Maternal folic acid supplementation and infant birthweight in low- and middle-income countries: A systematic review

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Abstract
The relationship between maternal folic acid supplementation in pregnancy and infant birthweight has not been well described in low- and middle-income countries. We conducted a systematic review and meta-analysis of the current evidence of the association between folic acid supplementation in pregnancy on three primary outcomes: the incidence of low birthweight, small for gestational age, and mean birthweight. Seventeen studies were identified, which satisfied the inclusion criteria, covering a total of 275,421 women from 13 cohort studies and four randomized controlled trials. For the primary outcome of mean birthweight (n = 9), the pooled mean difference between folic acid and control groups was 0.37 kg (95% confidence interval [CI]: 0.24 to 0.50), and this effect was larger in the randomized controlled trials (0.56, 95% CI: 0.15 to 0.97, n = 3). The pooled odds ratio was 0.59 for low birthweight (95% CI: 0.47 to 0.74, n = 10) among folic acid supplementation versus control. The pooled odds ratio for the association with small for gestational age was 0.63 (95% CI: 0.39 to 1.01, n = 5). Maternal folic acid supplementation in low- and middle-income countries was associated with an increased mean birthweight of infants and decreases in the incidence of low birthweight and small for gestational age.

KEYWORDS
birthweight, developing countries, folic acid, infant, nutritional status, pregnancy, systematic review

INTRODUCTION

Low birthweight (LBW) is a significant public health issue in low- and middle-income countries. Poor nutrition before and during pregnancy is recognized as an important cause of LBW. Two main causes of LBW are preterm birth (before 37 weeks of gestation) and intrauterine growth restriction (World Health Organization, & Unicef, 2004). Multiple pregnancies, infections, and chronic diseases can also contribute to LBW (World Health Organization, 2014). Birthweight is also affected by the mother’s own fetal development and diet throughout her life, and upon pregnancy, the mother’s nutrition and health play an important role in birthweight (ACC/SCN, 2000). In high-income countries, LBW primarily occurs due to preterm birth; however, in low- and middle-income countries, the cause is primarily intrauterine growth restriction (Wardlaw, 2004).

A concurrent measure to LBW is small for gestational age (SGA), defined as infants whose weight is less than the 10th percentile for gestational age (University of Rochester Medical Center, 2017). The...
causes of SGA may include relative placental insufficiency caused by multiple gestation, placental insufficiency, chronic maternal hypoxaemia caused by pulmonary or cardiac disease, maternal malnutrition, and conception using assisted reproductive technology (Stavis, 2017). SGA infants have similar outcomes as LBW infants; however, LBW is a more commonly used measure, as it is broader than SGA and more easily captured when the gestational age is not known.

According to the World Health Organization, 96.5% of all LBW births occur in low- and middle-income countries (World Health Organization & Unicef, 2004). LBW is often used as an indicator for the mother's health and nutritional status, as well as the infant's risk of mortality and morbidity, chances of survival, long-term health, and psychosocial development (World Health Organization, 2014).

For at least two decades, folic acid has been known to be associated with a reduction in pregnancy complications including neural tube defects, congenital malformations, haemorrhage, pre-eclampsia, spontaneous abortions, and fetal growth restriction (Ramakrishnan, Manjrekar, Rivera, Gonzáles-Cossío, & Martorell, 1999). In the human body, folate is required for the synthesis of pyrimidines and purines and the synthesis of DNA; therefore, in situations where there is rapid dividing of cells, such as in fetal development, a lack of folate may lead to alterations in DNA synthesis (Ramakrishnan et al., 1999). With this knowledge, it is clear that folate plays a critical role in fetal growth and development, and therefore, the maternal folate status can play an important role in the development of a variety of problems for the fetus. Despite the large amount of evidence linking poor maternal folate status to the development of neural tube defects, there has been relatively limited number of investigations into the association between low maternal folic acid (FA) supplementation and incidence of LBW.

The objective of this study was to examine the effects of FA supplementation in pregnant women on the birthweight of infants and the incidence of LBW and SGA in low- and middle-income countries. We sought to synthesize all available literature and produce pooled estimates of the association between FA supplementation and birthweight and prevalence of LBW/SGA.

