.

An important strength of this IPD meta-analysis was the large study population, enabling us to compare women who used antidepressants during pregnancy to an untreated control group suffering from depressive symptoms or a clinical diagnosis of depression, and to conduct the analyses separately for specific trimesters during pregnancy and for several individual antidepressants. Even in this large IPD meta-analysis, however, the power was too low to draw meaningful conclusions for some subgroups. Another strength was the availability of data on potential confounders which enabled us to adjust for several factors appropriately. Due to missing confounder data in some

studies, however, the study population decreased slightly for certain analyses as we applied complete case analyses. We decided not to use multiple imputations for the missing confounder data as imputation of variables in one-stage random-effect models is not always recommended.[61] Residual confounding may still influence our results, as we did not have any information on pregnancy-related risk factors for the outcomes, such as thyroid problems and hypertensive disorders, or on concomitant use of psychotropic medication other than antidepressants, such as anxiolytics and antipsychotic medication.

As no registry exists for observational studies, we included published databases only to avoid selection, but we could obtain data from only 27 databases out of the 215 eligible studies identified. Therefore, we examined the risk of participation bias within this IPD meta-analysis by performing a 'traditional' meta-analysis on the databases included. We compared the results with recently published meta-analyses focusing on the same exposures and perinatal outcomes: maternal depression in association with preterm birth and low birth weight,[62] and antidepressant use in association with preterm birth,[14,19] low birth weight,[19,63] SGA,[67] and 5 minute Apgar score.[13] We did not identify meta-analyses based on more than 4 studies on the associations between depression and SGA and Apgar scores. The results of our meta-analysis on the 27 included databases were in line with the published meta-analyses for all four perinatal outcomes. Therefore, we conclude that participation bias was limited.

IPD meta-analyses of observational studies are generally more difficult to perform than those of randomized controlled trials,[23] among others due to large amounts of heterogeneity. Observational studies can differ widely in their study design, study population, control group, and availability of confounders. Despite using one-stage random-effect models in the analyses, this may be an important limitation of this IPD meta-analysis in which we pooled many cohort studies that differed in design and availability of data on exposure, confounders, and outcome measures, as well as on

timing of the assessment of depressive symptoms or a clinical diagnosis of depression. For example, the assessment of depressive symptoms was conducted with self-completed questionnaires in some studies, whereas other databases contained data from telephone or face-to-face interviews performed by health care professionals. Clinical interviews are believed to be the most reliable assessment of depressive symptoms.[64] As interviews are usually not feasible in large observational studies, however, we used validated cut-off values that were proven to be reliable in previous research for all self-completed questionnaires.[27-33] These questionnaires often assess symptoms of depression as well as anxiety, so the depression cohort may include many women with symptoms of anxiety alongside depressive symptoms. However, women with only anxiety without depression were excluded from the analyses. Many studies did not have data available on the pregnancy outcome SGA, which resulted in lower power in the sub-analyses for this outcome. Therefore, the results for SGA should be interpreted with caution.

Exposure assessment of antidepressant use during pregnancy also differed among the included studies. Some studies based their exposure data on registries, such as birth registries, health registries, or claims databases, whereas others used pharmacy data or self-completed questionnaires to assess antidepressant use. By combining data from different studies, exposure misclassification resulting from both underreporting (self-reported methods of data collection)[65] and over-reporting due to non-adherence (registry and pharmacy data)[66] may have occurred. If this misclassification was non-differential, it may have resulted in underestimation of the effect estimates for the adverse pregnancy outcomes studied. Furthermore, most databases did not contain information on the dosages of the antidepressants used or on the severity of depression. To minimize treatment bias, we also performed the analyses within the restricted antidepressant use cohort, excluding all women who did not have a diagnosis of depression or depressive symptoms and could therefore not have been treated for depression. Still, women with less severe depression may not have been treated pharmacologically in the same amount as women with severe depression, so some treatment bias

may still have occurred. Regarding the specific analyses for the timing of exposure, it was not possible to rule out that women may also have been exposed in other trimesters, which may have led to over- or underestimation of the trimester-specific effects estimates.

