Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis


INTRODUCTION

Anemia remains a significant health problem globally, accounting for 60,534 deaths and 3.4% of global disability-adjusted life years (DALYs) in 2010 in women aged 15–49 y (1). The majority of DALYs that are due to anemia occur in low-income countries, particularly in South Asia (5.7% of DALYs in women) and Sub-Saharan Africa (3.9% of DALYs in women) (1). In high-income countries, 16% of women and 22% of pregnant women had anemia in 2011 (2). Rates of anemia are highest in low-income countries, especially in Central and West Africa (48% of reproductive-age women and 56% of pregnant women) and in South Asia (47% of reproductive-age women and 52% of pregnant women) (2). Despite achievements in maternal and child health-related programs over the past decade (3–6), anemia remains a key health problem in pregnant women in low- and middle-income countries (2, 7, 8). The principal causes of anemia are poor nutrition (iron, folic acid, and vitamin deficiencies), infectious diseases such as malaria, and untreated genetic hemoglobin disorders (7–12). Anemia during pregnancy may cause low birth weight, preterm birth, and perinatal, neonatal, and maternal mortality (13, 14), although findings on these risks have not been consistent, and systematic reviews are lacking for low- and middle-income countries. In the most-comprehensive review currently available, Haider et al. (13) compared risk of low birth weight and preterm birth in low- or middle-income countries combined with high-income countries. However, the review did not stratify results by country-income categories or regions for

1 Supplemental Protocol, Supplemental Figures 1–8, and Supplemental Tables 1–10 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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small-for-gestational-age and preterm births. Previous meta-analyses have not comprehensively studied the association between maternal anemia and adverse pregnancy outcomes by both geographic region and national income category despite the wide variation in anemia burden within and between regions and national income categories (1, 2). To our knowledge, no previous study has estimated the population-attributable fraction (PAF) of adverse pregnancy outcomes for maternal anemia. An understanding of these outcomes, the current trends in maternal anemia, and the association of maternal anemia with adverse pregnancy outcomes at the regional level and stratified by income is essential to inform policies and program development to prevent maternal anemia and improve maternal and child health outcomes.

In this study, we aimed to conduct a systematic review with a meta-analysis of published cohort studies of low birth weight, preterm birth, small for gestational age, perinatal mortality, neonatal mortality, gestational diabetes, preeclampsia, and mode of delivery according to maternal anemia status in low- and middle-income countries. To assess the role of maternal anemia at the population level, we estimated the PAF for selected adverse pregnancy outcomes for maternal anemia. In addition, we estimated the pooled prevalence of maternal anemia by geographic region, national income category, and year with the use of available Demographic and Health Survey data.

METHODS

Search strategy

This review was undertaken according to the protocol established in the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (15). With the help of a librarian, we searched PubMed, EMBASE, CINAHL, and British Nursing Index databases (Supplemental Tables 1–4) for studies concerning maternal anemia and risk of pregnancy and maternal and newborn health outcomes published between 1966 and February 2014 initially and updated in May 2015. Our search strategies consisted of a combination of free-text words, words in titles and abstracts, and Medical Subject Headings for exposure, participants, and study designs. The detailed search strategies and initial and updated search results for PubMed, EMBASE, CINAHL, and the British Nursing Index are presented in Supplemental Tables 1–4. Additional eligible studies on anemia and birth or health outcomes were sought by reviewing the reference lists of identified articles and searching relevant journals related to our search topic. We did not apply any language restrictions during the search. We defined low- and middle-income countries according to World Bank criteria in 2013 (16).