2 | METHODS

The study population was pregnant women and their infants in low- and middle-income countries, and the intervention was FA supplementation. The comparison was the absence of dietary FA supplementation, and the outcome was association between FA supplementation and LBW, SGA, and mean birthweight. For comparability across studies, effect estimates were calculated by the authors using extracted means and counts of events. The study design is a systematic review of studies published between 1990 and 2017.

2.1 | Data sources

Two databases were used: Ovid Embase (1974–2017) and Ovid Medline (including Epub Ahead of Print, In-Process & Other Non-

Key messages

- The relationship between folic acid supplementation in pregnancy and infant birthweight in low- and middle-income countries is not clear.
- We find a positive association between folic acid supplementation and infant birthweight and an inverse association with the incidence of low birthweight and small for gestational age.
- Although included studies were primarily observational, findings were consistent in a subset of randomized controlled trials.
- Changes in policy concerning folic acid supplementation or fortification of food with folic acid in low-income settings may have potential benefit for reducing the incidence of low birthweight.

Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®, 1946 to present). Keywords for folate included folate and folic acid. Low- and middle-income countries were selected using a definition from the UN World Economic Situation and Prospects 2016 (United Nations, 2016) including low-income countries, lower middle-income countries, least developed countries, small island developing countries, and landlocked developing countries. The full search strategy appears in Appendix A.

The search was limited to studies from 1990–present to align with the increased use of FA beginning in the 1990s. The search was limited studies in English or French. The search strategy was created by the authors and was reviewed and augmented by a professional medical librarian.

2.2 | Study selection

The systematic review program, Covidence, was used to manage all the studies produced by the search strategy. Two assessors independently reviewed the titles, abstracts, and full text articles, and differences in opinion were discussed until consensus was reached. Included studies covered pregnant women in low- and middle-income countries who used FA supplements, FA with iron supplements (IFA), or where dietary folate or serum/blood folate levels were captured. We compared women with FA use and those receiving higher levels of dietary folate intake to those who did not take supplements or who had low levels of dietary folate. Studies were excluded if the population was outside of low- and middle-income countries, no comparison group was defined, if women were only taking multivitamin supplements without indication of FA, or if FA was combined with another vitamin other than iron.

All studies identified through systematic searching were first screened against inclusion criteria based on titles and abstracts.
Following title and abstract screening, remaining studies were evaluated based on a full text screening using the same inclusion/exclusion criteria. Studies that did not fit the inclusion criteria were excluded, and the exclusion reason was noted for each study.

2.3 | Data extraction

The primary reviewer (H. J.) conducted data extraction. The following data were extracted from the studies: study title, last name of first author, date of publication, journal, contact information, funding source, industry involvement, type of publication, study design, country(ies) of study, study population, size of population, time period of the study, study objective, form of FA given, frequency of FA, how supplement use was verified, how birthweight was measured, definition of LBW, what births were excluded, mean birthweights for study and control groups, counts and percentage LBW or SGA for study and control groups, and any major limitations.

2.4 | Risk of bias assessment

All included studies were evaluated for risk of bias. Nonrandomized cohort and case–control studies were evaluated for risk of bias using the Newcastle–Ottawa Quality Assessment Scale (Wells et al., 2017). Nonrandomized studies were awarded stars for control of bias across the following domains of study design and quality of reporting: study methods for selection, comparability, and exposure ascertainment (Table 1). More stars indicate less risk of bias. Randomized controlled trials were evaluated using the Cochrane risk-of-bias tool for randomized trials (Higgins & Altman, 2008) and assessed for selection bias, performance bias, detection bias, attrition bias, and reporting bias. Studies were assessed as low, unclear, or high risk of bias across domains.

2.5 | Meta-analysis

A meta-analysis was conducted of the comparable data points from each study using Rev Man 5 software. The data points compared included mean birthweights for study and control groups, incidence of LBW for study and control groups, and incidence of SGA for study and control groups. Rev Man 5 software generated forest plots and funnel plots for each of these comparable data points to summarize the odds ratio and mean differences.