Our results are supported by several systematic reviews performed previously. Grigoriadis et al. concluded that depression during pregnancy must not be left untreated, as the potential for negative effects of depression on the newborn are not negligible.[67] Ross et al. found increased risks of preterm birth, low birth weight, and low Apgar scores among infants exposed to antidepressant medication in utero.[13] Although these results were statistically significant, the absolute effects identified were small. Eke et al. found an increased risk of preterm birth among women who received SSRIs during pregnancy.[14] In the current IPD meta-analysis, the highest risks were also observed for SSRI use during pregnancy. Huybrechts et al. concluded that the findings from their systematic review showed an association between antidepressant use during pregnancy and preterm birth, although the possibility of residual confounding by depression could not be completely ruled out.[15] All of these conclusions are in line with the results found in this IPD meta-analysis. However, the precise etiology and the biological mechanisms underlying adverse effects on pregnancy outcomes as a result of depressive symptoms or a clinical depression in pregnant women are still not fully understood. Therefore, this should be considered an important topic for future research to facilitate implementation of preventive measures.

From the results of this IPD meta-analysis, we venture to conclude that a clinical diagnosis of depression during pregnancy should not be left untreated. Most risks observed were still seen when the analyses were restricted to women without antidepressant use, ruling out the possibility that these associations were driven by pharmacological treatment alone. Although other treatments may be preferred, pharmacological treatment might be an option for women suffering from a clinically diagnosed moderate to severe depression. SSRI use, especially fluoxetine and sertraline use,

however, was also associated with increased risks of preterm birth and low Apgar scores. These associations remained, albeit with wider confidence intervals, when we restricted the analyses to women with depressive symptoms or a clinical diagnosis of depression, at least partly ruling out confounding-by-indication. This information is important for health care professionals when pharmacological treatment is indicated during pregnancy and decisions need to be made on which antidepressant to prescribe. The timing of the use of antidepressants throughout pregnancy did not seem to influence the risks of adverse pregnancy outcomes.

The results of this IPD meta-analysis may help health care professionals and pregnant women in making evidence-based decisions on whether the beneficial effects of pharmacological treatment of maternal depression outweigh the possible risks for the unborn child. Health care professionals should be aware of the risks of the underlying disorder itself and provide pregnant women with appropriate pharmacological treatment when necessary.

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Table 1. Maternal characteristics of the individual patient data study population and sub-cohorts.