Study selection

In the screening and article selection, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (17). Two reviewers (MMR and MSR) independently screened titles and abstracts and critically reviewed the full texts of all selected studies on the basis of the inclusion and exclusion criteria. Studies were included if they were cohorts (prospective or retrospective) with pregnant women aged ≥15 y as subjects. We included studies that examined maternal hemoglobin, hematocrit, or anemia status measured in the first or second trimester during pregnancy and pregnancy and perinatal outcomes. Anemia was defined as the exposure variable with hemoglobin concentrations <11 g/dL or hematocrit <33% (18). We included studies that reported any hemoglobin or hematocrit cutoffs. Birth and health outcomes including preterm delivery (defined as a birth before 37 wk of gestation), low birth weight (defined as weight <2500 g), small for gestational age (defined as birth weight below the sex-specific 10th percentile of the gestational age), perinatal mortality [defined as deaths including death of a fetus >22 wk of gestation (stillbirth)], early neonatal mortality (<7 d of life), neonatal mortality (defined as death of a neonate in the first month of life), gestational diabetes, preeclampsia, and cesarean delivery were included in our studies. We excluded cross-sectional and case-control studies because these trials do not allow for the assessment of the temporal association between exposure and outcome. Studies that considered high-risk subjects with HIV, AIDS, heart disease, or diabetes at baseline were not included in our review. A small sample size may introduce bias in the estimation of an effect size; therefore, we excluded studies if they recruited <100 subjects (19). Details of the inclusion and exclusion criteria and definitions of exposure and outcomes variables are presented in the Supplemental Protocol.

Data extraction and quality assessment

Two authors (MMR and MSR) independently extracted data on the country and year of the study, the study design, participants, exposures, the time of exposure assessment, outcomes, confounders, and measures of an association. We did not find any foreign-language articles that needed to be translated into English. We resolved any inconsistency through a consensus process. We used a specific checklist to assess the methodologic quality of all included cohort studies with the use of the Newcastle–Ottawa Scale recommended by Wells et al. (20).

Data analyses

RR was used as the common outcome measure in observational studies. We converted ORs into RRs according to the proposed methodology of Zhang (21, 22) when the incidence of an outcome was common (>10%) in the study population. If the RR or OR was unavailable, we estimated the unadjusted RR and 95% CI from raw data. We used fixed-effect (Mantel-Haenszel method) (23) or random-effect (DerSimonian-Laird method) (24) models for calculating summary estimates for the effects of maternal anemia with the model choice made on the basis of heterogeneity ($I^2$ statistic) assessments. An $I^2$ value refers to the percentage of total variation across studies that was due to between-study heterogeneity. Fixed-effects models were performed for $I^2 \leq 25\%$, and random-effects models were performed for $I^2 > 25\%$ (25). Prediction intervals were estimated on the basis of $\tau$ when the random model was used because of the presence of heterogeneity and a minimum of 3 studies. We presented summary estimates according to WHO thresholds for anemia and according to the definitions used in the original studies separately. Publication bias and biases related to a small sample size and reporting bias were assessed with the use of the regression
asymmetry test of Egger (26). In addition, we performed trim-
and-fill procedures to further evaluate possible effects of pub-
llication bias in the meta-analyses (27).

We investigated sources of heterogeneity through subgroup
and metaregression analyses (28) according to the study design
(prospective compared with retrospective), sample size above
or below the median observed sample size (≤800 compared
with >800), confounding factors (adjusted compared with un-
adjusted), country-income category, study location (South Asia
(Bangladesh, India, Nepal, Pakistan, India, and Sri Lanka), East-
West Asia (China, Malaysia, Iran, and Turkey), or Africa and
South America (Malawi, Tanzania, Ghana, and Peru), and mean
maternal age above or below the median from all studies (≤26
compared with 826 y). We undertook sensitivity analyses to
determine differences in summary effects by dropping a small
number of studies that we defined as highly influential on the
basis of variance and weight estimates from the meta-analysis.
We calculated the PAF for birth outcomes that were due to
anemia with the use of estimates obtained from the meta-analysis
on the assumption that attributable risk arises from any as-
soect and not only a causal relation. The PAF was cal-
culated on the basis of the pooled RR of pregnancy outcomes
and the proportion (P) of maternal anemia during pregnancy
as follows:

\[
P A F = \frac{P (R R - 1)}{1 + P (R R - 1)}
\]

The pooled prevalence of anemia by region and country-
icome level was estimated with the use of a random-effects
meta-analysis and available Demographic and Health Survey data
sets across 23 developing countries. We used the Freeman-Tukey
transformation method to estimate the pooled prevalence of
anemia (29). We used Stata version 12.1/MP software (StataCorp
LP) for all analyses.