3 | RESULTS

3.1 | Study characteristics

A total of 2,170 nonduplicated titles and abstracts were identified (Figure 1). After applying the inclusion and exclusion criteria, 674 articles were selected for full text review and assessment, which yielded 17 studies that were included in the final review and meta-analysis. Of these, 13 were cohort studies and four were randomized controlled trials (RCTs; Table 1). Eleven studies were conducted in Asia, four in the Middle East, and two in Africa. The total combined study population was 275,421 women (min/max among included studies: 120/231,179 women). The form of FA supplementation was primarily IFA or FA supplementation, and two studies measured the blood serum folate levels instead of FA supplementation. Nine studies had the outcome variable of mean birthweight, nine had the outcome variable of LBW, and five had the outcome variable of SGA. The average risk of bias score for the cohort studies was 7.5 stars, and for the RCTs, three studies had a low risk of bias and one had an unclear risk of bias.

3.2 | Mean birthweight

For those studies that had outcome variables of mean birthweight, the pooled mean difference across all studies (n = 9) was 0.37 kg (95% CI [0.18, 0.43]) with a range of effect sizes between 0.24 and 0.50 kg (Figure 2). There was statistical heterogeneity between the studies ($\chi^2$ = 28.13, df = 8, P = .00004; $I^2$ = 72%). Among a subset of three RCTs (n = 3), the pooled mean difference was 0.56 kg (95% CI [0.15, 0.97]). Individually, all studies had a statistically significant mean difference in birthweights by FA supplementation. The funnel plot for the mean difference between birthweights for all the studies demonstrates a fairly symmetric distribution of the data, which demonstrates low bias in the results, even considering that there was a small amount of studies compiled (Figure 3).

3.3 | Low birthweight

For the studies that had outcome variables of the incidence of LBW for FA supplementation groups versus control, the overall odds ratio was 0.59 (95% CI [0.47, 0.74], n = 10 studies; Figure 4). All studies had an odds ratio less than 1, and there was statistical heterogeneity between the FA supplementation and control groups ($\chi^2 = 0.07; \chi^2 = 44.34, df = 9, P < .00001; I^2 = 80$). Among a subset of two RCTs, the pooled odds ratio was 0.68 (95% CI [0.30, 1.58]), although there was less statistical precision due to smaller number of studies. The funnel plot of the odds ratios for LBW produced an asymmetrical distribution, which indicates some bias in the results (Figure 5).

3.4 | Small for gestational age

There were less studies with the outcome variable of SGA; however, five out of the six study groups had an odds ratio of less than 1, favouring FA supplementation (Figure 6). The total odds ratio for all six study groups was 0.71 (95% CI [0.46, 1.08]). One study group that used postconceptional FA supplementation later in the pregnancy had an odds ratio greater than 1, favouring no supplementation; however, because this form of supplementation was different from the rest, a second forest plot was created without this study group (Figure 7). The total odds ratio for this forest plot was 0.63 (95% CI [0.39, 1.01]). There were insufficient studies for this outcome variable to create an accurate funnel plot.
| Author and year of publication | Country     | Design                      | Study population size | Form of FA                                      | Outcome variables                  | Risk of bias score |
|-------------------------------|-------------|-----------------------------|-----------------------|------------------------------------------------|------------------------------------|--------------------|
| Abdullahi et al., 2014        | Sudan       | Cohort: cross-sectional     | 856                   | IFA or FA supplements                           | LBW and mean BW                   | 6 stars            |
| Achadi et al., 1995           | Indonesia   | Cohort: cross-sectional     | 451                   | IFA supplements                                 | Mean BW                            | 7 stars            |
| Amuna et al., 2012            | South Africa| Randomized controlled trial | 120                   | Daily diet and formulated food multimix         | Mean BW                            | Unclear            |
| Balarajjan et al., 2013       | India       | Cohort                      | 22,648                | IFA supplements                                 | LBW                               | 7 stars            |
| Bawadi et al., 2010           | Jordan      | Cohort                      | 700                   | Any form of supplementation                      | Mean BW                            | 8 stars            |
| Chaudhary et al., 2012         | India       | Cohort                      | 290                   | IFA supplements                                 | LBW and mean BW                    | 7 stars            |
| Christian et al., 2003        | Nepal       | Randomized controlled trial | 4,926                 | FA supplements                                  | LBW, SGA and mean BW               | Low risk           |
| Dwarkanath et al., 2013        | South India | Cohort                      | 1,838                 | Dietary folate and FA supplementation           | SGA                               | 8 stars            |
| Joseph et al., 2011           | South India | Cohort                      | 194                   | IFA supplementation                             | LBW                               | 8 stars            |
| Krishnaveeni et al., 2014      | India       | Cohort                      | 656                   | Serum folate and FA supplementation            | Mean BW                            | 9 stars            |
| Nisar et al., 2014             | Pakistan    | Cohort                      | 5,692                 | IFA supplements                                 | LBW and SGA                        | 7 stars            |
| Ndyomugenyi & Magnussen, 2000  | Uganda      | Randomized controlled trial | 860                   | IFA supplementation                             | Mean BW                            | Low risk           |
| Passerini et al., 2012         | Vietnam     | Randomized controlled trial | 463                   | IFA supplementation                             | LBW                               | Low risk           |
| Rao et al., 2001               | India       | Cohort                      | 797                   | Serum folate and FA supplementation            | Mean BW                            | 8 stars            |
| Roudbari et al., 2007          | Iran        | Cohort: cross-sectional     | 1,109                 | Any form of supplementation                      | LBW                               | 6 stars            |
| Wang et al., 2016              | China       | Cohort                      | 2,644                 | FA supplementation                              | LBW, SGA and Mean BW               | 8 stars            |
| Zheng et al., 2016             | China       | Cohort                      | 231,179               | FA supplementation                              | SGA                               | 9 stars            |

