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Association between anemia and maternal depression: A systematic review and meta-analysis

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ABSTRACT

Previous observational epidemiological studies have reported inconsistent findings regarding the association between anemia and the risk of maternal depression. In the present study, we investigated the relationship between anemia and the risk of maternal depression using a meta-analysis. We searched PubMed, EMBASE, and the bibliographies of relevant articles in May 2019. Three evaluators independently reviewed and selected the eligible studies based on the predetermined selection criteria. A random-effects model was employed to calculate meta-estimates of the association between anemia and maternal depression. Of the 1305 articles, 15 observational epidemiological studies (five case-control studies and 10 cohort studies) were included in the final analysis. A total of 32,792,378 women were included. Anemia was significantly associated with an increased risk of maternal depression in the random-effects meta-analysis of 15 studies (OR/RR: 1.53, 95% CI: 1.32–1.78). The association was consistent in both antepartum (OR/RR: 1.36, 95% CI: 1.07–1.72) and postpartum depression (OR/RR: 1.53, 95% CI: 1.32–1.78). Subgroup meta-analyses based on definition of anemia, definition of depression, and methodological quality reported consistent findings. The current meta-analysis showed that anemia was associated with an increased risk of maternal depression.

1. Introduction

Maternal depression is a serious mental illness that has a detrimental impact on both mother and child (Brummelte and Galea, 2016). Recent studies have reported that the prevalence of antepartum and postpartum depression is approximately 16% and 12%, respectively, although this varies depending on the diagnostic criteria of depression (Okagbue et al., 2019; Shorey et al., 2018). Maternal depression is more common in low and middle income countries: the prevalence of antepartum and postpartum depression in these countries is 25.3% and 19.0%, respectively. (Gelaye et al., 2016). In pregnant women, depression is associated with harmful health behaviors, such as alcohol and substance abuse, smoking, and poor nutrition, which lead to insufficient weight gain and inadequate prenatal care (Zuckerman et al., 1989). Moreover, depression may cause suboptimal fetal outcomes, such as preterm birth, low birth weight, and fetal growth restriction (Jarde et al., 2016; Lewis et al., 2016). Furthermore, depressive symptoms may continue in affected mothers after childbirth, causing impaired mother-child interaction and low cognitive function in the child (Kingsbury et al., 2015; McManus and Poehlmann, 2012a, 2012b).

Several risk factors of maternal depression have been proposed such as hormonal changes (fluctuations in estradiol levels, sustained high levels of glucocorticoids), psychosocial issues (stress, lack of social support), and nutritional factors (low level of serum vitamin D, magnesium, and zinc) (Brummelte and Galea, 2016; Etebary et al., 2010; Glynn et al., 2013; Razurel et al., 2013; Trujillo et al., 2018). In addition to these risk factors, some epidemiological studies have reported anemia as a potential risk factor (Albacar et al., 2011; Goshtasebi et al., 2013; Xu et al., 2018). In one study, the odds of postpartum depression were more than 4-fold higher among women with anemia (Goshtasebi et al., 2013). However, several studies have found no significant relationship between anemia and the risk of maternal depression (Chandrasekaran et al., 2018; Lukose et al., 2014). As inconsistent findings exist for the association between anemia and maternal depression, it is worthwhile determining whether anemia is a risk factor for maternal depression.

To our knowledge, no quantitative meta-analysis has been

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published on this topic. Thus, we investigated the association between anemia and the risk of maternal depression by carrying out a meta-analysis of observational epidemiological studies.

2. Materials and methods

2.1. Literature search

We searched PubMed and EMBASE databases using common keywords related to anaemia and maternal depression in May 2019. The keywords were as follows: “anemia” or “hemoglobin” for exposure factors; and “maternal” or “pregnancy” or “postpartum,” or “antepartum” and “depression” or “depressive mood” or “depressive symptoms” for outcome factors. Furthermore, we reviewed the bibliographies of relevant articles to locate additional papers. We tried to contact the authors to obtain more information if required.

2.2. Selection criteria

We included observational epidemiological studies that met all of the following criteria: (1) a case-control study or a cohort study; (2) investigated the association between anaemia and maternal depression; and (3) reported outcome measure with adjusted odds ratios (ORs) or relative risks (RRs) and 95% confidence intervals (CIs). If data were duplicated or shared in more than one study, we included the first published study. We excluded studies or abstracts that were not published in peer-reviewed journals or only presented in academic conferences. No restriction was applied to the language of publication.