RESULTS

Our search identified 8182 records from inception to May 2015
of which 7987 records remained after the removal of duplicates
(Figure 1). On the basis of title and abstract screening, 99
records were considered potentially eligible from databases. An
additional 6 articles were identified from reference lists and
hand searches. In total, 105 full-text articles were reviewed. In
this full-text screening, 74 articles were further excluded be-
cause of small sample sizes (<100 subjects), different study
designs (case-control, cross-sectional, and secondary data anal-
yses), nonresearch materials, hemoglobin measured only at the
third trimester during pregnancy, and high-risk populations,
which left 31 articles (Figure 1). Two articles were based on
overlapping data from the same cohort in China (30, 31). In
addition, 2 articles used the same data source in Pakistan (32,
33). To avoid the duplicate inclusion of data, we merged out-
comes and treated each of these pairs of studies as one study
(which left 29 studies in the systematic review). Of these 29
studies, 3 studies were dropped from the meta-analysis because
the articles did not assess health outcomes according to anemia
thresholds (34–36). This exclusion left 26 studies for the meta-
analysis.

Study characteristics

Of 29 studies, 12 studies were conducted in South Asia, 13
studies were conducted in East-West Asia, and 4 studies were
conducted in the African and South American regions (Sup-
plemental Table 5). Twenty-four articles included prospective
cohorts, and 5 articles were retrospective cohort studies. The
selected studies were published between 1994 and 2014. The
number of subjects per study ranged from 253 to 399,274 with
a total of ~0.72 million pregnant women with a mean age that
ranged from 20 to 30 y. In the 29 studies, 18 studies reported
low-birth-weight, 15 studies reported preterm birth, 12 studies
reported perinatal mortality, 5 studies reported small-for-
gestational-age, 3 studies reported gestational diabetes, 4 studies
reported preeclampsia, 2 studies reported neonatal mortality, 2
studies reported cesarean delivery, and one study reported still-
birth outcomes (Supplemental Table 5). All studies were of high
quality (Supplemental Table 6).

Pooled and sensitivity analysis

The pooled RR, publication bias, and trim-and-fill estimates
across all studies are presented in Table 1. Risk of low birth
weight was significantly higher in anemic pregnant women
during the first or second trimester than in the nonanemic group
(RR: 1.31; 95% CI: 1.13, 1.51; \( I^2 = 66\% \); 17 studies). We
showed significantly greater risk of preterm birth (RR: 1.63;
95% CI: 1.33, 2.01; \( I^2 = 88\% \); 13 studies), perinatal mortality
(RR: 1.51; 95% CI: 1.30, 1.76; \( I^2 = 0\% \); 12 studies), and neo-
natal mortality (RR: 2.72; 95% CI: 1.19, 6.25; \( I^2 = 0\% \); 2
studies) in our study. However, when we calculated 95% pre-
diction intervals, the associations become insignificant between
anemia and risk of low birth weight, preterm birth, and small for
gestational age (Supplemental Figure 1). Anemia during the
first or second trimester was also not significantly associated
with small for gestational age (RR: 0.87; 95% CI: 0.63, 1.20;
\( I^2 = 20\% \); 2 studies), gestational diabetes (RR: 1.02; 95% CI:
0.86, 1.21; \( I^2 = 20\% \); 2 studies), preeclampsia (RR: 2.66; 95%
CI: 0.61, 11.52; \( I^2 = 0\% \); not applicable; one study), or cesarean
delivery (RR: 1.68; 95% CI: 0.76, 3.72; \( I^2 = 0\% \); not applicable;
one study). Our narrative review showed mixed results for maternal
anemia and preeclampsia. One study indicated that a hemoglobin
concentration >13.2 g/dL during the first trimester was signifi-
cently associated with preeclampsia (OR: 1.73; 95% CI: 1.07,
2.81). However, 2 other studies showed that low concentra-
tions of hemoglobin during pregnancy were associated with
preeclampsia (\( P < 0.01 \)) (Supplemental Table 7) (34, 36). To
account for any form of publication bias, we performed a sen-
sitivity analysis with the use of the trim-and-fill method and
showed a negligible effect on the results from the inclusion of
possible imputed negative or small sample-size studies (Table
1). In the sensitivity analysis, low birth weight, preterm birth,
and perinatal mortality remained risks in anemic women after
highly influential studies were dropped (Supplemental Figures
2–4). In addition, we calculated pooled estimates of birth and
health outcomes according to the definition of anemia on the basis
of individual study definitions of anemia and showed almost
similar results when we considered only WHO thresholds for
anemia (Supplemental Figures 5–7). Furthermore, we calcu-
lated another sensitivity analysis of pregnancy outcomes after
dropping studies that reporting ORs, and pooled estimates of low birth weight, preterm birth, and perinatal mortality showed similar results to those in the analysis with the OR conversion (Supplemental Table 8).