Characteristic[a]	Depression cohort		Depression cohort restricted to women without antidepressant use		Antidepressant use cohort		Antidepressant use cohort restricted to women with depressive symptoms or clinical diagnosis of depression	
	No depressive symptoms or clinical diagnosis of depression Total N= 346 874 N (%)	Depressive symptoms or clinical diagnosis of depression Total N= 28 395 N (%)	No depressive symptoms or clinical diagnosis of depression Total N= 88 642 N (%)	Depressive symptoms or clinical diagnosis of depression Total N= 10 817 N (%)	No antidepressant use Total N= 115 473 N (%)	Any antidepressant use Total N= 2 624 N (%)	No antidepressant use Total N= 10 817 N (%)	Any antidepressant use Total N= 2 624 N (%)
Maternal age (yrs)								
<30	189 571 (54.7)	15 437 (54.4)	34 555 (39.0)	5 098 (47.1)	42 985 (37.2)	963 (36.7)	5 098 (47.1)	963 (36.7)
30-34	89 990 (25.9)	7 151 (25.2)	30 370 (34.3)	3 221 (29.8)	36 069 (31.2)	763 (29.1)	3 221 (29.8)	763 (29.1)
≥35	53 560 (15.4)	4 536 (16.0)	13 232 (14.9)	1 779 (16.4)	16 237 (14.1)	601 (22.9)	1 779 (16.4)	601 (22.9)
Level of education								
Low	87 242 (25.2)	7 904 (27.8)	6 728 (7.6)	1 922 (17.8)	10 340 (9.0)	264 (10.1)	1 922 (17.8)	264 (10.1)
Moderate	136 070 (39.2)	11 163 (39.3)	25 615 (28.9)	3 947 (36.5)	33 470 (29.0)	604 (23.0)	3 947 (36.5)	604 (23.0)
High	104 006 (30.0)	7 211 (25.4)	50 756 (57.3)	4 340 (40.1)	63 836 (55.3)	739 (28.2)	4 340 (40.1)	739 (28.2)
Race/ethnicity								
Non-Hispanic white	187 640 (54.1)	17 104 (60.2)	74 540 (84.1)	7 991 (73.9)	94 450 (81.8)	2 174 (82.9)	7 991 (73.9)	2 174 (82.9)
Hispanic	88 040 (25.4)	3 903 (13.7)	724 (0.8)	596 (5.5)	1 384 (1.2)	47 (1.8)	596 (5.5)	47 (1.8)
Black	18 790 (5.4)	3 025 (10.7)	127 (0.1)	74 (0.7)	235 (0.2)	4 (0.2)	74 (0.7)	4 (0.2)
Asian	12 029 (3.5)	1 247 (4.4)	642 (0.7)	487 (4.5)	1 391 (1.2)	18 (0.7)	487 (4.5)	18 (0.7)
Non classifiable	22 625 (6.5)	1 751 (6.2)	8 401 (9.5)	1 253 (11.6)	11 285 (9.8)	155 (5.9)	1 253 (11.6)	155 (5.9)
Pre-pregnancy BMI[b]								
Underweight	10 578 (3.0)	782 (2.8)	2 475 (2.8)	373 (3.4)	3 392 (2.9)	74 (2.8)	373 (3.4)	74 (2.8)
Normal weight	137 549 (39.7)	9 909 (34.9)	55 004 (62.1)	5 403 (49.9)	69 857 (60.5)	919 (35.0)	5 403 (49.9)	919 (35.0)
Overweight	53 286 (15.4)	4 433 (15.6)	18 534 (20.9)	2 031 (18.8)	23 688 (20.5)	369 (14.1)	2 031 (18.8)	369 (14.1)
Obese	35 874 (10.3)	3 631 (12.8)	8 091 (9.1)	1 177 (10.9)	10 704 (9.3)	271 (10.3)	1 177 (10.9)	271 (10.3)
Parity								
0 previous live births	129 393 (37.3)	9569 (33.7)	35 885 (40.5)	4 490 (41.5)	43 091 (37.3)	1 062 (40.5)	4 490 (41.5)	1 062 (40.5)
≥1 previous live births	193 126 (55.7)	16 994 (59.8)	42 245 (47.7)	5 570 (51.5)	52 133 (45.1)	1 140 (43.4)	570 (51.5)	1 140 (43.4)
Alcohol use during pregnancy								
No	284 458 (82.0)	20 554 (72.4)	64 754 (73.1)	8 233 (76.1)	83 752 (72.5)	1839 (70.1)	8 233 (76.1)	1 839 (70.1)
Yes	18 137 (5.2)	2 750 (9.7)	12 251 (13.8)	1 493 (13.8)	15 084 (13.1)	324 (12.3)	1 493 (13.8)	324 (12.3)
Smoking during pregnancy								
No	288 521 (83.2)	19 043 (67.1)	78 185 (88.2)	8 428 (77.9)	87 689 (75.9)	1 686 (64.3)	8 428 (77.9)	1 686 (64.3)
Yes	22 762 (6.6)	4 947 (17.4)	7 841 (8.8)	2 064 (19.1)	10 423 (9.0)	582 (22.2)	2 064 (19.1)	582 (22.2)
Illicit drug use during pregnancy								
No	267 269 (77.1)	18 755 (66.1)	70 525 (79.6)	7 482 (69.2)	90 165 (78.1)	1 689 (64.4)	7 482 (69.2)	1 689 (64.4)
Yes	4 353 (1.3)	1 248 (4.4)	483 (0.5)	357 (3.3)	900 (0.8)	100 (3.8)	357 (3.3)	100 (3.8)
Folic acid use								