Abbreviations: BW, birthweight; FA, folic acid; IFA, FA with iron supplements; LBW, low BW; SGA, small for gestational age.
In this systematic review and meta-analyses, we determined that maternal FA supplementation in low- and middle-income countries was associated with an increase in the mean birthweight of infants and a decrease in the incidence of LBW and SGA. The included studies were determined to be of high quality, and stratification by randomized and nonrandomized design indicated consistency in the direction and magnitude of association. Analyses of mean birthweight demonstrated a statistically significant difference between FA and control suggesting that maternal FA supplementation can potentially increase the mean birthweight of infants in these settings.

Analyses of LBW demonstrated statistically significant heterogeneity in the incidence of LBW between FA supplementation and control groups, and the odds ratios overall and for all studies individually were in favour of FA supplementation. The funnel plot for the LBW odds ratios demonstrated a less symmetric distribution of the data points, which points to some bias in the results; however, it is possible that with a greater number of studies to compare this distribution would become more symmetrical.
The SGA forest plot also demonstrated a statistically significant heterogeneity between the incidence of SGA in the FA supplementation and control groups. One study group was removed from this forest plot due to the fact that postconception FA supplementation was used and it was a different form of supplementation than the rest of the studies compared (Zheng et al., 2016). After this study was removed, the total odds ratio decreased even further, favouring FA supplementation (Figure 7). The total odds ratio for SGA was higher than the total odds ratio for LBW, and this is probably partially due to the fact that fewer studies had the outcome variable of SGA.

4.1 | Comparison with other studies

To our knowledge, this is the first comprehensive systematic review and meta-analysis on the effect of maternal FA supplementation on infant birthweight in low- and middle-income countries. The existing literature is composed of nonsystematic reviews without published search strategies or meta-analyses. One study that has been published has shown a positive association between FA supplementation and birthweight (Nguyen et al., 2012). Another article from 2009 indicated that blood serum folate levels were positively associated with birthweight and that IFA supplements increased birthweight (Muthayya, 2009). Another review article conducted in 2012 also found that IFA supplementation may have an association on the incidence of LBW in Ethiopia, India, and Nigeria (Mason et al., 2012). These findings have important implications for low- and middle-income countries where FA deprivation may continue over successive generations of mothers and contribute to intergenerational cycle of LBW infants.