2.3. Data extraction

Each of the authors (Kang SY, Sunwoo S, and Kim HB) independently evaluated the eligibility of all studies identified in the two databases. If any disagreements arose, these authors had a thorough discussion to resolve the issue. A standardized form was used to extract the following variables from the retrieved studies: first author name, publication year, type of study, country of study, duration of participant enrollment (in years), study population (age range and number of cases), definition of anemia, definition of depression, adjusted OR or RR and 95% CI as effect estimates, and confounding variables.

2.4. Assessment of methodological quality

We evaluated the methodological quality of the included studies using the Newcastle–Ottawa Scale (NOS), which assesses the quality of case-control and cohort studies in meta-analyses (Wells et al.). The scoring system of the NOS ranges from 0 to 9 and is based on three subscales: study selection, comparability, and exposure. As no established criteria was available to adjudge the quality of a study, we considered a study with more than a mean score assigned to each study type, as a high quality study.

2.5. Main and subgroup analyses

As our primary analysis, we investigated the association between anemia and the risk of maternal depression. We also performed subgroup analyses based on (1) study design type (case-control or cohort), (2) timepoint of maternal depression (antepartum or postpartum), (3) definition of anemia (based on hemoglobin level or others), (4) definition of depression (Edinburgh Postnatal Depression Scale [EPDS] score or others), (5) region (Asia, America, or Europe), (5) number of study participants (< 500 or ≥ 500), and (6) methodological quality (high or low).

2.6. Statistical analyses

We used the adjusted ORs or RRs and 95% CIs in each study to compute a pooled OR or RR with a 95% CI to report the association between maternal anemia and the risk of depressive mood. We evaluated heterogeneity across the studies by calculating the Higgins I2 (Higgins and Thompson, 2002) as follows:

$$I^2 = 100\% \text{ x } (Q\text{-}df)/Q$$

where Q is Cochran's heterogeneity statistic and df is the degree of freedom. The I^2 value ranges from 0% (no heterogeneity) to 100% (maximal heterogeneity). An I^2 value $> 50\%$ is considered to indicate substantial heterogeneity (Higgins and Thompson, 2002). In the present study, the pooled OR or RR with 95% CI was calculated using the DerSimonian and Laird method, which involves a random-effects model (DerSimonian and Laird, 1986). Publication bias was evaluated using Begg's funnel plot and Egger's test. When there is publication bias, Begg's funnel plot shows asymmetry, or Egger's test reports a p-value of < 0.05. All analyses were conducted using the Stata IC version 15.0 software package (StataCorp, College Station, Texas, USA).

3. Results

3.1. Identification of relevant studies

Fig. 1 is a flow diagram showing how relevant studies were identified. We found a total of 1305 studies from the two databases (PubMed and EMBASE) and by manually searching relevant bibliographies. We excluded 140 duplicate articles and an additional 1138 articles that did not meet the selection criteria. We completed a full text review of the remaining 27 articles. Among these, we excluded 12 articles for the following reasons: failure to report OR or RR with 95% CI ($n = 6$), review article ($n = 3$), intervention study ($n = 3$). The remaining 15 articles were included in the final analysis—five case-control studies (Alharbi and Abdulghani, 2014; Bansil et al., 2010; Lukose et al., 2014; Peppard et al., 2019; Räisänen et al., 2014) and 10 cohort studies (Albacar et al., 2011; Babu et al., 2018; Chandrasekaran et al., 2018; Eckerdal et al., 2016; Goshtasebi et al., 2013; Surkan et al., 2017; Tran et al., 2013; Vindhya et al., 2019; Woldetensay et al., 2018; Xu et al., 2018).

3.2. Characteristics of studies included in the final analysis

Table 1 shows the general characteristics of the studies included in the final analysis. A total of 15 studies published between 2010 and 2019 were included. The total number of participants was 32,792,348 women, with 257,984 of these having depression. In the studies that reported age, the mean age of the participants ranged from 22.6 to 34.8 years. Eight studies evaluated antepartum depression (Babu et al., 2018; Bansil et al., 2010; Lukose et al., 2014; Peppard et al., 2019; Räisänen et al., 2014; Tran et al., 2013; Vindhya et al., 2019; Woldetensay et al., 2018), while seven evaluated postpartum depression (Albacar et al., 2011; Alharbi and Abdulghani, 2014; Chandrasekaran et al., 2018; Eckerdal et al., 2016; Goshtasebi et al., 2013; Surkan et al., 2017; Xu et al., 2018). The studies were conducted in the following countries: India ($n = 3$) (Babu et al., 2018; Lukose et al., 2014; Vindhya et al., 2019), United States ($n = 2$) (Bansil et al., 2010; Peppard et al., 2019), Australia ($n = 1$) (Xu et al., 2018), Bangladesh ($n = 1$) (Surkan et al., 2017), Canada ($n = 1$) (Chandrasekaran et al., 2018), Ethiopia ($n = 1$) (Woldetensay et al., 2018), Finland ($n = 1$) (Räisänen et al., 2014), Iran ($n = 1$) (Goshtasebi et al., 2013), Saudi Arabia ($n = 1$) (Alharbi and Abdulghani, 2014), Spain ($n = 1$) (Albacar et al., 2011), Sweden ($n = 1$) (Eckerdal et al., 2016), and Vietnam ($n = 1$) (Tran et al., 2013). All included studies were written in English.