No	31 330 (9.0)	3 423 (12.1)	28 954 (32.7)	2 974 (27.5)	36 103 (31.3)	445 (17.0)	2 974 (27.5)	445 (17.0)
Yes	39 295 (11.3)	3 960 (13.9)	35 292 (39.8)	3 412 (31.5)	41 492 (35.9)	526 (20.0)	3 412 (31.5)	526 (20.0)
Use of reproductive techniques								
No	83 741 (24.1)	9 875 (34.8)	76 778 (86.6)	8 384 (77.5)	100 272 (86.8)	1 319 (50.2)	8 384 (77.5)	1 319 (50.2)
Yes	4211 (1.2)	379 (1.3)	3 916 (4.4)	327 (3.0)	5 090 (4.4)	59 (2.2)	327 (3.0)	59 (2.2)
Chronic maternal illnesses								
Diabetes	4 776 (1.4)	367 (1.3)	388 (0.4)	55 (0.5)	486 (0.4)	10 (0.4)	55 (0.5)	10 (0.4)
Hypertension	8 504 (2.5)	936 (3.3)	2 467 (2.8)	385 (3.6)	3 042 (2.6)	56 (2.1)	385 (3.6)	56 (2.1)
Thyroid disorder	5 270 (1.5)	614 (2.2)	1 366 (1.5)	172 (1.6)	1 824 (1.6)	84 (3.2)	172 (1.6)	84 (3.2)
Asthma	21 330 (6.1)	2 676 (9.4)	4 378 (4.9)	563 (5.2)	5 617 (4.9)	151 (5.8)	563 (5.2)	151 (5.8)
Epilepsy	558 (0.2)	107 (0.4)	454 (0.5)	80 (0.7)	586 (0.5)	20 (0.8)	80 (0.7)	20 (0.8)
No or other illnesses	282 321 (81.4)	19 456 (68.5)	76 544 (86.4)	8 716 (80.6)	99 927 (86.5)	2 214 (84.4)	8 712 (80.6)	2 214 (84.4)

[a] For all variables, numbers of women within the strata do not add up to the total number of women due to missing values or data not being available in all databases included.
[b] Underweight: <18.5kg/m², Normal weight: 18.5-24.9 kg/m², Overweight: >25.0-29.9 (kg/m²), Obese: ≥30 kg/m²

Table 2. Risks and associations of depressive symptoms and a clinical diagnosis of depression with preterm birth, low birth weight, small-for-gestational age, and low 5 minute Apgar scores.