4.2 | Strengths and limitations

Looking beyond predominantly larger RCTs, which mostly occur in high-income countries, this review included observational and RCTs conducted in low- and middle-income countries. The predominance of

| Study or Subgroup | Folic Acid Events Total | No Folic Acid Events Total | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|------------------------|---------------------------|--------------------------------|--------------------------------|
| 1.1.2 Randomized Studies | Christian 2003 | 628 | 1506 | 685 | 1578 | 17.5% | 0.93 [0.81, 1.04] |
| | Passey & 2012 | 5 | 168 | 22 | 295 | 4.0% | 0.18 [0.14, 1.02] |
| | Subtotal (95% CI) | 1674 | 1873 | 21.6% | 0.18 [0.30, 1.58] |
| Total events | 633 | 707 |
| Heterogeneity: Tau^2 = 0.27; Chi^2 = 3.08, df = 1 (P = 0.08); I^2 = 68%
| Test for overall effect: Z = 0.95 (P = 0.37) |
| 1.1.3 Non-Randomized Studies | Abidallah 2014 | 90 | 788 | 20 | 68 | 8.5% | 0.31 [0.18, 0.54] |
| | Balaraj 2013 (1998/1999 Cohort) | 1380 | 6448 | 207 | 804 | 17.1% | 0.79 [0.66, 0.95] |
| | Balaraj 2013 (2005/2006 Cohort) | 2577 | 13250 | 586 | 2146 | 18.1% | 0.64 [0.57, 0.71] |
| | Chaubary 2012 | 51 | 290 | 105 | 290 | 12.1% | 0.18 [0.10, 0.35] |
| | Josep 2011 | 21 | 110 | 7 | 18 | 3.6% | 0.37 [0.13, 1.07] |
| | Nisar 2014 | 103 | 467 | 48 | 135 | 11.5% | 0.51 [0.34, 0.74] |
| | Rabadi 2007 | 68 | 674 | 10 | 83 | 6.4% | 0.59 [0.43, 1.35] |
| | Wang 2016 | 1 | 33 | 48 | 2181 | 1.2% | 0.14 [0.05, 0.50] |
| Subtotal (95% CI) | 21958 | 5705 | 78.4% | 0.55 [0.44, 0.70] |
| Total events | 4371 | 1031 |
| Heterogeneity: Tau^2 = 0.05; Chi^2 = 22.56, df = 7 (P = 0.002); I^2 = 69%
| Test for overall effect: Z = 5.06 (P < 0.00001) |
| Total (95% CI) | 23632 | 7578 | 100.0% | 0.59 [0.47, 0.74] |

| Total events | 4904 | 1738 |
| Heterogeneity: Tau^2 = 0.07; Chi^2 = 44.34, df = 9 (P < 0.00001); I^2 = 80%
| Test for overall effect: Z = 4.60 (P < 0.00001) |
| Test for subgroup differences: Chi^2 = 0.23, df = 1 (P = 0.65); I^2 = 0% |

FIGURE 4  Forest plot meta-analysis of the incidence of low birthweight in study groups supplemented with folic acid versus control groups
observational data may have increased the potential for risk of bias or confounding; however, it was of particular interest to examine the situation in low- and middle-income countries where the greatest burden exists and greatest potential for benefit. The socio-economic context of low- and middle-income countries vary considerably from high-income countries, and in order to generate evidence to inform policy in these contexts, the review was restricted to low- and middle-income countries. Another strength of this study is that risk of bias was individually assessed for all studies included in the analysis and all cohort studies had above a six-star score and three out of four RCTs had a low risk of bias. This study also used a reproducible method that could be used to re-examine the literature in the future. Taken together and using the GRADE criteria for certainty in the level of evidence, we believe that the underlying effect is probably close to our pooled estimates (moderate certainty).