**Stratified analyses**

The study showed moderate heterogeneity in the low-birthweight outcome and severe heterogeneity in the preterm birth and small-for-gestational-age outcomes. To examine these heterogeneities, we conducted stratified analyses according to study designs, sample sizes, confounding adjustments, country-income categories, study locations, and maternal ages shown in Table 2 and Supplemental Table 9. The RR differed according to the subgroup analysis by country-income category. Risks of low birth weight and preterm delivery were substantially higher in low-income countries than in upper-middle-income countries. Stratification by geographic region revealed increased risk of low birth weight and preterm delivery in anemic pregnant women in South Asia than in East-West Asia and the African and South American regions. However, the result was not statistically significant ($P > 0.05$).

**Prevalence of anemia**

Figure 2 presents the random-effects estimate for maternal anemia during pregnancy by country-income category. Prevalence was estimated from 28 recent surveys and 25 countries with a pooled prevalence of 42.7% (95% CI: 37.0%, 48.4%) in low- and middle-income countries. There were slight differences
DISCUSSION

To date, most knowledge relating to the birth and health consequences of maternal anemia has come from cross-sectional, case-control, and cohort studies. This systematic review and meta-analysis summarizes these associations by region and country-income category in low- and middle-income settings with the use of high-quality cohort studies. This study also assesses the proportion of low birth weight, preterm birth, and perinatal mortality that were attributable to maternal anemia. Significant, positive associations were shown between anemia in the first or second trimester and low birth weight, preterm birth, and perinatal and neonatal mortality. However, no association was shown between maternal anemia and risk of small for gestational age, gestational diabetes, preeclampsia, and cesarean delivery. Maternal anemia was shown to be associated with a significant proportion of pregnancy outcomes in low-income countries with this proportion declining with increasing national income and varying substantially between countries and geographic regions.

Maternal anemia remains one of the most-serious health problems in low-income countries despite the high priority of maternal and child health programs. Our study showed nearly one-half (42.7%) of pregnant women were anemic in low- and middle-income countries and the prevalence of anemia varied by the country economic profile (45.4% in low-income, 39.8% in lower-middle-income, and 37.1% in upper-middle-income countries). Our study also identified substantial regional differences in the prevalence of anemia. Consistent with a recent multicountry study (2), there was a higher prevalence of maternal anemia in the South Asian region and African and South American regions (48.6% and 43.5%, respectively) than in East-West Asia (39.9%). Our study showed that the prevalence of anemia during pregnancy has remained almost unchanged in low-income countries since 2000. The main reason for this stable and high prevalence of maternal anemia during pregnancy in low-income countries, especially in African and Asian regions, may be because of the high prevalence of malaria and poor nutrition including underweight and iron deficiency (10–12, 37).

Consistent with previous studies (13, 38), women with anemia in the first or second trimester had a significantly greater risk of low birth weight, preterm birth, and perinatal and neonatal mortality. Sensitivity analyses confirmed a similar association after publication bias was accounted for or a small number of highly influential studies were dropped. In subgroup analyses, we showed an association between the hemoglobin concentration and risk of birth and health outcomes in low-income countries compared with in lower-middle-income or upper-middle-income countries. We showed substantial heterogeneity in low-birthweight, preterm birth, and small-for-gestational-age outcomes.

