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REVIEW ARTICLE

The impact of maternal prenatal mental health disorders on stillbirth and infant mortality: a systematic review and meta-analysis

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Abstract

Evidence about the association between maternal mental health disorders and stillbirth and infant mortality is limited and conflicting. We aimed to examine whether maternal prenatal mental health disorders are associated with stillbirth and/or infant mortality. MEDLINE, Embase, PsycINFO, and Scopus were searched for studies examining the association of any maternal prenatal (occurring before or during pregnancy) mental health disorder(s) and stillbirth or infant mortality. A random-effects meta-analysis was used to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs). The between-study heterogeneity was quantified using the I^2 statistic. Subgroup analyses were performed to identify the source of heterogeneity. Of 4487 records identified, 28 met our inclusion criteria with 27 contributing to the meta-analyses. Over 60% of studies examined stillbirth and 54% of them evaluated neonatal or infant mortality. Thirteen studies investigated the association between maternal depression and anxiety and stillbirth/infant mortality, pooled OR, 1.42 (95% CI, 1.16–1.73; I^2, 76.7%). Another 13 studies evaluated the association between severe maternal mental illness and stillbirth/infant mortality, pooled OR, 1.47 (95% CI, 1.28–1.68; I^2, 62.3%). We found similar results for the association of any maternal mental health disorders and stillbirth/infant mortality (OR, 1.59; 95% CI, 1.43–1.77) and in subgroup analyses according to types of fetal/infant mortality. We found no significant evidence of publication bias. Maternal prenatal mental health disorders appear to be associated with a moderate increase in the risk of stillbirth and infant mortality, although the mechanisms are unclear. Efforts to prevent and treat these disorders may reduce the scale of stillbirth/infant deaths.

Keywords Systematic review · Meta-analysis · Stillbirth · Infant mortality · Depression · Severe mental illness

Introduction

Maternal mental health disorders are common problems worldwide (Gold and Marcus 2008) and include anxiety and depression, psychotic disorders, and a range of other mental disorders. These disorders constitute a prominent public health issue given their scale; for instance, depression alone affects up to 25% of pregnancies (Gelaye et al. 2016) and their association with myriad adverse outcomes for mother and offspring (Pierce et al. 2019; Zhong et al. 2018). A large body of evidence highlights that women with a

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range of different mental disorders are at distinctly higher risk of delivering a preterm or low birthweight baby (Ding et al. 2014; Grigoriadis et al. 2018; Grote et al. 2010) and of having children with poorer developmental outcomes (Reupert et al. 2013). In addition, the results of a limited set of studies suggest that poor maternal mental health poses an increased risk for early life mortality (Webb et al. 2005; Zhong et al. 2018).

The mechanisms whereby maternal mental health impact on adverse fetal and infant outcomes are complex, not fully understood, and likely include alterations to the intrauterine environment as well as behavioural pathways. Depression and anxiety, for example, may alter the cortisol response to stress, which can affect fetal growth (Field et al. 2006; Zorn et al. 2017). For some women, mental health disorders are also associated with inadequate antenatal care, smoking, and misuse of illicit substances and drugs—all common risk factors of perinatal mortality (Judd et al. 2014; Weaver et al. 2003). However, only a limited number of studies have evaluated the association of maternal mental health disorders and stillbirth and infant mortality outcomes, with inconsistent findings (Di Prinzio et al. 2020; Heun-Johnson et al. 2018; Pavlov et al. 2014; Surkan et al. 2016; Vigod et al. 2014; Zhong et al. 2018).

To our knowledge, only two systematic reviews (Jacques et al. 2019; Webb et al. 2005) have focused on the risks for mortality, and none has comprehensively investigated the link between maternal pre-conception and prenatal (occurring before or during pregnancy) mental health disorders and perinatal and infant mortality. A 2005 review focused exclusively on the association between schizophrenia and stillbirth but did not include any other mental health disorders, and identified only six studies, all with important methodological limitations (Webb et al. 2005). A 2019 review examining maternal depression and infant hospitalization and mortality identified only three in-scope studies that examined infant mortality outcomes (Jacques et al. 2019). Notably, most of the included studies in these reviews (three in the first and two in the second) included maternal mental health disorders that occurred in the postnatal period or after the fetal/infant outcome, exposing the possibility of reverse causality bias.

The current systematic review and meta-analysis aimed to provide a comprehensive evaluation of published research that has examined the association between maternal prenatal mental health disorders and stillbirth and infant mortality. The resulting evidence can support prevention and early interventions that target the high proportion of women with mental health disorders.

Material and methods

Protocol and registration

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Moher et al. 2009) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al. 2000) guidelines. The review protocol has been published (Adane et al. 2020) and registered with the PROSPERO (# CRD42020159834).

Search strategy

The details of the search terms and strategies are available in the published protocol (Adane et al. 2020) and as a supplementary file (Supplementary Box 1) but, in summary, we searched MEDLINE, Embase, PsycINFO, and Scopus electronic databases using keywords tailored to each database, from their inception to December 2019. These searches were limited to studies published in English language and on humans only, with no restriction on the year of publication. The reference lists and citations of relevant articles were also checked manually for additional studies. Three authors were contacted for additional information, but only one provided further details (Di Prinzio et al. 2020).

Inclusion and exclusion criteria

Original studies examining the association of any prenatal mental health disorder (occurring at any time before or during pregnancy) and stillbirth (death of a fetus at 20 or more weeks of gestation), neonatal (the first 28 days of life), post-neonatal (the period after 28 days of life and before 1 year), or infant (under 1 year) mortality were eligible. The use of either a diagnostic measure of mental health or symptom screening measure formed part of the eligibility criteria. However, correspondence, theses, reviews, editorials, case-only studies, and conference abstracts were excluded. We also excluded studies where the onset of maternal mental health disorders in relation to the date of childbirth was unclear and/or when postnatal mental health disorders were combined with prenatal disorders.

