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REVIEW

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# Association between iron and folic acid supplementation and birth weight in Ethiopia: systemic review and meta analysis

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**Abstract**

**Background:** Previous studies on iron with folic acid supplementation and low birth weight indicated different findings. The aim of the current systemic review and meta-analysis was to examine the relationship between iron and folic acid supplementation and birth weight in Ethiopia.

**Main body:** The databases searched were PubMed, Google Scholar, Web of Science and Cochrane Library in January 2021. AZ, KTT and AAA carried out the data extraction and independently assessed the articles for inclusion in the review using risk-of-bias tool guided by PRISMA checklist. The combined Odds ratio with 95% confidence interval was calculated using random effect model. Twenty four observational studies involving 10,989 participants, 2423 newborns who were born LBW were included. The combined effect size (OR) for low birth weight comparing women who have Iron and Folic acid supplementation versus women who did not have iron and folic acid supplementation was 0.39 (95% CI 0.27–0.59, $p < 0.00001$, $I^2 = 91\%$). There was significant heterogeneity ($Q = 264.16$, $I^2 = 91\%$, $p < 0.00001$). No publication bias was observed (Egger's test: $p = 0.742$, Begg's test: $p = 0.372$). Overall 69.5% of women reported having iron and folic acid supplementation during current pregnancy. And the overall proportion of low birth weight was 22.1%.

**Conclusions:** Women who were supplied with iron and folic acid during pregnancy had a 67% decreased chance of delivering low birth weight new born in Ethiopia.

**Keywords:** Determinant of birth weight, Low birth weight, Iron and folic acid supplementation, Meta-analysis, Systematic review, Ethiopia

## Background

Low Birth Weight (LBW) is defined as having a birth weight of less than 2500 g irrespective of the gestational age of the neonate by World Health Organization (WHO) (UNICEF 2001). It is one of the major global public health problems and is associated with various consequences (WHO 2014).

According to an estimation of United Nations Children's Fund (UNICEF)-WHO, globally one in seven live births (20.5 million babies) suffered from low birth weight in 2015. This report also indicated that data on birth weight were not available for 39.7 million newborns in 2015 worldwide and half of those were from Africa (WHO 2019).

There is disparity on the prevalence of LBW in developing countries. A study which analyzed secondary data of 10 Demographic and Health Surveys (DHS) from developing countries found an overall LBW prevalence of 15.9% (Mahumud et al. 2017). Studies conducted among Indian and Malaysian women also found 16.5% and 6.38% prevalence of LBW respectively (Bharati et al. 2011; Kaur et al. 2019). A cross-sectional study conducted in five African counties found 13.4% prevalence of LBW in

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Burkina Faso, 10.2% in Ghana, 12.1% in Malawi, 15.7% in Senegal and 10% in Uganda (He et al. 2018).

Prevalence of LBW in varies across regions in Ethiopia. The 2016 Ethiopian Demographic and Health Survey (DHS) reported 13% prevalence of small size babies based on the subjective report of the mothers (CSA 2016). Studies conducted in different regions of Ethiopia have shown that prevalence of LBW ranged from 17.5 to 22.5% in Northwest and Southwest respectively (Demelash et al. 2015; Zeleke et al. 2012).

The two major processes that govern birth weight are duration of gestation and intrauterine growth rate, thus LBW is caused by either a short gestation period or intrauterine growth retardation (or a combination of both factors) (Kramer 1987; WHO 2011, 2019). Some of the factors that are found to be predicators of LBW in one study may not necessarily be a predictor factor in another study. Supporting the argument on possible determinants of LBW vary across the geographical location (Mulatu et al. 2016).

Different studies reported inconsistent results regarding the association between LBW and Iron and Folic acid (IFA) supplementation. A randomized clinical trial (RCT) conducted in rural China for instance found no differences in birth weight or other infant outcomes with iron supplementation (Zhao et al. 2015). On the other hand, according to a RCT conducted in Cleveland, daily iron supplements given to non anemic pregnant women lead to significant reduction in the incidence of infants with LBW (Cogswell et al. 2003). Similarly, previous studies in Ethiopia (Mulatu et al. 2016; Girma et al. 2019; Asmare et al. 2018a; Mehare and Sharew 2020; Gebregzabiherher et al. 2017) have shown a relationship between IFA supplementation and LBW and other studies in Ethiopia have shown absence of association between IFA supplementation and LBW (Teklehaimanot 2014; Alemu et al. 2018; Edris and Erakli 1996; Toru and Anmut 2020; Chanie and Dilie 2018; Gebrehawerya et al. 2018; Baye Mulu et al. 2020; Dilnessa et al. 2018; Dadi 2015).