The limitations of this systematic review include the fact that LBW is a very complicated issue with many multidimensional factors that contribute to its aetiology, including maternal nutrition, socio-economic status, chronic diseases, infectious diseases, pollution, pre-term birth, and genetics. We only considered FA supplementation as a single aspect of maternal nutrition. Another confounding factor in this study is that many of the studies included in the review used IFA supplementation, so the effects of the supplementation with FA cannot be entirely separated from iron supplementation. We chose to include these studies despite this concern due of the limited number of studies, and in low-income settings, FA is typically combined with iron in a single supplement. As with all reviews, there is the possibility that publication bias may have skewed the direction of association in the published literature. Another confounding factor may be the patterning of the use of FA supplements by socio-economic status and other maternal characteristics that may have not been completely controlled for in the observational studies. Due to heterogeneity across studies in the number and types of covariate-adjusted analyses, we pooled only the unadjusted effect estimates. Although these estimates may be subject to residual confounding in the observational studies, there was a consistency in the effect estimates between the randomized

FIGURE 6 Forest plot meta-analysis of the incidence of small for gestational age in study groups supplemented with folic acid versus control groups

FIGURE 7 Forest plot meta-analysis of the incidence of small for gestational age in study groups supplemented with folic acid versus control groups (Zheng, 2016, postconceptional use removed)
and nonrandomized studies. Future research is needed to evaluate the other factors contributing to LBW in low- and middle-income countries in order to find interventions to decrease its incidence.

5 | CONCLUSIONS AND IMPLICATIONS

In conclusion, maternal FA supplementation had a statistically significant and positive association on birthweight and an inverse association with incidence of LBW and SGA in low- and middle-income countries. FA supplementation is already widely recommended for the prevention of neural tube defects; however, changes in policy concerning FA supplementation or fortification of food with FA has lagged behind in low- and middle-income countries. These results and potential benefit of FA supplementation can contribute to simple low-cost interventions aimed at reducing the incidence of LBW worldwide.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

PROTOCOL REGISTRATION

The systematic review protocol was registered on Prospero (CRD42017068273).

CONTRIBUTIONS

HJ, MW, and DC conceived and designed the study. HJ and NC performed the review. HJ analysed the data and drafted the manuscript. All authors participated in interpretation of the data and critical revisions of the manuscript.

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APPENDIX A

SEARCH STRATEGY

The search strategy included the following keyword and Medical Subject Heading search terms: folic acid, folate, drug administration, drug combination, drug therapy, oral drug administration, therapy, supplement, diet, pill, oral, therapy, pregnancy, pregnancy outcome, pregnancy complication, perinatal care, prenatal care, perinatal mortality, perinatal morbidity, maternal mortality, maternal welfare, maternal, perinatal, prenatal, pregnant, developing country, low-income country, developing nation, least developed, less developed, third world, under developed, and low income or middle income. In addition to these keywords, a list of low-income countries, lower middle-income countries, least developed countries, small island developing countries, and landlocked developing countries was amalgamated from the UN World Economic Situation and Prospects 2016 document and these country names were added to the search strategy (United Nations, 2016).

APPENDIX B

RISK OF BIAS ASSESSMENT

| Author       | Date | Adequate generation of allocation sequence | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessors | Incomplete outcome data | Selective outcome reporting | Other sources of bias | Total risk of bias |
|--------------|------|--------------------------------------------|------------------------|---------------------------------------|-------------------------------|------------------------|--------------------------|----------------------|-------------------|
| Amuna        | 2012 | Yes                                       | Unclear                | Unclear                               | Unclear                        | No                     | No                      | No                   | Unclear           |
| Christian    | 2003 | Yes                                       | Yes                    | Yes                                   | Yes                           | No                     | No                      | No                   | Low               |
| Ndyomugyenyi | 2000 | Yes                                       | Yes                    | Unclear                               | Unclear                        | No                     | No                      | No                   | Low               |
| Passerini    | 2012 | Yes                                       | Yes                    | No                                    | Yes                           | No                     | No                      | No                   | Low               |
| Author      | Representativeness of the exposed cohort | Selection of the nonexposed cohort | Ascertainment of exposure | Outcome of interest not present at the start of the study | Comparability of cohorts on the basis of design or analysis | Assessment of outcomes | Follow-up long enough for outcome to occur | Adequacy of follow-up | Total stars |
|-------------|------------------------------------------|-----------------------------------|---------------------------|----------------------------------------------------------|----------------------------------------------------------|-----------------------|---------------------------------------------|----------------------|-------------|
| Abdullahi   | Representative of the average pregnant women in developing countries* | Drawn from the same community as the exposed cohort | Self-report | Yes’ | Both” | Self-report | Yes’ | No statement | 6 |
| Achadi      | Representative of the average pregnant women in developing countries* | Drawn from a different source | Self-report | Yes’ | Both” | Record linkage* | Yes’ | Complete follow-up— all subjects accounted for | 7 |
| Balarajan   | Representative of the average pregnant women in developing countries* | Drawn from the same community as the exposed cohort | Self-report | Yes’ | Both” | Self-report | Yes’ | Complete follow-up— all subjects accounted for | 7 |
| Bawadi      | Representative of the average pregnant women in developing countries* | Drawn from the same community as the exposed cohort | Self-report | Yes’ | Both” | Record linkage* | Yes’ | Complete follow-up— all subjects accounted for | 8 |
| Nisar       | Representative of the average pregnant women in developing countries* | Drawn from the same community as the exposed cohort | Self-report | Yes’ | Both” | Self-report | Yes’ | Subjects lost to follow-up unlikely to introduce bias— small number lost (i.e., >90% followed up or description provided of those lost not indicative of a difference in attrition between exposed and nonexposed groups) | 7 |
| Chaudhary   | Representative of the average pregnant women in developing countries* | Drawn from the same community as the exposed cohort | Record linkage* | Yes’ | Record linkage* | Yes’ | Complete follow-up— all subjects accounted for | 7 |