Study selection

First, all citations identified through database searches were imported into an Endnote library, and duplicates were removed. The titles of the remaining records were screened, with eligible studies uploaded to Rayyan (Ouzzani et al. 2016) and abstracts and full-texts independently evaluated by two of the authors (AAA and HDB). Disagreements between assessors were resolved by face-to-face discussion.

Data extraction

Using a standardized excel sheet, one of the researchers (AAA) extracted the data from articles that passed the full-text evaluation, and the second author (HDB) verified the results. Extracted data included the first author's last name,

country and year of publication, study population and design, exposure and outcome assessment, and association/s as well as confounders adjusted for. When available, adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were extracted. For studies which did not report ORs, crude measures were manually calculated when enough data were available. Some studies provided relative risk (RR) estimates, which were converted to ORs using a previously developed package (Barendregt 2016).

Assessment of methodological quality and risk of bias

We used the Newcastle-Ottawa quality assessment scale (Wells 2001), which includes the following: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure (for case-control studies) or outcome of interest (for cohort studies). We also employed the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Guyatt et al. 2008) to assess the degree of risk of bias for each included study (Higgins et al. 2011). Two of the authors (AAA and HDB) independently performed the quality and risk of bias assessments. When the involved authors differ in the results of the quality assessments, an agreement was reached during a face-to-face discussion.

Data analysis

We have included studies with several differences between them, such as in the type of maternal mental disorders investigated, diagnostic classification system, mortality outcome measure, geographical location, and time period. As such, we do not expect them to share a common effect (fixed effect). Therefore, we employed a random-effects model (Harris et al. 2008), which accounts for between-study heterogeneity and provides an estimate of the average effect, to calculate pooled ORs with 95% CIs for the overall and subgroup meta-analyses of the associations between maternal mental health disorders and stillbirth/infant mortality outcomes. The maternal mental health disorders were grouped into depression and anxiety (including major depressive disorder) and severe mental illness (including schizophrenia, bipolar, schizoaffective/affective psychosis, and psychotic disorders not otherwise specified). We undertook further subgroup analyses for each outcome (stillbirth, perinatal, and infant mortality) separately and collectively as a 'stillbirth/infant mortality' variable within each maternal mental health disorder group. Eight studies only reported perinatal mortality (includes stillbirth and neonatal death) as an aggregate outcome, so the perinatal mortality subgroup includes these studies and those studies that separately reported stillbirth and neonatal mortality. Additional sensitivity and subgroup analyses were conducted by excluding each study and also based on whether an adjustment was made for smoking (yes/no), the number of offspring mortality in women with mental health disorders (< 20 vs. ≥ 20 cases), year of publication (≤ 2010 vs. > 2010), and risk of bias based on the GRADE approach (low vs. moderate). We also ran a sensitivity analysis by excluding studies using symptom only screening measures for depression and anxiety. A few of the included studies contributed two or more estimates for stillbirth, neonatal, post-neonatal, and infant death as they assessed different mental disorders. So to check the effect of non-independent effect sizes, we repeated the primary analyses by including an average measure (obtained via a fixed effect model) for studies with two or more estimates. Analyses were conducted using STATA 15 (StataCorp, College Station).

Assessment of heterogeneity and publication bias

Between-study heterogeneity was examined using the I^2 statistic (Higgins et al. 2003) and was considered low ($I^2 < 50\%$), moderate (I^2, 50–74.9%), or high ($I^2 \geq 75\%$). The risk of publication bias was graphically examined using funnel plot asymmetry and further quantified using the Egger's test (p value ≤ 0.05 suggests significant publication bias) (Harbord et al. 2009).

Results

Search results

A total of 4487 records were identified through the database and manual searches. After duplicates were removed, 3756 were screened by title and abstract. Full-text assessments were made on 78 articles with 50 of these excluded for reasons such as no assessment ($n = 22$) or separate reporting ($n = 6$) of early mortality, and no assessment of prenatal mental health ($n = 6$) or inclusion of postnatal mental health cases ($n = 7$). Finally, 28 studies (Ban et al. 2012; Bansil et al. 2010; Bitew et al. 2017; De Lange et al. 2008; Di Prinzio et al. 2020; Gardosi et al. 2013; Hanlon et al. 2009; Heun-Johnson et al. 2018; Hizkiyahu et al. 2010; Howard et al. 2003; Howard et al. 2007; Huang et al. 2017; MacCabe et al. 2007; Mei-Dan et al. 2015; Navaratne et al. 2016; Nilsson et al. 2002; Pare-Miron et al. 2016; Pavlov et al. 2014; Raisanen et al. 2014; Simoila et al. 2018; Vigod et al. 2014; Webb et al. 2006; Webb et al. 2010; Weobong et al. 2014; Wrede et al. 1980; Yedid Sion et al. 2016; Zax et al. 1977; Zhong et al. 2018) were included in this systematic review ($n = 78{,}492{,}940$), with all but one (Hanlon et al. 2009) contributing at least one estimate for the meta-analyses (Fig. 1).