### TABLE 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Studies, n</th>
<th>RR (95% CI)</th>
<th>Heterogeneity index</th>
<th>P-bias test</th>
<th>Missing studies, n</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low birth weight</td>
<td>17</td>
<td>1.31 (1.13, 1.51)</td>
<td>65.7</td>
<td>0.03</td>
<td>4</td>
<td>1.18 (1.02, 1.37)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>13</td>
<td>1.63 (1.33, 2.01)</td>
<td>88.2</td>
<td>0.05</td>
<td>0</td>
<td>1.63 (1.33, 2.01)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>5</td>
<td>0.87 (0.63, 1.20)</td>
<td>95.0</td>
<td>0.41</td>
<td>0</td>
<td>0.87 (0.63, 1.20)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>12</td>
<td>1.51 (1.30, 1.76)</td>
<td>0</td>
<td>&lt;0.001</td>
<td>5</td>
<td>1.43 (1.24, 1.65)</td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>2</td>
<td>2.72 (1.19, 6.25)</td>
<td>0.0</td>
<td>0.72</td>
<td>0</td>
<td>2.72 (1.19, 6.25)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>2</td>
<td>1.02 (0.86, 1.21)</td>
<td>19.8</td>
<td>0.16</td>
<td>0</td>
<td>1.02 (0.86, 1.21)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1</td>
<td>2.66 (0.61, 11.52)</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>2.66 (0.61, 11.52)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>1</td>
<td>1.68 (0.76, 3.72)</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>1.68 (0.76, 3.72)</td>
</tr>
</tbody>
</table>

1Trim-and-fill method simulated studies that were likely to be missing from the literature because of publication or other forms of bias. Trim-and-fill RRs estimate what the pooled RRs would be if the missing studies were included in the analysis.
2On the basis of random-effects methods.
3On the basis of fixed-effects methods.
4No pooling method was used because there was only a single study.
5NA, not applicable.

Role of anemia

The PAFs for selected adverse pregnancy outcomes that were attributable to maternal anemia during pregnancy are presented in Table 3. The prevalence of anemia with data sources used in the PAF calculations is presented in Supplemental Table 10. Overall, 12% of low birth weight, 19% of preterm birth, and 18% of perinatal mortality were attributable to maternal anemia during pregnancy in low- and middle-income countries. There was a wide difference in the PAF of pregnancy outcomes across geographic regions and country-income levels. In low-income countries, 25% of low birth weight, 44% of preterm births, and 21% of perinatal mortality were attributable to anemia during pregnancy. However, the respective PAFs were substantially smaller in lower-middle- and upper-middle-income countries. In low-income and lower-middle-income countries, there was a relatively higher anemia-attributable proportion of adverse low birth weight in Pakistan and Bangladesh than in Ghana and India. The highest anemia-attributable proportion of preterm birth was observed in Pakistan (54%) and followed by India (27%) and Iran (18%).
TABLE 2
Stratified analysis of pooled RRs of low birth weight, small for gestational age, perinatal mortality, and preterm birth for anemic pregnant women