(Continues)
| Author   | Representativeness of the exposed cohort                       | Selection of the nonexposed cohort | Ascertainment of exposure | Outcome of interest not present at the start of the study | Comparability of cohorts on the basis of design or analysis | Follow-up long enough for outcome to occur | Adequacy of follow-up | Total stars |
|----------|----------------------------------------------------------------|-----------------------------------|---------------------------|-----------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------|-----------------------|-------------|
| Dwarkanath | Representative of the average pregnant women in developing countries | Drawn from the same community as the exposed cohort | Self-report | Yes | Both | Record linkage | Yes | Subjects lost to follow-up unlikely to introduce bias—small number lost (i.e., >90% followed up or description provided of those lost not indicative of a difference in attrition between exposed and nonexposed groups) | 8 |
| Joseph | Representative of the average pregnant women in developing countries | Drawn from the same community as the exposed cohort | Self-report | Yes | Both | Record linkage | Yes | Subjects lost to follow-up unlikely to introduce bias—small number lost (i.e., >90% followed up or description provided of those lost not indicative of a difference in attrition between exposed and nonexposed groups) | 8 |
| Krishnaveni | Representative of the average pregnant women in developing countries | Drawn from the same community as the exposed cohort | Record linkage | Yes | Both | Record linkage | Yes | Subjects lost to follow-up unlikely to introduce bias—small number lost (i.e., >90% followed up or description provided of those lost not indicative of a difference in attrition between exposed and nonexposed groups) | 9 |
| Rao | | | Self-report | Yes | Both | | Yes | | 8 |
| Author   | Representativeness of the exposed cohort | Selection of the nonexposed cohort | Ascertainment of exposure | Outcome of interest not present at the start of the study | Comparability of cohorts on the basis of design or analysis | Assessment of outcomes | Follow-up long enough for outcome to occur | Adequacy of follow-up | Total stars |
|----------|----------------------------------------|----------------------------------|---------------------------|------------------------------------------------------------|------------------------------------------------------------|------------------------|----------------------------------------|-----------------------|-------------|
| Roudbari | Representative of the average pregnant women in developing countries* | Drawn from the same community as the exposed cohort* | Self-report | Yes’ | Both” | Self-report | Yes’ | Complete follow-up—all subjects accounted for | No statement | 6           |
| Wang     | Representative of the average pregnant women in developing countries* | Drawn from the same community as the exposed cohort* | Self-report | Yes’ | Both” | Record linkage’ | Yes’ | Complete follow-up—all subjects accounted for | 8          |
| Zheng    | Representative of the average pregnant women in developing countries* | Drawn from the same community as the exposed cohort* | Self-report | Yes’ | Both” | Record linkage’ | Yes’ | Complete follow-up—all subjects accounted for | 9          |

Note: Asterisks indicate the star rating for quality.