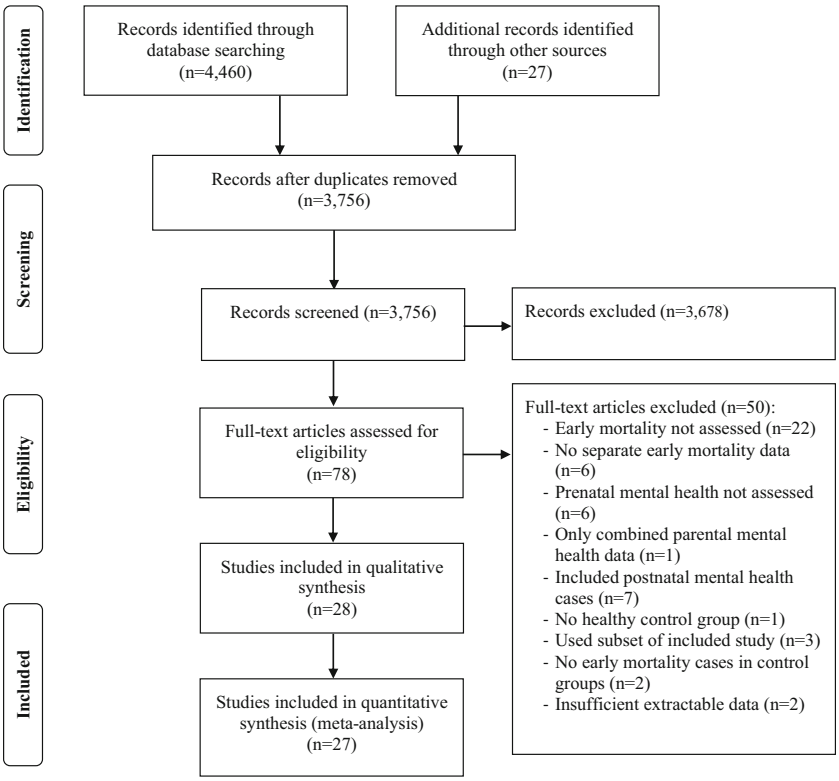


Fig. 1 Study identification and selection flow chart for the systematic review and meta-analysis of maternal mental health disorders, and stillbirth/infant mortality

Characteristics of included studies

The included studies are described in Table 1 and summarized in Box 1. The majority of studies were from European countries ($n = 12$) and the USA ($n = 5$). The most common maternal mental health disorders examined were depression ($n = 8$) and schizophrenia and related disorders ($n = 5$). The most common outcome was stillbirth ($n = 17$). The vast majority ($n = 24$) of studies were cohort studies, while two each were case-control and analytical cross-sectional studies. The sample size (births) of included studies ranged from 56 to 32,156,438 (Table 1).

Included studies varied considerably in terms of confounder or covariate adjustments. While most studies adjusted for maternal age, very few studies fully adjusted for other maternal sociodemographic and lifestyle factors (Supplementary Table 1).

Methodological quality and risk of bias

Based on the Newcastle-Ottawa quality assessment scale, 17 studies scored eight or nine, and the remaining 11 studies received scores of six or seven out of nine (Supplementary Tables 2 and 3). Using the GRADE approach, the risk of bias in most studies was low ($n = 15$) or moderate ($n = 12$) with only one study having a high risk of bias (Supplementary Table 4).

Results of the meta-analyses

Depression and anxiety

Using 16 estimates (i.e., ORs) from 13 unique studies (a study can assess more than one child outcome; so it can contribute more than one estimate) including 39,526,270 births, the pooled OR for the association between maternal depression and anxiety and stillbirth/infant mortality was 1.42 (95% CI, 1.16–1.73; I^2, 76.7%). There were similar associations for stillbirth and perinatal mortality, but the association for infant mortality was marginally lower and spanned the null value (Fig. 2). The pooled ORs (95% CI) were 1.46 (1.17–1.82: I^2, 75.1%) for the association between maternal depression and stillbirth/infant mortality, 1.51 (1.17–1.96: I^2, 81.3%) for the association between maternal depression and stillbirth, 1.46 (1.16–1.84: I^2, 76.4%) for the association between maternal depression and perinatal mortality, and 1.36 (0.90–2.05: I^2, 54.6%) for the association between maternal depression and infant mortality.

Severe mental illness

Using 27 estimates from 13 unique studies which included 36,038,106 births, the pooled OR for the association between severe maternal mental illness and stillbirth or infant mortality was 1.47 (95% CI, 1.28–1.68; I^2, 62.3%). We found similar associations with stillbirth (OR, 1.42; 95% CI, 1.20–1.69; 12 estimates from 10 unique studies and 33,365,387 births; I^2,

Table 1 Characteristics of studies included in the systematic review and meta-analysis of maternal mental health disorders, and stillbirth/infant mortality