Nowadays using study result from meta-analysis can provide concrete evidence and have got due attention worldwide (Dadi 2015). No meta-analysis was conducted to show the effect of Iron with folic acid supplementation on low birth weight in Ethiopia. Therefore, the aim of the current meta-analysis was to determine the pooled effect size of association between IFA supplementation and LBW by reviewing evidences from studies conducted in Ethiopia.

## Main text

### Study design

Meta-analysis of the association between IFA supplementation and birth weight in Ethiopia was done.

### Search approach and appraisal of studies

PubMed, Google Scholar, Web of Science and Cochrane Library were searched in January 2021. We also searched for unpublished works and government documents through Google search. The search for relevant studies to be included in this meta-analysis was conducted by two of the authors independently. EndNote software was used for search of studies from PubMed and Web of science databases. The other articles were searched from Google scholar and Google individually downloaded and manually entered into EndNote. References of studies that meet eligibility criteria were also used to identify similar articles.

Studies were searched using primary key terms of 'determinant of birth weight', 'birth weight', 'iron supplementation', 'iron and folic acid supplementation and birth weight', 'Ethiopia' and to generate additional keywords for the search we used the following search strategies; "iron and folic acid supplementation + birth weight + Ethiopia"; iron and folic acid supplementation + birth weight through electronic databases on reference manager software.

### Inclusion criteria and exclusion criteria

Available studies and data were included based on the following predefined inclusion criteria. (1) All studies that assessed the relationship between iron with folic acid supplementation and birth weight in Ethiopia, (2) studies which considered LBW outcome of interest (3) studies that reported the percentage of low birth weight according to IFA supplementation and (4) studies that meet quality assessment were included in the study.

On the other hand, Studies that (1) were duplicates, (2) published in languages other than English, (3) studies with birth weight not dichotomized as low and normal and (4) studies with iron with folic acid supplementation not dichotomized as 'Yes' and 'No' were excluded from the study.

### Data extraction

AZ, KTT and AAA carried out the data extraction. The extracted information from eligible studies were the name of the author(s), study design, sample size, study area, the number and percentage of low birth weight and the number and percentage of iron with folic acid supplementation.

### Risk of bias and quality assessment

To assess external and internal validity, a risk-of-bias tool was used. The tool has seven items: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants (performance