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study design</th>
<th>Confounding factors</th>
<th>Country-income category</th>
<th>Geographic region</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td></td>
<td>Prospective</td>
<td>Adjusted</td>
<td>Low income</td>
<td>South Asia</td>
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<tr>
<td></td>
<td>Retrospective</td>
<td>Unadjusted</td>
<td>Lower-middle income</td>
<td>East-West Asia</td>
</tr>
<tr>
<td>Low birth weight</td>
<td></td>
<td></td>
<td>Upper-middle income</td>
<td>Africa and South America</td>
</tr>
<tr>
<td>Study design</td>
<td>1.41 (1.18, 1.68)</td>
<td>1.28 (1.03, 1.59)</td>
<td>1.72 (1.32, 2.25)</td>
<td>1.36 (1.11, 1.66)</td>
</tr>
<tr>
<td>Confounding factors</td>
<td>0.95 (0.60, 1.50)</td>
<td>1.34 (1.13, 1.59)</td>
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<tr>
<td>Preterm birth</td>
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<tr>
<td>Study design</td>
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</tr>
<tr>
<td>Prospective</td>
<td>1.94 (1.31, 2.89)</td>
<td>1.63 (1.16, 2.31)</td>
<td>2.73 (1.29, 5.79)</td>
<td>2.03 (1.23, 3.36)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>1.18 (1.09, 1.27)</td>
<td>1.70 (1.17, 2.46)</td>
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<tr>
<td>Confounding factors</td>
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<td>Adjusted</td>
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<td>Country-income category</td>
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<td>Low income</td>
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<td>Lower-middle income</td>
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<tr>
<td>Upper-middle income</td>
<td>1.27 (0.89, 1.79)</td>
<td>NA</td>
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<tr>
<td>Geographic region</td>
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<tr>
<td>South Asia</td>
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<tr>
<td>East-West Asia</td>
<td>1.27 (0.89, 1.79)</td>
<td>1.20 (1.00, 1.44)</td>
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<tr>
<td>Africa and South America</td>
<td>1.32 (0.76, 2.29)</td>
<td>NA</td>
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<tr>
<td>Small for gestational age</td>
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<tr>
<td>Study design</td>
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</tr>
<tr>
<td>Prospective</td>
<td>0.95 (0.65, 1.40)</td>
<td>1.00 (0.84, 1.19)</td>
<td>0.84 (0.38, 1.88)</td>
<td>0.65 (0.60, 0.72)</td>
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<td>0.85 (0.57, 1.25)</td>
<td>0.65 (0.60, 0.72)</td>
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<td>Confounding factors</td>
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<td>Lower-middle income</td>
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<tr>
<td>Upper-middle income</td>
<td>1.36 (0.97, 1.91)</td>
<td>1.20 (1.00, 1.44)</td>
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<tr>
<td>Geographic region</td>
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<tr>
<td>Africa and South America</td>
<td>1.32 (0.76, 2.29)</td>
<td>NA</td>
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<tr>
<td>Perinatal mortality</td>
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<tr>
<td>Study design</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Prospective</td>
<td>1.67 (1.30, 2.14)</td>
<td>1.72 (1.28, 2.32)</td>
<td>1.61 (1.16, 2.23)</td>
<td>2.05 (1.18, 3.55)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>1.43 (1.18, 1.73)</td>
<td>1.45 (1.22, 1.73)</td>
<td>1.44 (1.18, 1.76)</td>
<td>1.63 (1.18, 2.25)</td>
</tr>
<tr>
<td>Confounding factors</td>
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<tr>
<td>Adjusted</td>
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<tr>
<td>Unadjusted</td>
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<tr>
<td>Country-income category</td>
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<tr>
<td>Low income</td>
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<tr>
<td>Lower-middle income</td>
<td></td>
<td></td>
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<tr>
<td>Upper-middle income</td>
<td>1.63 (1.18, 2.25)</td>
<td>0.79</td>
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<tr>
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<tr>
<td>South Asia</td>
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<tr>
<td>East-West Asia</td>
<td>1.63 (1.18, 2.25)</td>
<td>0.79</td>
<td></td>
<td></td>
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<tr>
<td>Africa and South America</td>
<td>1.43 (1.20, 1.72)</td>
<td>0.44</td>
<td></td>
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</tbody>
</table>

1NA, not applicable.

2Metaregression P values represent a test of the entire characteristic.
When the substantial heterogeneity in 95% prediction intervals was accounted for, the results indicated that the association between anemia and risks of low birth weight, preterm birth, and small for gestational age became insignificant. These results do not necessarily indicate that there is no impact of maternal anemia on birth outcomes. However, the results do indicate that there is still substantial uncertainty about the significance of the association. Our findings expand significantly on the recent meta-analysis of Haider et al. (13), which collapsed findings across countries and accessed only limited information on birth outcomes. We compared risks of preterm birth and low birth weight separately for low- or middle-income countries rather than conducting a combined comparison against high-income countries. In addition, we presented information on pregnancy outcomes by geographic regions and country-income categories in recognition of the substantially differing patterns of prevalence and birth outcomes in these country categories. Our study showed a consistent regional variation in risks of low birth weight, preterm birth, and perinatal mortality. Highest risk of perinatal mortality attributable to maternal anemia was shown in Ghana, Pakistan, India, and Malawi. Greater risk of low birth weight was also observed in Pakistan, Bangladesh, and Ghana.

In some low-income and lower-middle-income countries, the control of infectious diseases such as HIV, AIDS, and malaria has not yet been achieved, and health-service delivery, access, and effective coverage and access to affordable care are limited (11, 39–45). In previous studies anemia, malnutrition, and malaria during pregnancy were shown to be significant risks to both maternal and neonatal health (2, 8, 11, 37). However, many low-income countries are facing challenges in implementing immunization, malaria control, and nutrition support programs (5, 46, 47). The war in Afghanistan and internal conflict in Pakistan targeted female health workers, and thus, many parts of these areas are severely affected by workforce-related barriers to the