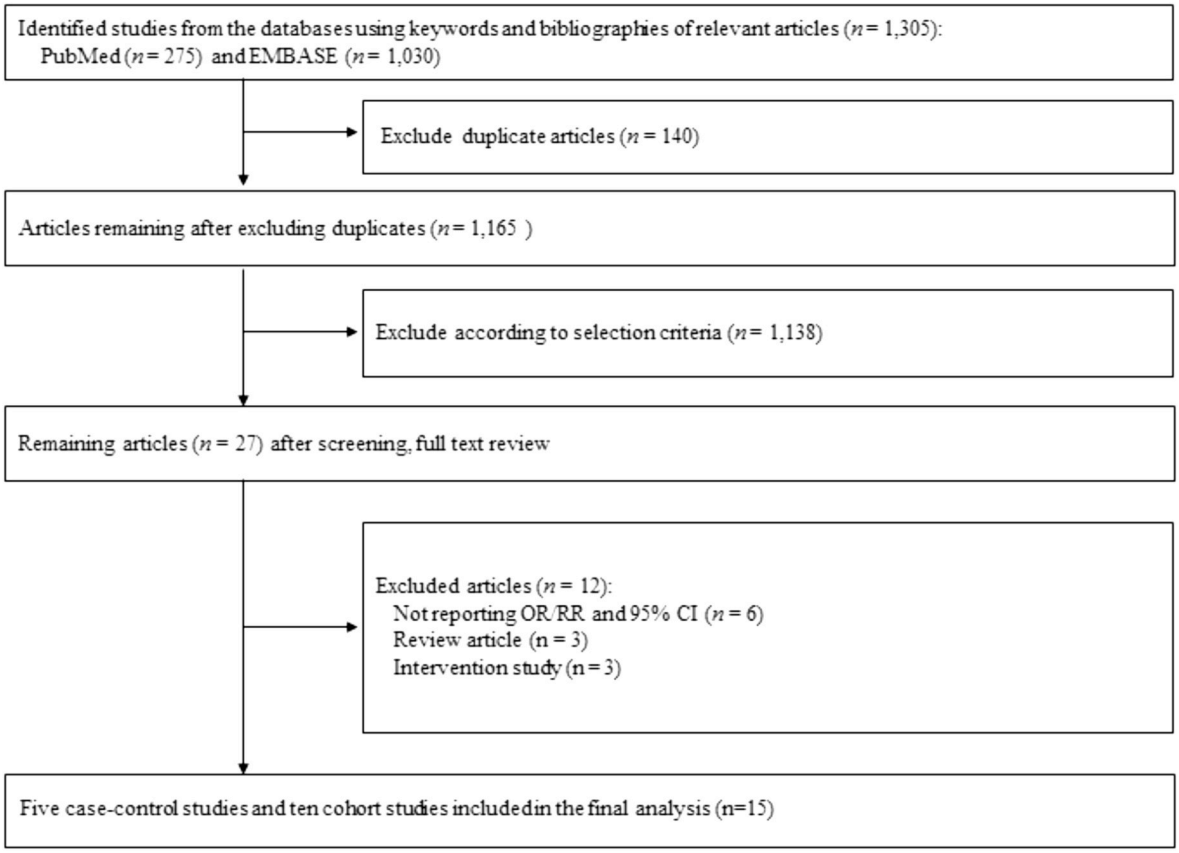

Fig. 1. Flow diagram for identifying relevant studies.

3.3. Methodological quality of studies

Table 2 shows the methodological quality of the included studies based on the NOS. The quality score ranged from 4 to 8, and the average score was 6 for case-control studies and 6.5 for cohort studies. Two case-control studies and 5 cohort studies (score of > 6) were considered high quality.