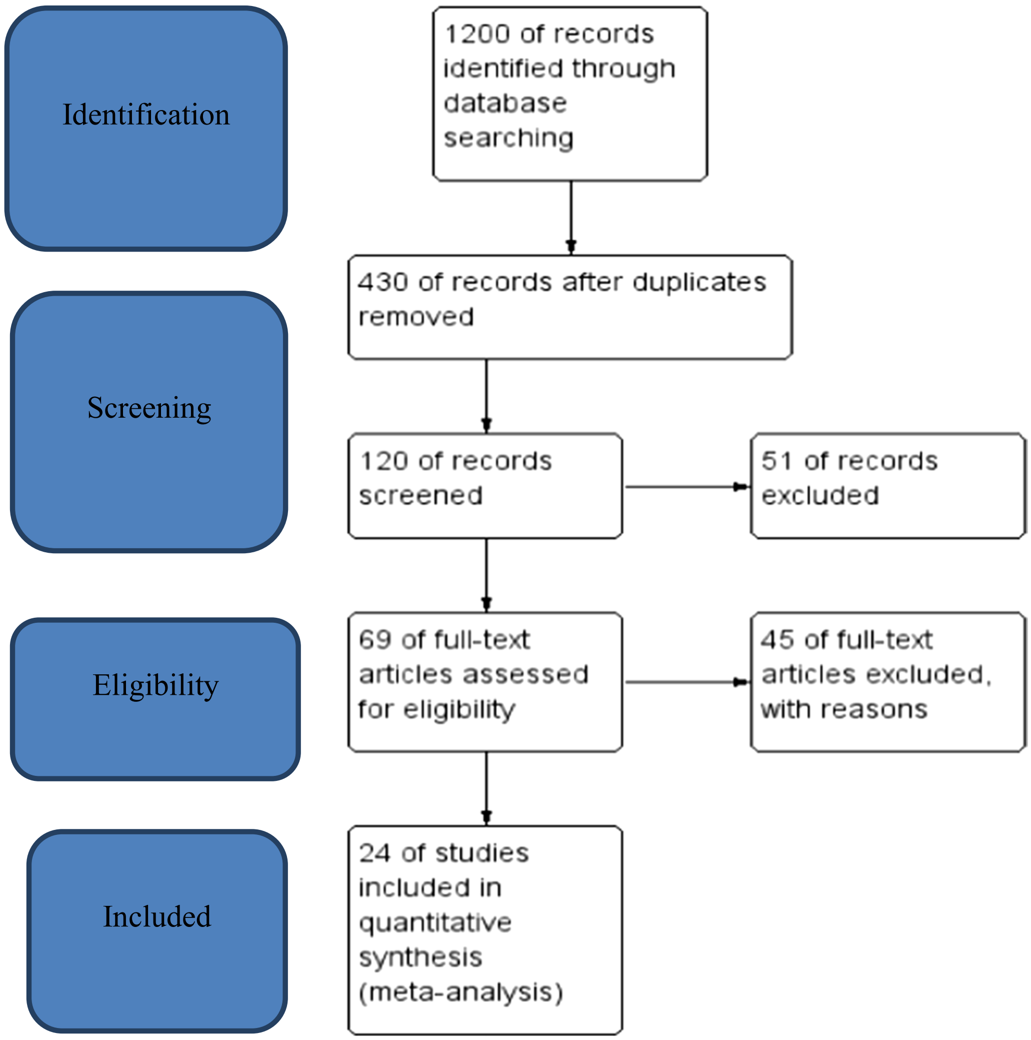


**Fig. 1** PRISMA flow chart of selection process of the included studies

bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data, (6) selective reporting and (7) other bias. All of these items are rated based on the author's subjective judgment given responses to the preceding seven items rated as low, moderate or high risk (Rev 2014).

Three reviewers assessed the articles independently for inclusion in the review using risk-of-bias tool and guided by PRISMA checklist. A discrepancy faced by reviewers on selection of studies and data extraction was resolved by discussion. Additionally, all potential confounding variables were controlled by multivariable analysis in all included studies.

### Measures

Outcome variable Low Birth Weight (LBW) was having a birth weight of less than 2500 g irrespective of the gestational age of the neonate.

### Statistical analysis

The necessary information was extracted from each original study by using a format prepared in Microsoft Excel spreadsheet and transferred to Meta-essential and Revman software for further analysis. Pooled effect size of LBW was estimated from the reported proportion of eligible studies using RevMan V.5.3 software. Forest plots were generated displaying MH odd ratio with the corresponding 95% CIs for each study. As the test statistic showed significant heterogeneity among studies ($I^2 = 90.91\%$, $Q = 253.04$, $p < 0.00001$) the random effects model was used to estimate the DerSimonian and Laird's (DL's) pooled effect.

### Assessment of heterogeneity

To examine the magnitude of the variation between studies, heterogeneity was quantified the by using the $I^2$ measure and its p value. Meta regression was

**Table 1** Characteristics of included studies for association between IFA supplementation and birth weight in Ethiopia, 2020 (n = 24)