Author	Country	Sample size[c]	Data collection	Exposure (assessment)	Outcome (n)	OR/RR, (95% CI)
Ban et al. 2012	UK	512,574	Record extraction	Depression or anxiety (medical record)	Perinatal death (2,096)	RR, 1.30 (1.10–1.50)
Bansil et al. 2010[a]	USA	32,156,438	Record extraction	Depression (ICD-9)	Stillbirth (142,909)	OR, 2.02 (1.83–2.22)
Bitew et al. 2017	Ethiopia	1,240	Questionnaire	Depression (Patient Health Questionnaire, PHQ-9)	Neonatal death (19)	OR, 2.03 (0.73–5.63)
De Lange et al. 2008[b]	Australia	87,231	Record extraction	Psychiatric disorder (medical record)	Perinatal death (648)	OR, 1.85 (1.29–2.65)
Di Prinzio et al. 2020	Australia	467,945	Record linkage	Severe mental illness (ICD-9)	Stillbirth (3,597)	OR, 1.04 (0.73–1.48)
					Neonatal death (3,564)	OR, 1.15 (0.71–1.86)
					Post-neonatal death (3,547)	OR, 1.67 (1.00–2.78)
Gardosi et al. 2013	UK	92,218	Record extraction	History of mental health problems (medical record)	Stillbirth (340)	RR, 1.40 (1.00–1.90)
Hanlon et al. 2009	Ethiopia	1,065	Questionnaire	Common mental disorders (Self-Reporting Questionnaire, SRQ-20)	SRQ score (≥ 6)	
					Stillbirth (40)	RR, 1.70 (0.60–5.50)
					Neonatal death (35)	RR, 0.80 (0.20–3.00)
Heun-Johnson et al. 2018[a]	USA	5,518,766	Record extraction	Schizophrenia, bipolar disorder, major depressive disorder (ICD-9)	Major depressive disorder	
					Stillbirth (27,446)	RR, 1.71 (1.34–2.19)
					Bipolar disorder	
					Stillbirth (27,658)	RR, 1.08 (0.96–1.23)
					Schizophrenia	
					Stillbirth (27,420)	RR, 1.10 (0.81–1.51)
Hizkiyahu et al. 2010	Israel	186,554	Record extraction	Schizophrenia (medical record)	Perinatal death (2,391)	OR, 2.50 (0.80–7.70)
Howard et al. 2003	UK	986	Record extraction	Psychotic disorders (medical record)	Stillbirth (10)	OR, 4.03 (1.14–4.25)
Howard et al. 2007[b]	UK	831	Record extraction	Depression (ICD-10)	SIDS (13)	OR, 4.93 (1.10–22.1)
Huang et al. 2017	Taiwan	25,088	Record extraction	Depression (ICD-9)	Stillbirth (124)	OR, 1.69 (1.12–2.56)
Maccabe et al. 2007	Sweden	2,317	Record extraction	Affective psychosis (ICD-8/9/10)	Stillbirth (NS)	OR, 1.48 (0.87–2.56)
					Infant death (NS)	OR, 0.99 (0.59–1.66)
Mei-Dan et al. 2015	Canada	437,941	Record extraction	Bipolar disorder, major depressive disorder (ICD-9/10)	Major depressive disorder	
					Stillbirth (2,251)	OR, 0.90 (0.55–1.47)
					Neonatal death (1,011)	OR, 0.84 (0.40–1.76)
					Infant death (1,401)	OR, 0.99 (0.56–1.75)
					Bipolar disorder	
					Stillbirth (2,246)	OR, 1.20 (0.66–2.18)
					Neonatal death (≈1,004)	OR, 0.72 (0.23–2.23)
					Infant death (1396)	OR, 0.99 (0.44–2.22)
Navaratne et al. 2016	Australia	26,110	Record extraction	Depression (EPDS questionnaire, self-reported)	Neonatal death (45)	OR, 2.52 (1.20–5.00)
Nilsson et al. 2002	Sweden	1,556,910	Record extraction	Schizophrenia (ICD-8/9/10)	Stillbirth (NS)	OR, 1.70 (0.90–3.50)
					Infant death (NS)	OR, 1.40 (0.70–2.80)
Pare-Miron et al. 2016	USA	8,487,892	Record extraction	Borderline personality disorder (ICD-9)	Stillbirth (57,003)	OR, 1.59 (0.94–2.70)
Pavlov et al. 2014	Israel	256,088	Record extraction	Anxiety disorders (diagnosed by a psychiatrist)	Perinatal death (3,454)	OR, 0.66 (0.16–2.65)
Raisanen et al. 2014	Finland	511,938	Record extraction	Major depression (ICD-10)	Stillbirth (NS)	OR, 1.77 (1.19–2.63)
Simoila et al. 2018	Finland	5,845	Record extraction	Schizophrenia, schizoaffective disorder (ICD-8/9/10)	Perinatal death (21)	OR, 1.26 (0.46–3.45)
Vigod et al. 2014	Canada	433,749	Record extraction	Schizophrenia (ICD-9/10)	Stillbirth (2,247)	OR, 1.66 (0.94–2.93)
					Neonatal death (≈1,004)	OR, 1.27 (0.47–3.39)
					Infant death (1,396)	OR, 1.58 (0.75–3.34)

Table (continued)

Author	Country	Sample size[c]	Data collection	Exposure (assessment)	Outcome (n)	OR/RR, (95% CI)
Webb et al. 2006	Denmark	1,457,962	Record extraction	Schizophrenia and related disorders, affective disorders alcohol-related disorders, drug-related disorders (ICD-8/10)	Schizophrenia	
					Stillbirth (7,633)	RR, 1.71 (1.14–2.55)
					Neonatal death (6,646)	RR, 1.92 (1.26–2.92)
					Post-neonatal death (3,511)	RR, 1.51 (0.81–2.82)
					Affective disorders	
					Stillbirth (7,633)	RR, 1.66 (1.29–2.19)
					Neonatal death (6,646)	RR, 2.46 (1.93–3.13)
					Post-neonatal death (3,511)	RR, 1.31 (0.84–2.03)
					Alcohol-related disorders	
					Stillbirth (7,633)	RR, 1.64 (1.10–2.45)
					Neonatal death (6,646)	RR, 2.59 (1.83–3.66)
					Post-neonatal death (3,511)	RR, 3.83 (2.62–5.59)
					Drug-related disorders	
					Stillbirth (7,633)	RR, 1.39 (0.90–2.13)
					Neonatal death (6,646)	RR, 2.33 (1.64–3.32)
					Post-neonatal death (3,511)	RR, 3.02 (1.98–4.59)
Webb et al. 2010	Sweden	2,480,320	Record extraction	Nonaffective psychoses, alcohol/drug disorders (ICD-8/9/10)	Nonaffective psychoses	
					SIDS (1,419)	OR, 1.8 (0.60–3.90)
					Alcohol/drug disorders	
					SIDS (1,462)	OR, 6.50 (4.90–8.70)
Weobong et al. 2014	Ghana	20,679	Interview/questionnaire	Depression (Patient Health Questionnaire, PHQ-9)	Stillbirth (507)	RR, 1.06 (0.80–1.40)
					Neonatal death (468)	RR, 1.02 (0.76–1.37)
Wrede et al. 1980	Finland	288	Record extraction	Schizophrenia (medical records, diagnosed by a psychiatrist)	Perinatal death (9)	OR, 29.6 (3.6–242.5)
					Stillbirth (5)	OR, 14.8 (1.6–135.5)
Yedid Sion et al. 2016	Israel	256,312	Record extraction	Depression (diagnosed by psychiatrist)	Perinatal death (3,336)	OR, 1.36 (0.61–3.03)
Zax et al. 1977	USA	56	Record extraction/interview	Neurotic depression (psychiatric record)	Perinatal death (5)	OR, 6.08 (0.66–55.9)
Zhong et al. 2018	USA	23,507,597	Record extraction	Psychosis (ICD-9)	Stillbirth (154,856)	OR, 1.37 (1.23–1.53)