3.4. Anemia and maternal depression

As shown in Fig. 2, anemia was significantly associated with an increased risk of maternal depression in this random-effects meta-analysis of 15 studies (pooled OR/RR = 1.53, 95% CI 1.32–1.78). In the subgroup analyses based on study design, cohort studies reported that anemia had a significant positive effect on maternal depression (pooled OR/RR = 1.64, 95% CI: 1.34–2.00); however, case-control studies showed no significant association between anemia and maternal depression (pooled OR/RR = 1.36, 95% CI 0.98–1.90).

Table 3 shows the findings of the subgroup meta-analyses based on various factors. Anemia was associated with an increased risk of both antepartum (OR/RR = 1.36, 95% CI: 1.07–1.72) and postpartum depression (OR/RR = 1.53, 95% CI: 1.32–1.78). Furthermore, anemia was consistently associated with an increased risk of maternal depression in the subgroup meta-analyses based on definition of anemia, definition of depression, and methodological quality. The subgroup meta-analysis based on the number of study participants reported a significant association when the number of the participants was ≥500 (OR/RR = 1.67, 95% CI: 1.42–1.96); however, no significant association was observed when the number of the participants was < 500. Furthermore, the subgroup meta-analysis based on region reported a significant association in Asia (OR/RR = 1.36, 95% CI: 1.03–1.78) and Europe (OR/RR = 2.16, 95% CI: 1.22–3.81), but not in America. Moreover, a much stronger association was observed within Europe than within other continents.

3.5. Publication bias

Neither Begg's funnel plot test nor Egger's test showed any publication bias. (Begg's funnel plot was symmetric; Egger's test, p for bias = 0.70; not shown in Figure).

4. Discussion

In this meta-analysis of observational epidemiological studies, we found that anemia was associated with an increased risk of maternal depression. Subgroup meta-analyses based on the timepoint of maternal depression, definition of anemia, definition of depression, and methodological quality demonstrated similar findings.

Previous epidemiological studies carried out in different populations have reported a potential link between anemia and depression. Furthermore, the relationship has been observed in both healthy individuals and those with comorbidities (Bergis et al., 2019; Vulser et al., 2016). Both adolescents and the elderly tend to experience depressive mood when they have anemia, and this association is consistent across countries (Chen et al., 2013; Onder et al., 2005; Trevisan et al., 2016), and recent studies have reported an association between anemia and other mental disorders, including schizophrenia and cognitive impairment, implying that iron plays a role in brain regulation (Chen et al., 2013; Dlugaj et al., 2016; Kim et al., 2018).

Several plausible biological mechanisms have been posited to explain the link between anemia and depression. Dopamine is a brain neurotransmitter that helps regulate emotional responses. Iron deficiency alters dopamine metabolism by downregulating dopamine receptor-1 expression and reducing dopamine transporter density

Table 1
General characteristics of the studies included in the final analysis.