| S. no. | Author(s) and year | Sample size | Study design | Region | IFA | Birth weight | |
|---|---|---|---|---|---|---|---|
| | | | | | | Low | Normal |
| 1 | Aynie et al. (2020) | 292 | Cross-sectional | Amhara | Yes | 39 | 221 |
| | | | | | No | 15 | 17 |
| 2 | Liyew et al. (2020) | 1502 | Cross-sectional | National | Yes | 108 | 745 |
| | | | | | No | 90 | 559 |
| 3 | Desalegn (2015) | 441 | Case–control | Amhara | Yes | 18 | 43 |
| | | | | | No | 129 | 251 |
| 4 | Mulatu et al. (2017) | 457 | Cross-sectional | AA | Yes | 17 | 258 |
| | | | | | No | 23 | 159 |
| 5 | Lake and Fite (2019) | 304 | Cross-sectional | SNNP | Yes | 24 | 189 |
| | | | | | No | 24 | 67 |
| 6 | Toru and Anmut (2020) | 196 | Cross-sectional | SNNP | Yes | 5 | 125 |
| | | | | | No | 12 | 42 |
| 7 | Chanie and Dilie (2018) | 243 | Cross-sectional | Amhara | Yes | 50 | 163 |
| | | | | | No | 14 | 16 |
| 8 | Mingude et al. (2020) | 300 | Case–control | SNNP | Yes | 33 | 202 |
| | | | | | No | 27 | 38 |
| 9 | Asmare et al. (2018b) | 453 | Case–control | Amhara | Yes | 95 | 244 |
| | | | | | No | 48 | 42 |
| 10 | Gebrehawerya et al. (2018) | 287 | Case–control | Amhara | Yes | 74 | 175 |
| | | | | | No | 22 | 16 |
| 11 | Girma et al. (2019) | 279 | Case–control | Oromia | Yes | 64 | 166 |
| | | | | | No | 29 | 20 |
| 12 | Desta et al. (2020) | 381 | Case–control | Tigray | Yes | 112 | 234 |
| | | | | | No | 15 | 20 |
| 13 | Mulu et al. (2020) | 279 | Case–control | AA | Yes | 65 | 145 |
| | | | | | No | 25 | 35 |
| 14 | Bekela et al. (2020) | 354 | Case–control | Sidama | Yes | 15 | 104 |
| | | | | | No | 90 | 112 |
| 15 | Hailemichael et al. (2020) | 405 | Case–control | Tigray | Yes | 89 | 239 |
| | | | | | No | 46 | 31 |
| 16 | Gizaw and Gebremedhin (2018) | 470 | Case–control | Oromia | Yes | 26 | 159 |
| | | | | | No | 68 | 217 |
| 17 | Jember et al. (2020) | 358 | Cross-sectional | Amhara | Yes | 40 | 261 |
| | | | | | No | 16 | 41 |
| 18 | Siyoum and Melese (2019) | 330 | Case–control | Sidama | Yes | 47 | 169 |
| | | | | | No | 63 | 51 |
| 19 | Gebremeskel et al. (2017) | 420 | Case–control | SNNP | Yes | 144 | 130 |
| | | | | | No | 14 | 131 |
| 20 | Adem et al. (2020) | 464 | Case–control | Tigray | Yes | 82 | 279 |
| | | | | | No | 34 | 51 |
| 21 | Alemu et al. (2018) | 282 | Case–control | SNNP | Yes | 38 | 204 |
| | | | | | No | 19 | 21 |
| 22 | Ekubagewargies et al. (2019) | 240 | Cross-sectional | Amhara | Yes | 20 | 189 |
| | | | | | No | 12 | 19 |
| 23 | Dendir and Dayesa (2017) | 347 | Case–control | AA | Yes | 205 | 93 |
| | | | | | No | 30 | 19 |
| 24 | Gudeta et al. (2019) | 1980 | Cross-sectional | SNNP | Yes | 64 | 1600 |
| | | | | | No | 84 | 232 |