Abbreviations: *CI*, confidence interval; *ICD*, International Statistical Classification of Diseases; *OR*, odds ratio; *NS*, not stated; *RR*, relative risk; *SIDS*, sudden infant death syndrome

[a] Analytical cross-sectional study; [b] case control study and all the rest are cohort studies; [c] refers to the number of births

Box 1 Descriptive summary of studies included in the systematic review and meta-analysis

Country/region study conducted	Maternal mental health exposure[a]	Fetal/infant outcome
• Europe, n=12 – Scandinavia, n=7 – UK, n=5 • USA, n=5 • Australia, n=3 • Israel, n=3 • Africa, n=3 • Other, n=2	• Depression and anxiety, n=13 – Depression, n=8 – Major depressive disorder, n=3 – Depression and anxiety, n=1 – Anxiety disorders, n=1 • Severe mental illness, n=13 – Schizophrenia or related, n=5 – Psychosis, n=4 – Bipolar disorder, n=2 – Other, n=3 • Other non-specific, n=4	• Stillbirth, n=17 • Neonatal mortality, n=7 • Perinatal mortality, n=8 • Post-neonatal/infant mortality, n=6 • Sudden infant death syndrome, n=2

[a] *The total number of studies exceed 28 because of two studies contributing to both depression and anxiety and severe mental illness groups.*

68.5%), perinatal mortality (OR, 1.51; 95% CI, 1.28–1.79; 19 estimates from 12 unique studies and 33,557,786 births; I^2, 72.6%), and infant mortality (OR, 1.49; 95% CI, 1.20–1.85; 13 estimates from seven unique studies and 6,812,821 births; I^2, 46.2%) (Fig. 2).

Any maternal prenatal mental health disorders

Overall, using 52 estimates from 27 unique studies including 78,316,822 births, the pooled OR for the association between any maternal prenatal mental health disorders (listed in Table 1) and stillbirth/infant mortality was 1.59 (95% CI, 1.43–1.77; I^2, 75.5%). We found similar associations for stillbirth and perinatal mortality and a stronger association for infant mortality, particularly for post-neonatal mortality and sudden infant death syndrome (Fig. 2 and Fig. 3).

Hanlon et al. (Hanlon et al. 2009), which is not included in the meta-analyses, assessed common mental health disorders using the Self-Reporting Questionnaire (SRQ-20). The study did not find a statistically significant association between maternal antenatal SRQ score (≥ 6) and stillbirth (RR, 1.7; 95% CI, 0.6–5.5) or neonatal mortality (RR, 0.8; 95% CI, 0.2–3.0), perhaps because of low statistical power.

Heterogeneity and publication bias

The between-study heterogeneity was high for the associations of maternal depression and anxiety and stillbirth/infant mortality, and any maternal mental health disorders and stillbirth/infant mortality. A high degree of between-study heterogeneity remained in subgroup analyses according to the types of mortality outcomes, particularly for stillbirth and perinatal mortality. These could be partly due to differences in the types of maternal mental health disorders, confounders adjusted for, sample size, and year of publication, as shown in the stratified and sensitivity analyses (Supplementary Table 5). We found no evidence of publication bias for studies evaluating the associations of maternal depression and anxiety and stillbirth/infant mortality; severe maternal mental illness and stillbirth/infant mortality, and studies assessing any maternal prenatal mental health disorders and stillbirth (Supplementary Fig. 1).

Sensitivity and subgroup analysis

We did not find any significant changes for the associations between maternal depression and anxiety and severe mental illness with stillbirth/infant mortality outcomes when conducting sensitivity analyses that removed each study one by one (Supplementary Fig. 2). However, we found considerable differences in pooled ORs in the stratified analyses based on whether the adjustment was made for smoking, year of publication, and degree of risk of bias using the GRADE approach. While the pooled effect estimates for maternal depression and anxiety were stronger for studies adjusted for smoking and those published after 2010, those estimates for severe maternal mental illness were stronger if studies did not adjust for smoking, published in 2010 or earlier, and had a moderate risk of bias (Supplementary Table 5). Overall, we found slightly stronger associations and lower between-study heterogeneity in the sensitivity analyses excluding studies that used symptom only screening measures for depression and anxiety: stillbirth/infant mortality (OR, 1.47; 95% CI, 1.18–1.82; I^2, 74.0%), stillbirth (OR, 1.67; 95% CI, 1.35–2.08; I^2, 65.1%), perinatal mortality (OR, 1.48; 95% CI, 1.19–1.85; I^2, 75.5%), and infant mortality (OR, 1.22; 95% CI, 0.59–2.53; I^2, 55.3%). We found similar results to the primary analyses in the sensitivity analyses using the average measure for studies with two or more estimates (Supplementary Fig. 3 and Fig. 4). However, the between-study heterogeneity slightly increased (Supplementary Fig. 3), and the pooled estimate for neonatal death slightly attenuated and spanned the null value (Supplementary Fig. 4).