Study (reference)	Type of study	Country	Years enrolled (follow-up duration)	Population	Definition of anemia	Definition of depression	OR/RR (95% CI)	Adjusted variables
Bansil et al. (2010)	Case-control study	United States	1998–2005	32,156,438 women (244,939 cases and 31,911,499 controls) aged 15–44 years with delivery hospitalization drawn from NIS data	ICD-9-CM codes: 648.2, 280–285	ICD-9-CM codes: 296.2, 296.3, 300.4, 311, 298.0, 309.0, 309.1	1.81 (1.73–1.89)	Age, insurance status, location, region
Albacar et al. (2011)	Prospective cohort study	Spain	2003–2004 (32 weeks)	729 Spanish-origin (Caucasian) women aged > 18 years	Ferritin < 7.26 μg/L	A score of ≥9 on the EPDS	3.73 (1.84–7.56)	Employment status, transferrin saturation, CRP
Goshtasebi et al. (2013)	Prospective cohort study	Iran	2009 (6 weeks)	254 primipara women aged 18–35 years with normal BMI and singleton pregnancy	Hb < 11 g/dL	A score of ≥13 on the EPDS	4.64 (1.33–16.08)	Age, educational level, type of delivery, newborn's sex, gestational age at delivery
Tran et al. (2013)	Prospective cohort study	Vietnam	2009–2010 (8–16 weeks)	378 women	Hb < 11 g/dL	A score of ≥4 on the EPDS	1.09 (0.76–1.56)	Unclear
Alharbi and Abdulghani (2014)	Hospital-based case-control study	Saudi Arabia	2013	352 postpartum females (117 cases and 235 controls) from 19 to 47 years	Hb < 11 g/dL	A score of ≥10 on the EPDS	1.70 (1.05–2.74)	Age, education level, occupation, obstetric history variables, past psychiatric history
Lukose et al. (2014)	Hospital-based case-control study	India	2008–2010	365 women (121 cases and 244 controls) aged between 18 and 40 years	Hb < 11 g/dL	A score of ≥6 on the Kessler Psychological Distress Scale (K-10)	0.67 (0.47–0.96)	Education, nausea, vomiting
Raisanen et al. (2014)	Case-control study	Finland	2002–2010	511,938 women (4120 cases and 507,818 controls) with singleton births from the Finnish Medical Birth Register	Hb ≤ 100 g/L	ICD-10 codes: F31.3, F31.5, F32–34	1.49 (1.22–1.81)	History of depression prior to pregnancy, maternal age, parity, smoking status, marital status, SES, prior miscarriages, prior terminations, IVF, gestational diabetes, pre-existing diabetes, fear of childbirth, fetal sex
Eckerdal et al. (2016)	Nested cohort study	Sweden	2006–2007 2009–2012	446 women (168 from UPPSAT and 278 from BASIC)	Hb < 110 g/L	A score of ≥12 on the EPDS	2.29 (1.15–4.58)	Previous psychological contact, mood during pregnancy, lack of exclusive breastfeeding at 6 weeks postpartum
Surkan et al. (2017)	Retrospective cohort study	Bangladesh	2001–2007	39,434 married women aged 13–44 years who participated, during pregnancy and the early postpartum period, in the JiVitA-1 trial and gave birth to singletons	Both symptoms present in the past 30 days: (1) breathlessness at rest, and (2) weakness resulting in an inability to work	≥3 symptoms on a five-item scale based on items modified from PHQ-9 and CES-D	1.38 (1.31–1.46)	Age, parity, education, living standard index, religion, all maternal illnesses (reproductive tract infection, uterine prolapse, urinary tract infection, SRI and CDU, severe headache, convulsions, night blindness, pneumonia, gastroenteritis, hepatobiliary disease), village cluster, vitamin supplementation group
Babu et al. (2018)	Nested cohort study	India	2013–2015	823 pregnant women aged 18–40 years with a gestational age of 14–24 weeks	Hb < 11 g/dL	A score of ≥20 on the Kessler Psychological Distress Scale (K-10)	1.92 (1.17–3.15)	Age, gestational age, parity
Chandrasekaran et al. (2018)	Prospective cohort study	Canada	(6 weeks)	103 women ≥ 18 years of age, with a full term, singleton pregnancy undergoing elective Caesarean section	Hb quartile 1 before c/section	A score of ≥10 on the EPDS	0.44 (0.08–1.74)	Age, parity, prenatal vitamins, breastfeeding at week 6
, Peppard et al., 2019	Case-control study	United States	2005–2006	174 pregnant women	Hb < 12 g/dL	A score of ≥10 on the PHQ-9	1.60 (0.45–5.70)	Serum vitamin B12, age, ethnicity, education, marital status, poverty ratio, food security, pre-pregnancy BMI, folate

(*continued on next page*)

Table 1 (*continued*)

Study (reference)	Type of study	Country	Years enrolled (follow-up duration)	Population	Definition of anemia	Definition of depression	OR/RR (95% CI)	Adjusted variables
Woldetensay et al. (2018)	Prospective cohort study	Ethiopia	2014–2016 (1 year)	4680 pregnant women between 12 and 32 weeks of gestation	Hb < 11 g/dL	A score of ≥8 on the PHQ-9	1.30 (1.04–1.61)	Age, religion, marital status, education, family size, address, household food insecurity, mid-upper arm circumference, chat chewing, maternal social support, intimate partner violence
Xu et al. (2018)	Retrospective cohort study	Australia	2004–2008	75,954 women who gave birth to their first child in New South Wales between Jan 2004 and Dec 2008	ICD-10-AM diagnosis codes: (1) D50–D53 nutritional anemia, (2) D55–D59 hemolytic anemia, (3) D60–D64 aplastic and other anemia, (4) O99.0 anemia complicating pregnancy, childbirth and the puerperium	ICD-10-AM diagnosis codes: (1) F32–F33 depressive disorder, (2) F53 mental and behavioral disorders associated with the puerperium	2.01 (1.70–2.38)	Maternal age, maternal country of birth, maternal diabetes mellitus and hypertension, gestational diabetes, smoking status during pregnancy, remoteness of living are, delivery method, gestational age, baby's death, place of birth, socioeconomic indicators
Vindhya et al. (2019)	Nested cohort study	India	2017–2018	280 women above the age of 18 years	Hb < 11 g/dL	EPDS (does not report the cut-off)	1.62 (0.97–2.70)	Age, religion, education, occupation, socio-economic status, obstetric factors, PRAQ scores, BMI