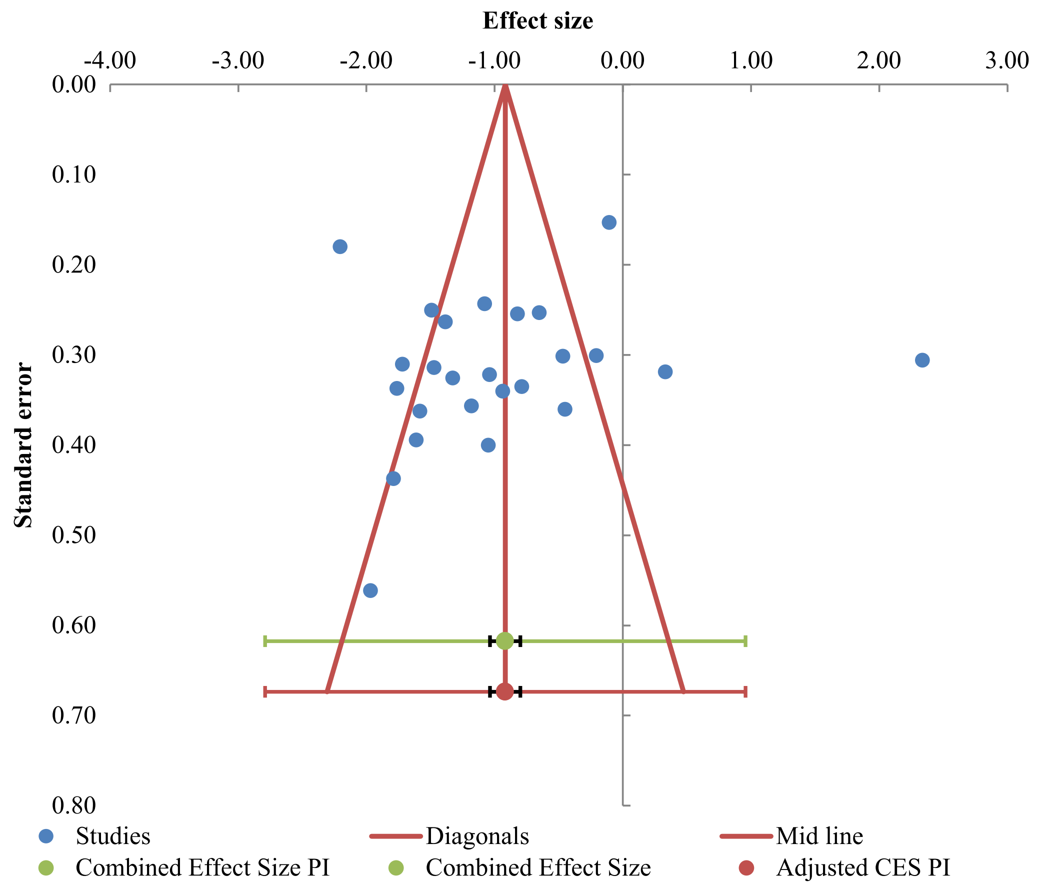


**Fig. 2** Funnel plot for IFA supplementation and birth weight in Ethiopia

undertaken by taking low birth weight and iron with folic acid supplementation to identify the potential source of heterogeneity.

### Assessment of publication bias

Funnel plot asymmetry and Egger's test was used to check for publication bias.

## Result

### Selected studies

Figure 1 shows selection process of studies 1200 of records identified through database searching 430 of records after duplicates removed 120 of records screened and 51 of records excluded, 69 of full-text articles assessed for eligibility and 45 of full-text articles excluded, with reasons, studies not in Ethiopia and studies not examining birth weight and iron with folic acid supplementation and finally 24 of studies included in quantitative synthesis (meta-analysis) (Fig. 1).

### Characteristics of included studies

Twenty four (24) studies; 10,967 participants, 2423 newborns who have LBW were included. Table 1 shows description of original studies included (n = 24). The studies constitute populations from the different regions of Ethiopia. Three studies from the Tigray region, 7 from Amhara region, 2 studies from the Oromia region, 6 studies from Southern region, 2 studies from Sidama region, 3 studies from Addis Ababa city and one national study were included in the study. Regarding the study design of the included studies; nine were done by cross-sectional study design and fifteen studies by case–control study design (Table 1).

### Magnitude of low birth weight

Overall 7622 (69.5%) women have taken IFA supplementation during current pregnancy. The overall burden of LBW was 22.1%. The proportion of LBW among women reported IFA supplementation during current pregnancy was 19.34% and the proportion of LBW among women with no IFA supplementation was 28.37%.