	Depression cohort[a]					Depression cohort restricted to women without antidepressant use[a]				
	Index outcome									
Preterm birth	No	Yes	Risk (%)	Crude OR[b] (95% CI)	Adjusted OR[b,c] (95% CI)	No case	Cases	Risk (%)	Crude OR[b] (95% CI)	Adjusted OR[b,c] (95% CI)
Depressive symptoms or clinical diagnosis (26 studies)										
No	293 718	30 617	9.4			64 031	3 388	5.3		
Yes	23 386	2 725	10.4	1.4 (1.1-1.7)	1.2 (1.1-1.4)	8 228	689	7.7	1.2 (0.9-1.8)	1.2 (0.9-1.7)
Depressive symptoms (18 studies)										
No	102 760	5 842	5.4			62 655	3 313	5.0		
Yes	13 608	1 018	7.0	1.3 (1.0-1.7)	1.2 (1.1-1.4)	7 073	564	7.4	1.2 (0.8-1.9)	1.2 (0.9-1.7)
Clinical diagnosis (10 studies)										
No	191 829	24 839	11.5			1 995	97	4.6		
Yes	9 805	1 710	14.9	1.4 (1.0-2.1)	1.6 (1.2-2.1)	1 164	125	9.7	1.8 (0.9-3.4)	2.2 (1.7-3.0)
Low birth weight[d]										
Depressive symptoms or clinical diagnosis (25 studies)										
No	292 888	21 837	6.9			64 597	1 947	2.9		
Yes	22 670	2 031	8.2	1.3 (1.1-1.6)	1.0 (0.9-1.1)	8 168	534	6.1	1.4 (1.0-2.0)	1.3 (0.9-1.9)
Depressive symptoms (17 studies)										
No	97 064	4 461	4.4			63 190	1 907	2.9		
Yes	12 521	799	6.0	1.2 (1.0-1.6)	1.1 (0.9-1.3)	7 065	361	4.9	1.3 (0.9-1.9)	1.2 (0.8-1.8)
Clinical diagnosis (10 studies)										
No	196 690	17 432	8.1			2 015	61	2.9		
Yes	10 177	1 234	10.8	1.4 (0.9-2.1)	1.0 (0.8-1.2)	1 112	173	13.5	1.9 (0.8-4.5)	1.9 (0.8-4.7)
Small-for-gestational age										
Depressive symptoms or clinical diagnosis (11 studies)										
No	76 763	5 067	6.2			70 771	4 391	5.8		
Yes	9 552	805	7.8	1.1 (0.7-1.8)	1.1 (1.0-1.3)	7 826	652	7.7	1.1 (0.6-2.0)	1.1 (0.7-1.7)
Depressive symptoms (9 studies)										
No	75 451	5 048	6.3			69 466	4 371	5.9		
Yes	9 145	792	8.0	1.3 (0.8-2.1)	1.1 (1.0-1.3)	7 659	652	7.8	1.3 (0.8-2.2)	1.2 (0.7-1.9)
Clinical diagnosis (4 studies)										

No	2 168	85	3.9			1 928	26	1.3		
Yes	434	16	3.6	0.4 (0.1-2.6)	0.1 (0.0-7.4)	176	0	0	-	-
Low 5 minute Apgar score										
Depressive symptoms or clinical diagnosis (22 studies)										
No	302 372	4 768	1.6			74 607	916	1.2		
Yes	20 799	482	2.3	1.2 (0.9-1.6)	1.2 (1.0-1.5)	8 122	163	2.0	1.2 (0.9-1.7)	1.2 (0.9-1.6)
Depressive symptoms (15 studies)										
No	91 402	1 083	1.2			73 211	893	1.2		
Yes	10 640	202	1.9	1.2 (0.9-1.6)	1.1 (0.8-1.6)	7 576	149	1.9	1.2 (0.9-1.7)	1.2 (0.9-1.7)
Clinical diagnosis (9 studies)										
No	211 861	3 700	1.7			2 011	36	1.8		
Yes	10 187	281	2.7	1.6 (1.4-1.8)	1.5 (1.3-1.7)	555	14	2.5	1.4 (0.8-2.6)	1.0 (0.2-4.5)

[a] The subgroups (depressive symptoms or clinical diagnosis; depressive symptoms; clinical diagnosis) are not mutually exclusive
[b] Based on one-stage random-effects logistic regression analyses in which clustering of participants within studies was preserved and heterogeneity among studies was taken into account
[c] Analysis adjusted for race/ethnicity, parity, and smoking during pregnancy
[d] Preterm births were not excluded from the low birth weight cases, so these two groups are not mutually exclusive.

Table 3. Risks and associations of antidepressant use with preterm birth, low birth weight, small-for-gestational age, and low 5 minute Apgar scores.