Discussion

Summary of main findings

In this systematic review and meta-analysis, which included 28 studies comprising over 78 million births, we

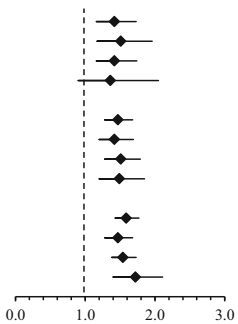
found a moderate and statistically significant higher risk of stillbirth and infant mortality for women with prenatal mental health disorders (including high and low prevalence disorders), compared with women without prenatal mental health disorders. These findings persisted in sensitivity and subgroup analyses according to the types of maternal mental health disorders and fetal or infant mortality outcomes, with results typically indicating a 40–50% increase in the risk of stillbirth and infant mortality. However, considerable heterogeneity was observed in effect sizes across studies included in the meta-analysis, and very few studies evaluated the impact of common maternal mental health disorders, particularly anxiety disorders.

Research in context and potential biological mechanisms

The previous meta-analyses found that women with depression and anxiety disorders were 40 to 80% more likely to have preterm birth and low birthweight (Ding et al. 2014; Grigoriadis et al. 2018; Grote et al. 2010), the leading causes of perinatal mortality. The findings of this systematic review and meta-analysis extend the evidence base by including a broader range of mental health disorders and further corroborated the detrimental impact of maternal prenatal mental health disorders. The underlying reasons for the higher risk of adverse perinatal outcomes among women with prenatal mental health disorders are not yet fully understood, but they are likely to include a complex array of mechanisms that include direct disease effects, behavioural factors and comorbidities, and increased risk of pregnancy complications.

There are several hypothesised pathways through which fetal health may be compromised by intrauterine exposure to psychological distress, including pathways that impact fetal neurodevelopment, placental function, and physical growth (Kinsella and Monk 2009; Lewis et al. 2016). Recent studies, for example, have linked maternal prenatal anxiety and depression with disruptions in the placental 11β-hydroxysteroid dehydrogenase type 2 (11B-HSD2) enzyme and cortisol transfer to the fetus (Cottrell et al. 2014; Duthie and Reynolds 2013; O'Donnell et al. 2012), inflammatory pathways, and altered physiological responses (Christian 2014; Seth et al. 2016). While these effects have generally been associated with greater morbidity, a link with mortality risks is less clear (Ding et al. 2014; Field and Diego 2008). Unhealthy lifestyles and behaviours are highly correlated with psychiatric disorders, and their interplay plausibly accounts

	Number of studies/ estimates[a]	Total births	Total births to women with MH problems[b]	Total offspring mortality[b]	Total offspring mortality in women with MH problems[b]	Pooled OR (95% CI)	I^2, %
Depression and anxiety							
All mortality (*A*)	16	39,526,270	339,437	185,085	2,998	1.42 (1.16-1.73)	76.7
Stillbirth (*A1*)	6	38,626,488	265,895	173,237	2,419	1.51 (1.17-1.96)	81.3
Perinatal mortality (*A2*)	14	39,525,439	339,268	183,671	2,979	1.42 (1.16-1.74)	78.1
Infant mortality (*A3*)	6	477,127	8,871	2,957	86	1.36 (0.90-2.05)	54.6
Severe mental illness							
All mortality (*B*)	27	36,038,106	220,073	219,722	2,365	1.47 (1.28-1.68)	62.3
Stillbirth (*B1*)	12	33,365,387	213,004	198,006	2,214	1.42 (1.20-1.69)	68.5
Perinatal mortality (*B2*)	19	33,557,786	214,263	210,897	2,310	1.51 (1.28-1.79)	72.6
Infant mortality (*B3*)	13	6,812,821	19,360	19,306	153	1.49 (1.20-1.85)	46.2
Any maternal mental illness							
All mortality (*C*)	52	78,316,822	629,388	430,778	5,516	1.59 (1.43-1.77)	75.5
Stillbirth (C*1*)	21	74,656,802	482,346	398,889	4,621	1.47 (1.28-1.68)	79.4
Perinatal mortality (*C2*)	40	75,835,671	559,224	421,823	5,320	1.54 (1.38-1.73)	75.6
Infant mortality (*C3*)	23	6,861,091	90,557	18,964	346	1.72 (1.40-2.11)	72.1



Abbreviations: CI, confidence interval; MH, mental health; OR, odds ratio

[a]*A study can contribute two or more estimates*

[b]*Some studies did not report the number of births to women with mental health problems, the overall mortality, or the number of mortality cases among offspring of women with mental health problems so the numbers shown are the sum of the available numbers/cases.*

Note, mortality categories are not mutually exclusive as perinatal mortality includes stillbirth and neonatal deaths whereas infant mortality includes any death from birth to one year.