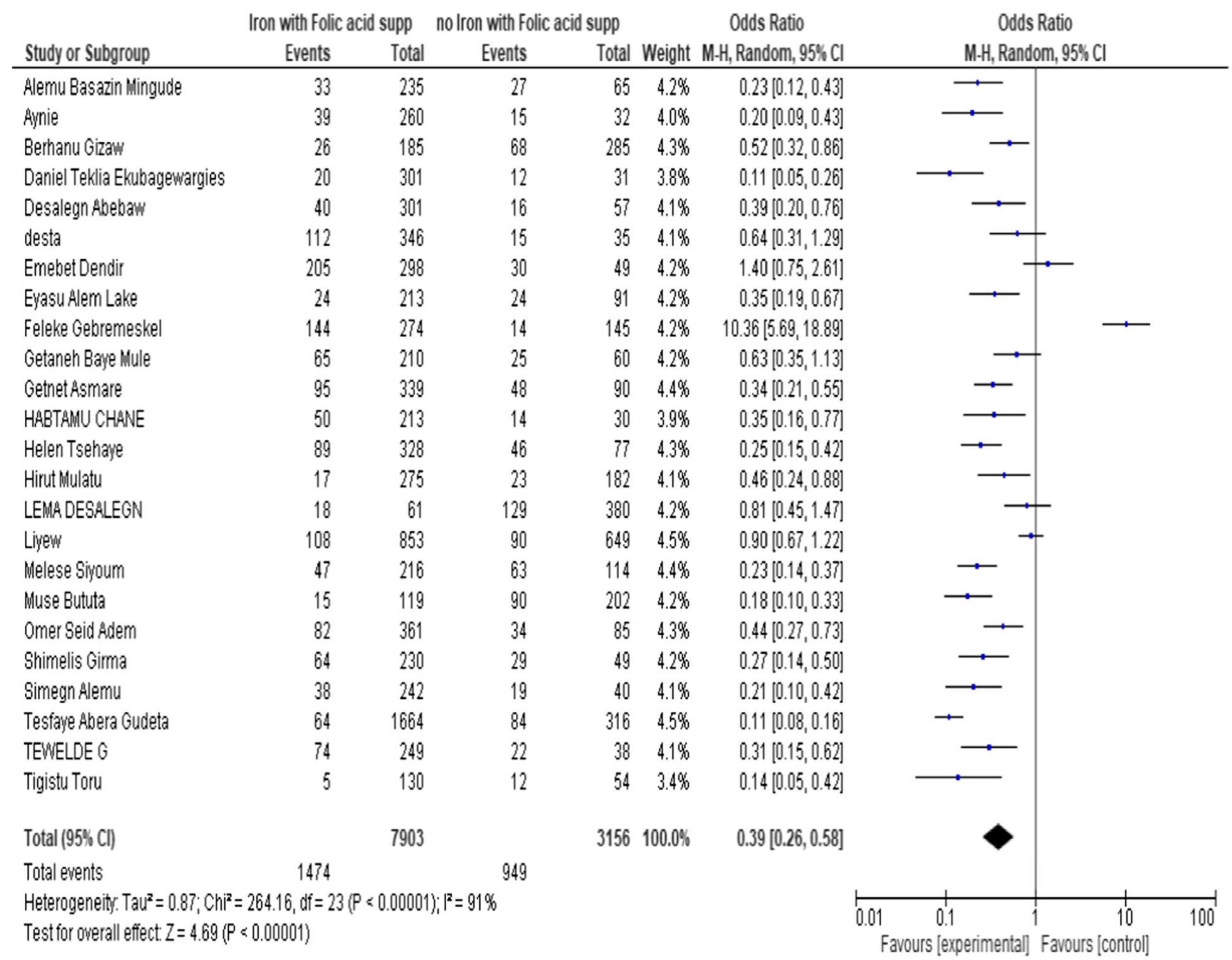


**Fig. 3** Forest plot for the association between IFA supplementation and LBW in Ethiopia

### Publication bias and heterogeneity

The $I^2$ test for heterogeneity showed significant difference among studies ($I^2 = 91\%$, $p < 0.00001$)). No publication bias was observed (Egger's test: $p = 0.742$, Begg's test: $p = 0.372$) (Fig. 2).

### Pooled effect size

The pooled effect size of low birth weight among women with IFA supplementation in the form of odds ratio (OR) was 0.39 (95% CI 0.27–0.59), $p < 0.00001$. $I^2 = 90.91\%$) as compared to those without iron/folic acid supplementation (Fig. 3).

### Meta regression

The DerSimonian and Laird random effect model was used to determine the pooled effect size. According to the Meta regression analysis in the random effect model, prevalence of low birth weight and effect size showed significant difference, i.e., the larger the prevalence of low birth weight the larger the effect size would be (B = 0.03, $p < 0.00001$) (Fig. 4).

Similarly, as IFA supplementation decreases the odds of low birth weight increases (B = − 0.02, $p < 0.00001$) (Fig. 5).

Another sub group analysis was done to see the relationship between LBW and sample size of the studies and the result showed a significant association between LBW and sample size. Accordingly LBW decreases as the sample size of the included studies increases (B = − 0.89, $p = 0.036$) (Fig. 6).

## Discussion

In the current meta-analysis, we estimated the pooled effect size of association between IFA supplementation and LBW in Ethiopia. The study showed that the odds of LBW among women with IFA supplementation was decreased by 61% (OR = 0.39, 95% CI 0.27–0.59,