	Cohort antidepressant use[a]					Cohort antidepressant use restricted to women with depressive symptoms or clinical diagnosis of depression[a]				
	Index outcome									
Preterm birth	No	Yes	Risk (%)	Crude OR[b] (95% CI)	Adjusted OR[b,c] (95% CI)	No case	Cases	Risk (%)	Crude OR[b] (95% CI)	Adjusted OR[b,c] (95% CI)
Any antidepressant use (15 studies)										
No	74 651	4 385	5.5			8 228	689	7.7		
Yes	1 900	216	10.2	1.3 (0.9-1.9)	1.4 (1.1-1.8)	1 900	216	10.2	1.1 (0.8-1.6)	1.1 (0.9-1.5)
SSRI use (3 studies)										
No	55 823	3 267	5.5			5 184	468	8.2		
Yes	1 188	140	10.5	1.5 (1.0-2.3)	1.9 (1.2-2.8)	1 188	140	10.5	1.3 (0.8-2.0)	1.6 (1.0-2.5)
Low birth weight[d]										
Any antidepressant use (14 studies)										
No	75 321	2 708	3.5			8 168	534	6.1		
Yes	1 924	160	7.7	1.4 (1.0-2.1)	1.1 (0.8-1.5)	1 924	160	7.7	1.1 (0.8-1.7)	0.9 (0.7-1.3)
SSRI use (3 studies)										
No	58 607	1 973	3.3			5 317	409	7.1		
Yes	1 237	94	7.1	1.3 (0.9-2.1)	0.9 (0.6-1.2)	1 237	94	7.1	1.1 (0.7-1.7)	0.7 (0.5-1.1)
Small-for-gestational age										
Any antidepressant use (8 studies)										
No	84 912	5 622	6.2			7 826	652	7.7		
Yes	1 375	96	6.5	1.1 (0.6-2.1)	0.9 (0.6-1.3)	1 375	96	6.5	0.8 (0.4-1.6)	0.9 (0.6-1.3)
SSRI use (1 study)										
No	66 650	4 535	6.3			4 305	362	7.8		
Yes	892	61	6.4	1.0 (0.3-2.8)	0.9 (0.6-1.4)	892	61	6.4	0.6 (0.3-1.5)	0.8 (0.5-1.3)
Low 5 minute Apgar score										
Any antidepressant use (14 studies)										
No	89 275	1 313	1.4			8 122	163	2.0		
Yes	1 891	54	2.8	1.7 (1.1-2.6)	1.6 (1.1-2.5)	1 891	54	2.8	1.6 (1.0-2.7)	1.6 (0.9-2.8)
SSRI use (3 studies)										
No	71 031	993	1.4			5 199	88	1.7		
Yes	1 254	35	2.7	1.6 (1.0-2.6)	1.7 (1.1-2.8)	1 254	35	2.7	1.4 (0.8-2.5)	1.4 (0.8-2.4)

SSRI, selective serotonin-reuptake inhibitor

[a] The subgroups (any antidepressant use and SSRI use) are not mutually exclusive

[b] Based on one-stage random-effects logistic regression analyses in which clustering of participants within studies was preserved and heterogeneity among studies was taken into account

[c] Analysis adjusted for race/ethnicity, parity, and smoking during pregnancy

[d] Preterm births were not excluded from the low birth weight cases, so these two groups are not mutually exclusive.

Figure 1. Flow diagram of the individual participant data meta-analysis.

Figure 2. Composition of depression cohorts (n=375,269) (**A**) and antidepressant use cohorts (n=118,097) (**B**).