A Ban et al. 2012, Bansil et al. 2010, Bitew et al. 2017, Heun-Johnson et al. 2019, Howard et al. 2007, Huang et al. 2017, Mei-Dan et al. 2015, Navaratne et al. 2016, Pavlov et al. 2014, Raisanen et al. 2014, Weobong et al. 2014, Yedid Sion et al. 2016 and Zax et al. 1977

A1 Bansil et al. 2010, Heun-Johnson et al. 2019, Huang et al. 2017, Mei-Dan et al. 2015, Raisanen et al. 2014 and Weobong et al. 2014

A2 All included in A except Howard et al. 2007

A3 Bitew et al. 2017, Howard et al. 2007, Mei-Dan et al. 2015, Navaratne et al. 2016 and Weobong et al. 2014

B Di Prinzio et al. 2020, Heun-Johnson et al. 2019, Hizkiyahu et al. 2010, Howard et al. 2003, MacCabe et al. 2007, Mei-Dan et al. 2015, Nilsson et al. 2002, Simoila et al. 2018, Vigod et al. 2014, Webb et al. 2006, Webb et al. 2010, Wrede et al. 1980 and Zhong et al. 2018

B1 All included in B except Hizkiyahu et al. 2010, Vigod et al. 2014 and Webb et al. 2010

B2 All included in B except Webb et al. 2010

B3 Di Prinzio et al. 2020, MacCabe et al. 2007, Mei-Dan et al. 2015, Nilsson et al. 2002, Vigod et al. 2014, Webb et al. 2006 and Webb et al. 2010

C Ban et al. 2012, Bansil et al. 2010, Bitew et al. 2017, De Lange et al. 2008, Di Prinzio et al. 2020, Gardosi et al. 2013, Heun-Johnson et al. 2019, Hizkiyahu et al. 2010, Howard et al. 2003, Howard et al. 2007, Huang et al. 2017, MacCabe et al. 2007, Mei-Dan et al. 2015, Navaratne et al. 2016, Nilsson et al. 2002, Pare-Miron et al. 2016, Pavlov et al. 2014, Raisanen et al. 2014, Simoila et al. 2018, Vigod et al. 2014, Webb et al. 2006, Webb et al. 2010, Weobong et al. 2014, Wrede et al. 1980, Yedid Sion et al. 2016, Zax et al. 1977 and Zhong et al. 2018

C1 Bansil et al. 2010, Di Prinzio et al. 2020, Gardosi et al. 2013, Heun-Johnson et al. 2019, Howard et al. 2003, Huang et al. 2017, MacCabe et al. 2007, Mei Dan et al. 2015, Nilsson et al. 2002, Pare-Miron et al. 2016, Raisanen et al. 2014, Vigod et al. 2014, Webb et al. 2006, Weobong et al. 2014 and Zhong et al. 2018

C2 All included in C except Howard et al. 2007 and Webb et al. 2010

C3 Bitew et al. 2017, Di Prinzio et al. 2020, Howard et al. 2007, MacCabe et al. 2007, Mei-Dan et al. 2015, Navaratne et al. 2016, Nilsson et al. 2002, Vigod et al. 2014, Webb et al. 2006, Webb et al. 2010 and Weobong et al. 2014

Fig. 2 Summary of pooled odds ratios with 95% confidence intervals for studies included in the meta-analysis

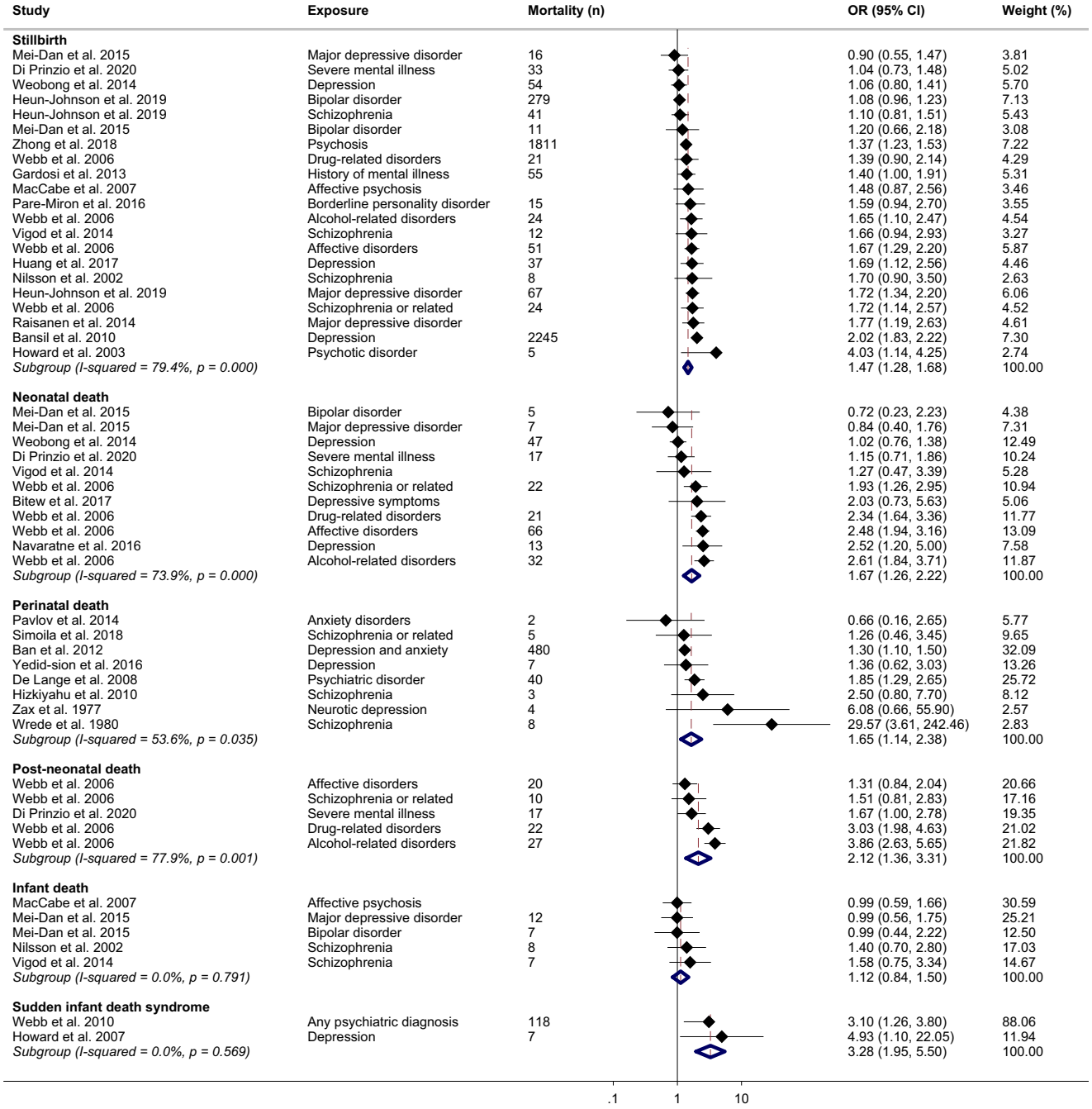


Fig. 3 Pooled odds ratios for the association between maternal prenatal mental health disorders, and stillbirth/infant mortality