**FIGURE 2** Random-effects meta-analysis pooled prevalence estimates during 2010–2013 by country-income categories. Open diamonds represent pooled prevalence (95% CIs). Small filled diamonds represent the prevalence for each survey, and black bars denote 95% CIs. ES, prevalence; I^2, percentage of variation attributable to heterogeneity; n, total number of anemic women during pregnancy; N*, total number of pregnant women.
resolving their maternal and child health issues (5). Cost is another barrier to accessing health services in low-income countries (48, 49), and many poor households may avoid consulting doctors during pregnancy to minimize financial risks associated with high-treatment costs. Consequently, these women may be unaware of their nutritional status during pregnancy. Service delivery, effective coverage, and access and affordable care during pregnancy can be ensured by introducing universal health coverage plans (43, 45, 48, 49). For example, in Ghana, Indonesia, Uganda, and China, after health insurance was introduced, the burden of treatment costs sharply decreased and access to care increased (48, 50). Ensuring access to comprehensive, integrated primary care and maternal and child health services through better health-financing methods will help to ensure that women understand their nutritional status and are able to act earlier in pregnancy to minimize worst risks associated with maternal anemia.

Our study had several strengths. We used comprehensive search techniques and validated systematic review methods, followed a predesigned protocol, and observed the Meta-analysis of Observational Studies in Epidemiology (15) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (17) guidelines, which strengthened the review quality and conclusions. We investigated the possible association between maternal anemia and birth and health outcomes by region, country-income category, and specific countries. In the meta-analysis, appropriate statistical techniques were used to estimate the pooled prevalence, RR, and presence of bias.

Despite these strengths, limitations of this systematic review and meta-analysis must be considered. We included studies from low- and middle-income countries, and thus, the results of review are not applicable to high-income countries. We only included studies that measured hemoglobin during the first or second trimester and may have overlooked some studies that addressed the effect of anemia in the third trimester. However, a recent meta-analysis suggested that anemia during the third trimester is not a potential risk factor for adverse birth outcomes, and its exclusion was unlikely to have biased this review (8). We defined anemia on the basis of WHO standard thresholds based on hemoglobin [anemic: <10–11 g hemoglobin/dL or hematocrit <30–34%; nonanemic: >11 g hemoglobin/dL (18), but some studies did not use these categorizations. Different definitions and categorizations can lead to variations in RRs or ORs even within a single data set. However, in our systematic review, almost all studies used WHO cutoffs except for 5 studies from Ghana, Bangladesh, India, China, and Turkey. We performed a pooled analysis separately in which thresholds proposed by the WHO and other thresholds according to the definitions of the original studies. Despite different definitions, there was no significant difference in pooled estimates between WHO thresholds and others. This stable pooled estimate may have been because only 5 studies used different cutoffs to those recommended by the WHO. We also had to use estimated RRs for 7 studies that reported ORs, which were converted to RRs for the meta-analysis. There was risk that the variance of the derived RRs could have been underestimated in the proposed conversion methodology of Zhang (15, 21). However, we performed a sensitivity analysis that excluded the affected studies and showed negligible effect on the results. Finally, we did not include gray literature, which may have contained smaller null-result studies that were not
accepted for publication, but we adjusted for this publication bias with the use of the trim-and-fill method and showed little effect on our results from the inclusion of possible imputed negative studies.

In conclusion, maternal anemia is a risk factor for adverse birth and perinatal health outcomes in low- and middle-income countries. Significantly higher risk of low birth weight and preterm birth were observed in low-income countries and in South Asian countries despite the greater priority and larger investment on maternal and child health programs in recent decades. On the basis of our review findings, we advocate that greater attention be placed on the impact of maternal and child health programs on anemia-related outcomes in low-income countries. With the management of maternal anemia during pregnancy in low-income countries, a substantial proportion of anemia-related adverse pregnancy outcomes could be avoided.

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The authors’ responsibilities were as follows—MMR: contributed to the study design, data analysis, interpretation of the data, and wrote the first draft of the manuscript; MMR and MSR: performed the literature screening and data extraction; MMR, SKA, MK, and SN: collaborated on the quality assessment; SKA: collaborated on the writing of the first draft of the manuscript; SKA and VB: checked for the consistency of the study; EO, SG, and KS: revised the manuscript critically for important intellectual content; and all authors: reviewed and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

REFERENCES