Abbreviations: OR, odds ratio; RR, relative ratio; CI, confidence interval; NIS, nationwide inpatient sample; ICD, international classification of diseases; CM, clinical modification; EPDS, Edinburgh Postnatal Depression Scale; CRP, c-reactive protein; BMI, body mass index; Hb, hemoglobin; SES, socioeconomic status; IVF, *in vitro* fertilization; PHQ-9, patients health questionnaire-9; CES-D, center for epidemiologic studies depression scale; SRI, stress-related incontinence; CDU, continuously dripping urine; AM, Australian modification; PRAQ, pregnancy-related anxiety questionnaire.

(Erikson et al., 2001; Kim and Wessling-Resnick, 2014). Furthermore, since iron is a cofactor for rate-limiting enzymes in norepinephrine and serotonin synthesis, iron deficiency may alter norepinephrine and serotonin signaling, which may in turn contribute to changes in emotions (Kim and Wessling-Resnick, 2014). Attenuated glutamatergic signaling, altered GABA metabolism, and metal-mediated oxidative stress combined with decreased iron concentration influence emotional changes (Kim and Wessling-Resnick, 2014; Rao et al., 2003). In addition, iron deficiency is associated with decreased cytochrome C levels, which is one mechanism of depression pathogenesis (Mu et al., 2007; Siddappa et al., 2002). Taken together, it is clear that brain iron status influences emotional behaviors and mental health by altering neurotransmitter homeostasis and monoamine metabolism.

Women of a reproductive age, especially during pregnancy and in the postpartum period, experience fluctuations in steroid and peptide hormones. This plays a significant role in depression. For instance, estradiol levels gradually rise during the third trimester of pregnancy, but suddenly fall after birth (Bloch et al., 2003), leading to estradiol withdrawal and contributing to depression. Furthermore, women during pregnancy and in the postpartum period show sustained high levels of glucocorticoids, much like depressive patients (Glynn et al., 2013). Combined with these changes in hormone levels, iron deficiency may increase patients' vulnerability to depressive mood during the antepartum and postpartum periods.

The study of Peppard et al. categorized hemoglobin as either < 12 g/dL or ≥12 g/dL, which was a higher cut-off than in other studies; this may have influenced overall outcome (Peppard et al., 2019). The World Health Organization defines anemia as a hemoglobin level < 11 g/dL in the first trimester, < 10.5 g/dL in the second trimester, and < 10 g/dL postpartum. These definitions vary during pregnancy and the postpartum period because there is a discrepancy between the increase in plasma volume (50%) and the increase in red blood cell count (25%) (World Health Organization, 2001). Future research should use a hemoglobin level cut-off that is appropriate to the pregnancy period. Furthermore, Chandrasekaran et al. mentioned that the biological association between postpartum depression and anemia may be due to iron deficiency, rather than to low hemoglobin levels (Chandrasekaran et al., 2018). Plausible mechanisms for the association between iron deficiency and depression already exist in the literature, so the role of iron in maternal psychology should be addressed in future research.

Two of the 15 included studies (Chandrasekaran et al., 2018; Lukose et al., 2014) show a potentially protective effect of anemia on maternal depression. In Chandrasekaran's study, a potential selection bias could exist as only 103 out of the 248 study participants completed the planned follow-up. There is a possibility that the women who did not complete follow-up might have postpartum depression. Furthermore, the authors addressed that the incidence of anemia was lower in the study population, thereby limiting the ability to detect significant effects. As for the study by Lukose et al., the Kessler Psychological Distress Scale (K-10) score for depression is much lower compared with Babu et al.'s study, which may have caused the opposite outcome from other studies.

Currently, the recommendations regarding iron supplementation during pregnancy vary across countries. The American College of Obstetrics and Gynecology recommends iron supplementation if iron deficiency anemia is identified (American College of Obstetricians and Gynecologists, 2008), while the British Committee for Standards in Hematology recommends iron supplementation if the patient's serum ferritin level is < 30 μg/L (Pavord et al., 2012). On the contrary, the World Health Organization recommends universal iron supplementation of 30–60 mg/day (World Health Organization, 2016). One recent randomized double-blind placebo-controlled trial reported that early iron supplementation in mothers with postpartum depression significantly improved both iron stores and depressive mood (Sheikh et al., 2017). If new evidence emerges regarding the association between

Table 2
Methodological quality of the studies included in the final analysis based on the Newcastle–Ottawa Scale[a] for assessing the quality of case-control and cohort studies.