for part of the association between maternal mental health disorders and perinatal morbidities and mortality. Women with mental health disorders tend to have poor health-seeking behaviour (late and less frequent antenatal care) (Ben-Sheetrit et al. 2018; Lin et al. 2009) and are more likely to misuse illicit substances, alcohol, and drugs, smoke tobacco, and have poor nutrition (Barker et al. 2013; Frayne et al. 2019; Judd et al. 2014; Teasdale et al. 2019; Weaver et al. 2003), all of which can have profound consequences for fetal development. Most prenatal mental disorders are likely to persist in the postnatal period and directly compromise the quality of essential parenting, which may contribute to the increased infant mortality risk (Chen et al. 2010). Recent evidence also indicates that some mental disorders and/or their medications increase the risk of pregnancy complications such as gestational diabetes and pre-eclampsia (Galbally et al. 2020; Qiu et al. 2009; Uguz 2017), which are key risk factors for perinatal morbidity and mortality (Hutcheon et al. 2011; Schmidt et al. 2001). However, the evidence about the association of mental disorders or antipsychotic treatments and

pregnancy complications is inconsistent and likely to include complex pathways (Vigod et al. 2015; Vigod et al. 2014). Collectively, these underscore the need for comprehensive support, care, and careful treatment for women with a mental health disorder.

Strengths and limitations

The strengths of this systematic review and meta-analysis are that it is based on a pre-published protocol and employed independent reviews and quality assessments on records obtained via electronic searches in multiple databases (supplemented with a manual search). To the best of our knowledge, this is the first systematic review and meta-analysis that has comprehensively evaluated the association between maternal prenatal mental health disorders and stillbirth or infant mortality—providing the most robust evidence to date on this topic.

The review does, however, have some limitations. Although a restriction was not imposed on the year of publication, electronic search results were limited to English language and hence relevant non-English studies could have been excluded. Relatively fewer studies were available with different maternal mental health disorders and assessments. This precluded us from a comprehensive investigation of the source of heterogeneity and publication bias. Most studies included in the systematic review did not adequately control for potential socioeconomic and lifestyle factors and, among those that did, there was variation in the choice of modelled covariates (Supplementary Table 1). In addition, there is always a possibility of residual confounding. However, a statistically significant association remained (albeit attenuated for severe maternal mental illness) in the meta-analysis, which included studies that adjusted for smoking. Additionally, one of the largest studies (Zhong et al. 2018) included in this systematic review demonstrated a significant association between maternal psychosis and stillbirth (OR, 1.37; 95% CI, 1.23–1.53) after adjustment for several factors including sociodemographic (age, race, and income) and lifestyle (smoking and alcohol/substance abuse) factors. The other limitation is that the studies included in the review did not examine or provide separate data for mentally ill mothers with and without psychotropic medications, so we could not evaluate the effect of the use of psychotropic drugs.

Implications

The findings of this review have important implications for public health, particularly given the high prevalence of maternal mental health problems (especially anxiety and depression) in populations worldwide. Efforts to prevent chronic and acute prenatal mental health disorders and treat those suffering from mental health disorders are likely to be critical in reducing the scale of stillbirth and infant mortality and the consequent grief experienced by families and communities. Focusing interventions on the earliest stages of family planning and prenatal period is important as many mental health problems are chronic at the time of conception (O'Hara and Wisner 2014). In terms of policy, holistic healthcare models, with a multidisciplinary approach, are preferable (Frayne et al. 2019; Galbally et al. 2013; Tachibana et al. 2019). Evidence-based treatments for women with severe mental illness, particularly depression, may reduce the rate of adverse birth outcomes, including perinatal and infant mortality, but this requires further investigation as the evidence in this area is conflicting (Ban et al. 2012; Jarde et al. 2016; Ross and Grigoriadis 2014). The fact that most of the studies included in this review were not designed to assess the associations of maternal prenatal mental health disorders and perinatal or infant mortality highlights the need for high-quality prospective cohort studies to better understand the issue.

Conclusions

The findings of this comprehensive systematic review and meta-analysis have demonstrated that women with prenatal mental health disorders are at a higher risk of perinatal and infant mortality, compared with women without prenatal mental health disorders, with consistent effects across a range of mental health disorders. Prenatal screening and access to treatment for mental health disorders with better and co-ordinated antenatal, obstetric, and psychiatric care may reduce the risk of perinatal and infant mortality. Further well-designed studies are required to better understand the nature of the problem, underlying mechanisms, and to confirm whether medical treatments for women with prenatal mental illness reduce perinatal and infant mortality.

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Authors' contributions AAA, HDB, and CCJS conceived and designed the study. AAA conducted the statistical analyses and drafted the manuscript. HDB, VAM, MG, BMF, RM, SWW, and CCJS participated in the analysis or interpretation of data. All authors critically revised the manuscript for methodological and intellectual content and have read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Consent to participate Not applicable.

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Code availability Not applicable.

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