PEER REVIEW HISTORY

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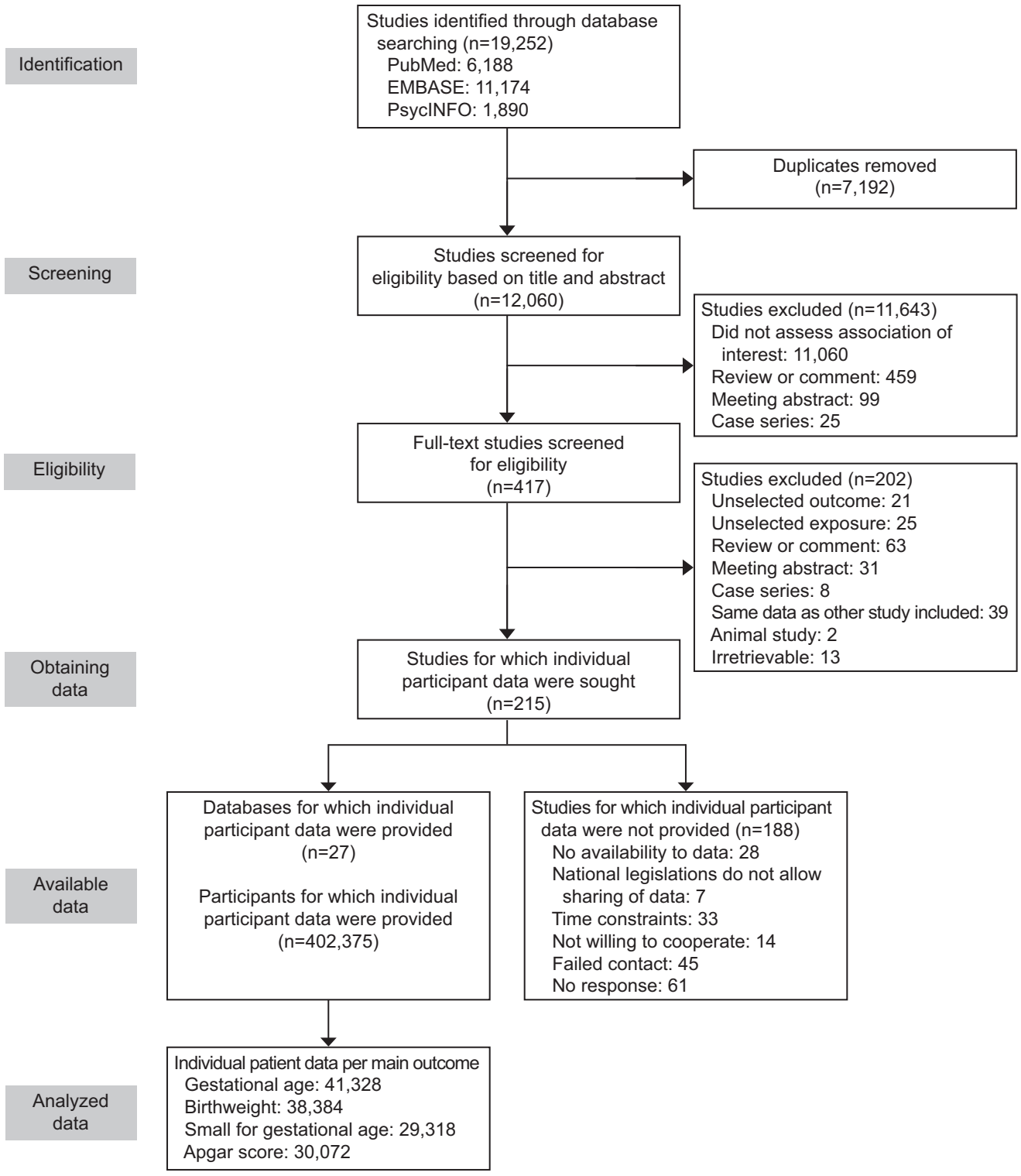
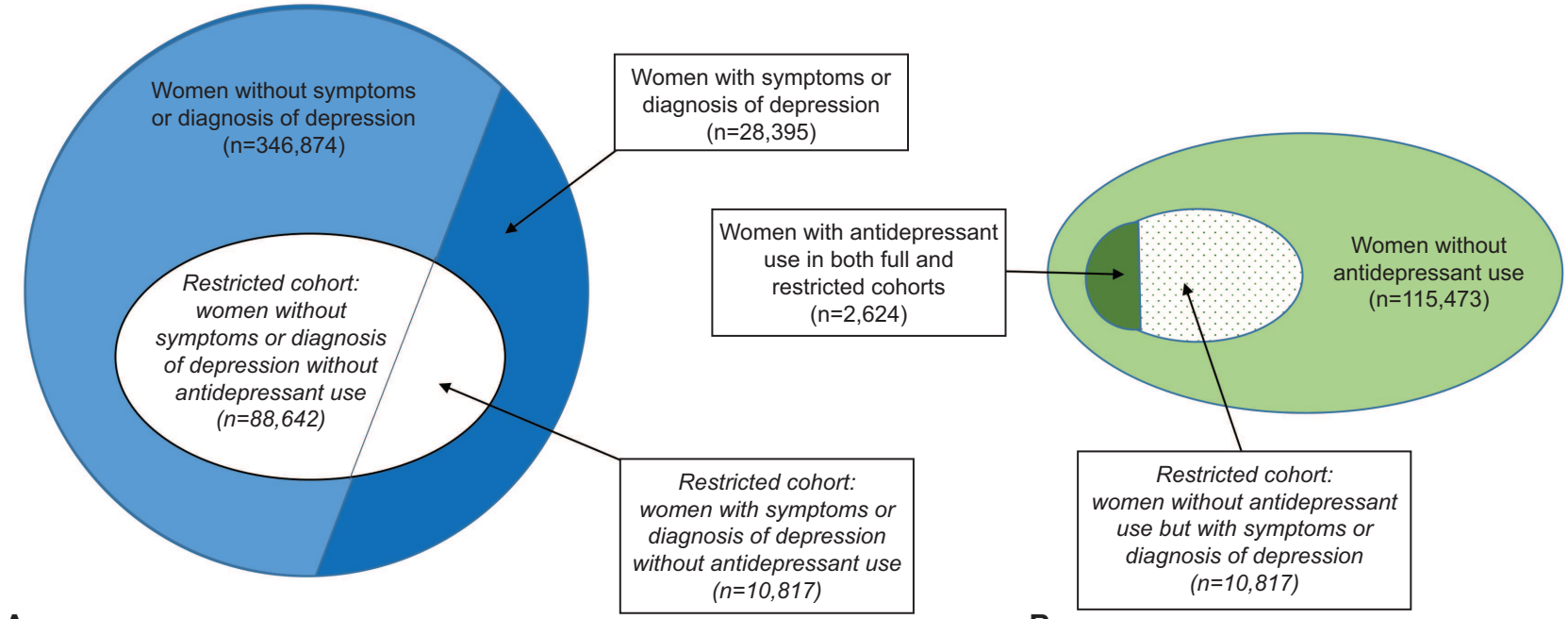
Figure 1