Case-control studies (n = 5)	Selection				Comparability (control for important factors or additional factor)	Exposure			Total
	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls		Ascertainment of exposure (blinding)	Same method of ascertainment for participants	Non-response rate	
Alharbi and Abdulghani (2014)	1	1	0	1	0	1	1	0	5
Bansil et al. (2010)	1	1	1	0	1	1	1	0	6
Raisanen et al. (2014)	1	1	1	0	2	1	1	0	7
Lukose et al. (2014)	1	1	0	0	1	1	1	0	5
Peppard et al. (2019)	1	1	1	0	2	1	1	0	7
Cohort studies (n = 9)	**Selection**				**Comparability (control for important factors or additional factor)**	**Outcome**			**Total**
	Representative-ness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Chandrasekaran et al. (2018)	1	1	1	1	1	1	0	0	6
Surkan et al. (2017)	1	1	1	1	2	1	0	0	7
Eckerdal et al. (2016)	1	1	1	1	1	1	0	0	6
Goshtasebi et al. (2013)	1	1	1	1	2	1	0	1	8
Xu et al. (2018)	1	1	1	1	2	1	0	1	8
Albacar et al. (2011)	1	1	1	1	1	1	0	1	7
Tran et al. (2013)	1	1	1	1	0	1	0	0	5
Vindhya et al. (2019)	1	1	1	1	0	0	0	0	4
Woldetensay et al. (2018)	1	1	1	1	2	1	0	1	8
Babu et al. (2018)	1	1	1	1	1	1	0	0	6

[a] Each study can be awarded a maximum of one star for each numbered item within the selection and exposure categories, while a maximum of two stars can be given for the comparability category.