Identification
Studies identified through database searching (n=19,252)
PubMed: 6,188
EMBASE: 11,174
PsycINFO: 1,890
Duplicates removed (n=7,192)
Screening
Studies screened for eligibility based on title and abstract (n=12,060)
Studies excluded (n=11,643)
Did not assess association of interest: 11,060
Review or comment: 459
Meeting abstract: 99
Case series: 25
Eligibility
Full-text studies screened for eligibility (n=417)
Studies excluded (n=202)
Unselected outcome: 21
Unselected exposure: 25
Review or comment: 63
Meeting abstract: 31
Case series: 8
Same data as other study included: 39
Animal study: 2
Irretrievable: 13
Obtaining data
Studies for which individual participant data were sought (n=215)
Available data
Databases for which individual participant data were provided (n=27)
Participants for which individual participant data were provided (n=402,375)
Studies for which individual participant data were not provided (n=188)
No availability to data: 28
National legislations do not allow sharing of data: 7
Time constraints: 33
Not willing to cooperate: 14
Failed contact: 45
No response: 61
Analyzed data
Individual patient data per main outcome
Gestational age: 41,328
Birthweight: 38,384
Small for gestational age: 29,318
Apgar score: 30,072


Women without symptoms or diagnosis of depression (n=346,874)
Restricted cohort: women without symptoms or diagnosis of depression without antidepressant use (n=88,642)
Women with symptoms or diagnosis of depression (n=28,395)
Restricted cohort: women with symptoms or diagnosis of depression without antidepressant use (n=10,817)
A
Women with antidepressant use in both full and restricted cohorts (n=2,624)
Women without antidepressant use (n=115,473)
Restricted cohort: women without antidepressant use but with symptoms or diagnosis of depression (n=10,817)
B