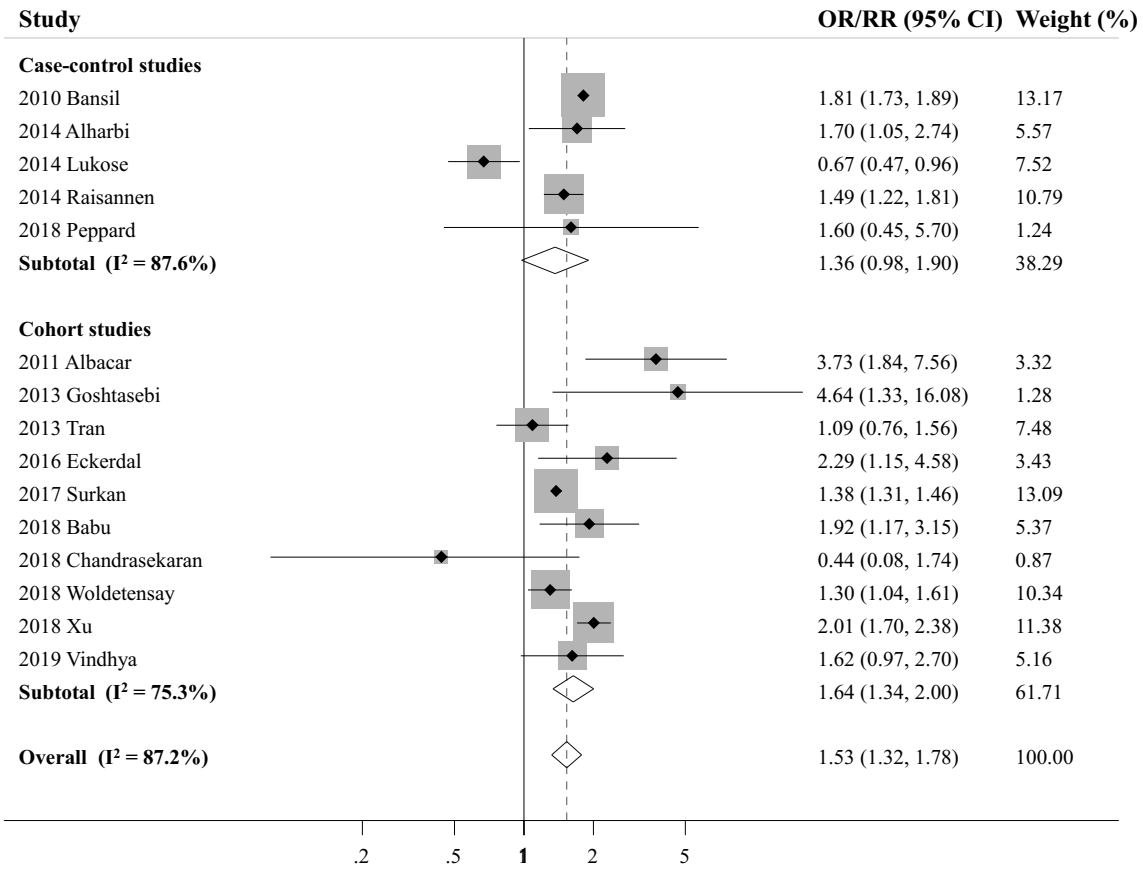

Fig. 2. Association between anemia and maternal depression in a meta-analysis of observational epidemiological studies (n = 15).

anemia and the risk of maternal depression, the recommendations surrounding iron supplementation in pregnant women could be modified.

The current study was the first quantitative meta-analysis to report the association between anemia and risk of maternal depression. In addition, our meta-analysis included research from several regions. Despite these strengths, there were several limitations. Firstly, we were unable to include randomized controlled trials because no published examples were found. Secondly, the definitions of exposure variable and outcome variable varied among the included studies. Most studies defined anemia based on the hemoglobin level, although several studies defined anemia using ferritin level, symptoms, or the ICD code. Furthermore, most studies defined maternal depression using the EPDS; however, other studies used the Kessler Psychological Distress Scale, the PHQ-9, or the ICD code. This discrepancy in the definition of the main variables among studies may have influenced the final analyses. Furthermore, subgroup analyses based on various factors failed to overcome this heterogeneity. Thirdly, most cohort studies assessed

Table 3
Association between anemia and the risk of maternal depression in the subgroup meta-analyses based on various factors.

Factors	Number of studies	Summary OR/RR (95% CI)	Heterogeneity, I^2, %	Model used
All	15	1.53 (1.32–1.78)	87.2	Random-effects
Timepoint of maternal depression				
Antepartum	8	1.36 (1.07–1.72)	84.9	Random-effects
Postpartum	7	1.53 (1.32–1.78)	81.4	Random-effects
Definition of anemia				
Hb level	11	1.38 (1.10–1.74)	65.1	Random-effects
Others	4	1.80 (1.45–2.24)	95.6	Random-effects
Definition of depression				
EPDS score	7	1.80 (1.20–2.69)	63.6	Random-effects
Others	8	1.47 (1.24–1.74)	92.4	Random-effects
Region				
Asia	7	1.36 (1.03–1.78)	74.7	Random-effects
America	3	1.45 (0.76–2.77)	38.9	Random-effects
Europe	3	2.16 (1.22–3.81)	71.4	Random-effects
Number of participants				
< 500	8	1.36 (0.91–2.03)	70.2	Random-effects
≥ 500	7	1.67 (1.42–1.96)	91.9	Random-effects
Methodological quality				
High quality	7	1.65 (1.35–2.02)	79.2	Random-effects
Low quality	8	1.39 (1.01–1.92)	82.6	Random-effects

AbbreviationsOR, odds ratio; RR, relative ratio; CI, confidence interval; Hb, hemoglobin; EPDS, Edinburgh Postnatal Depression Scale.

anemia once, but anemia status can fluctuate over time for various reasons. This may question the accuracy of the causal relationship of anemia on maternal depression. Fourthly, it is unclear what specific type of anemia is involved in maternal depression. Most studies did not evidently demonstrated the type of anemia investigated. Fifthly, proximal factors were not entirely adjusted in the present study. For example, sleep problems may be a known risk factor for pregnancy-related depression (Eichler et al., 2019), but none of the included studies have adjusted for it. Lastly, we did not include unpublished work, including abstracts, which could have led to publication bias.

In addition, future research is needed to examine the risks of maternal depression of persons with treated and untreated anemia, and the duration of exposure to anemia that poses a risk of maternal depression.

5. Conclusion

In conclusion, the current meta-analysis of observational epidemiological studies showed that anemia was associated with an increased risk of maternal depression in both the antepartum and postpartum periods. Further larger prospective cohort studies providing continuous and convincing measurements of anemia with all possible adjusting factors should be conducted to confirm the link between anemia and perinatal depression.

Author contributions

Hong-bae Kim designed the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Seo Young Kang, Hong-bae Kim, and Sung Sunwoo managed the literature searches and undertook the data acquisition. Seo Young Kang and Hong-bae Kim performed statistical analysis. Seo Young Kang wrote the manuscript. Seo Young Kang, Hong-bae Kim, and Sung Sunwoo critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Declaration of competing interest

None.

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