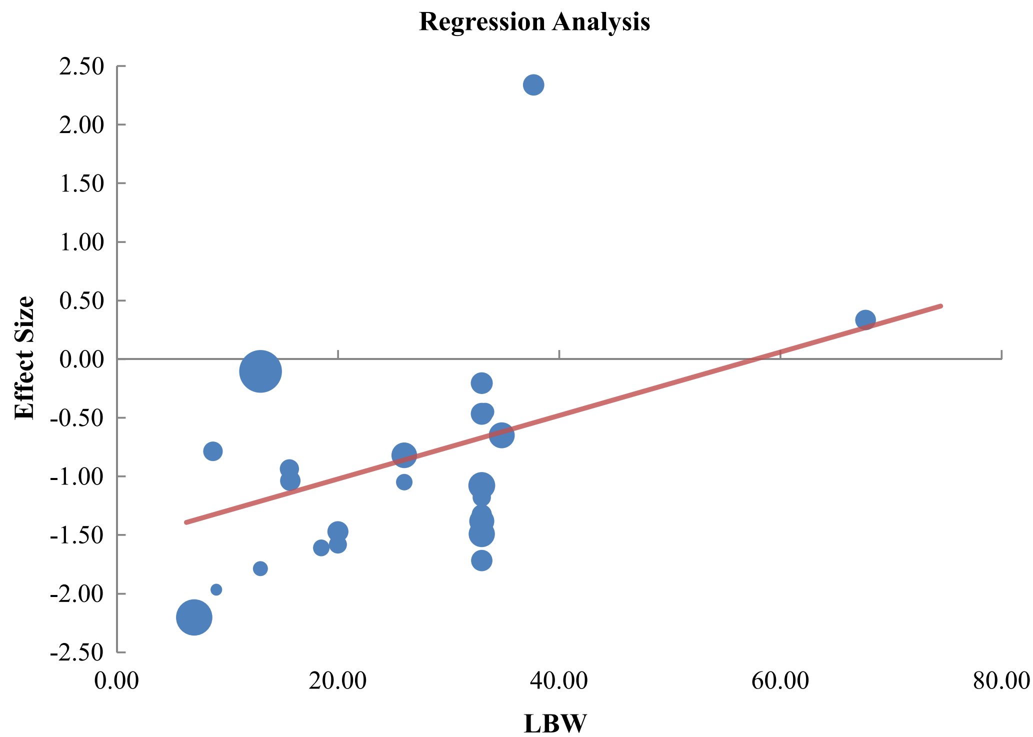


**Fig. 4** Prevalence of low birth weight and effect size in Ethiopia

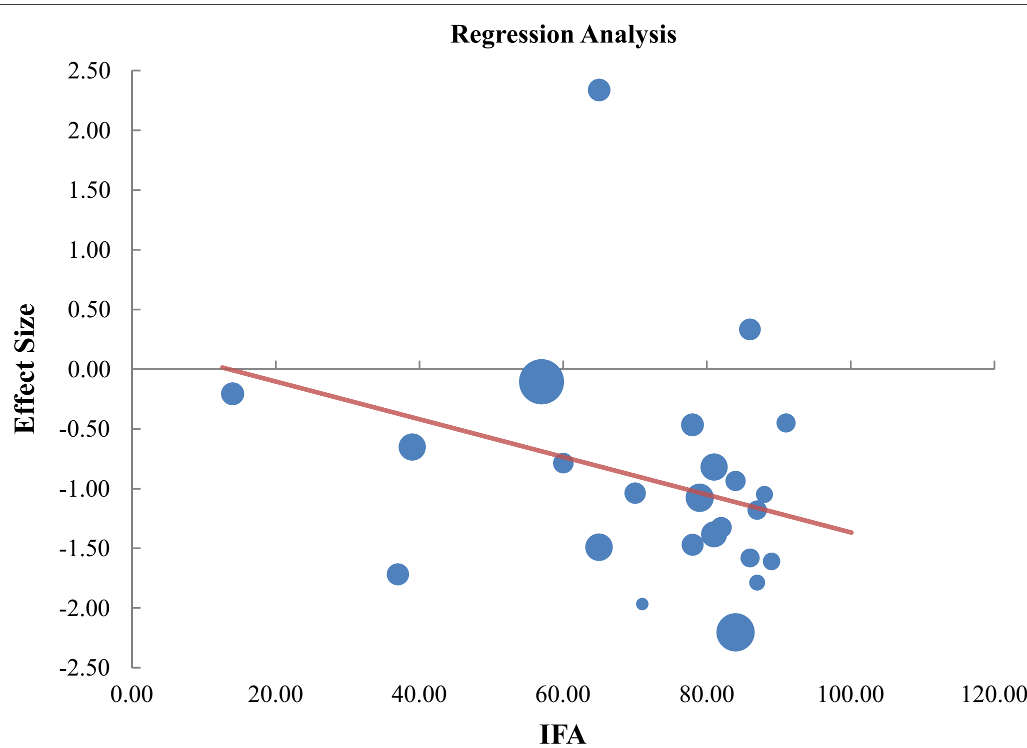


**Fig. 5** Iron with folic acid supplementation and effect size in Ethiopia

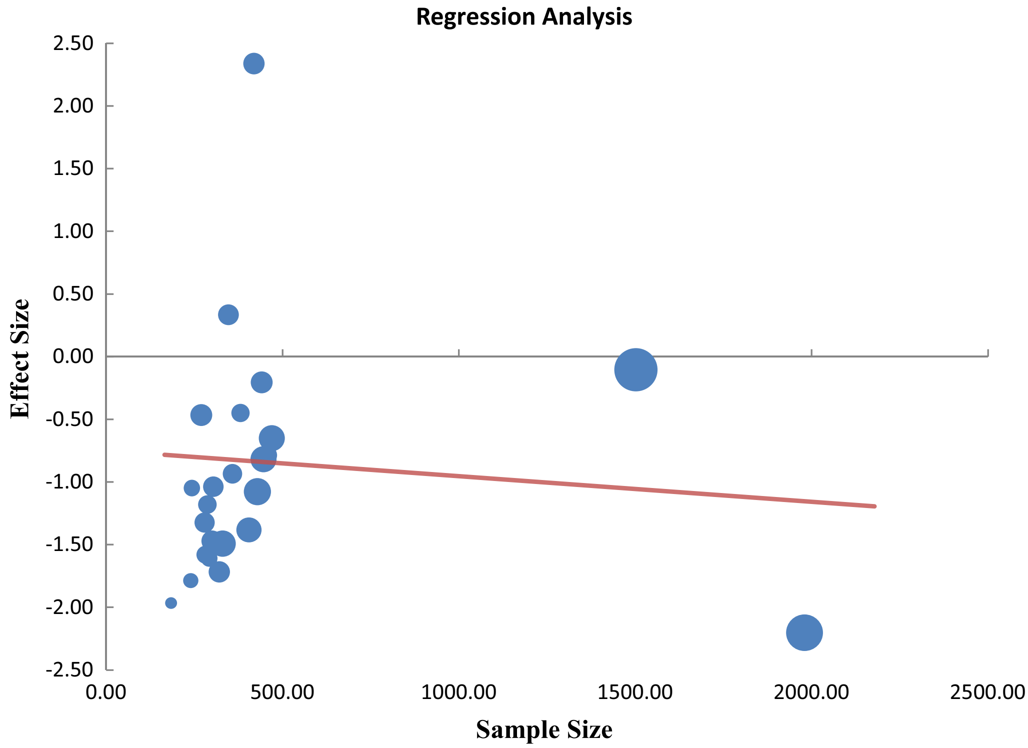


**Fig. 6** Sample size and effect size in Ethiopia

$p < 0.00001$) compared to women who have no IFA supplementation. This finding is consistent with previous studies in Ethiopia (Mulatu et al. 2016; Girma et al. 2019; Asmare et al. 2018a; Mehare and Sharew 2020; Gebregzabiherher et al. 2017), Ghana (Zakariah 2016), India (Manna et al. 2013; Ismail and Venugopalan 2016), Bangladesh (Martin et al. 2008), Nepal (Khanal et al. 2006), America (Cogswell et al. 2003) and Mexico (Ramakrishnan et al. 2003).

Even though the mechanism of IFA supplementation on BW is not well understood, there are two hypotheses explaining about improvements in birth weight due to iron supplements (Cogswell et al. 2003). The first hypothesis is that, taking IFA supplementation improves appetite of the mother which leads to improve the overall nutritional status of mothers which sequentially reduces the chance of having LBW newborn. Second, Iron deficiency anemia (IDA) leads to change in norepinephrine, cortisol and corticotrophin which results in oxidative stress to fetal growth leading to having LBW baby which can be reduced by iron supplementation (Cogswell et al. 2003; Allen 2001; Huang et al. 2015).

IFA supplementation for pregnant mothers has a great importance to prevent anemia during pregnancy, thereby enhancing better health outcome for both the mother and the fetus (Kramer 1987; Abu-Ouf and Jan 2015). Women who were supplemented with iron were less likely to deliver to a LBW baby. This could be due to the fact that, the growing fetus shares nutrients from mother for its intrauterine development.

But it is different from previous studies in Ethiopia (Teklehaimanot 2014; Alemu et al. 2018; Edris and Erakli 1996; Toru and Anmut 2020; Chanie and Dilie 2018; Gebrehawerya et al. 2018; Baye Mulu et al. 2020; Dilnessa et al. 2018) and India (Chiniwar and Menasinkai 2020) which did show any association between iron with folic acid supplementation and low birth weight. The possible explanations for the observed differences of associations between Iron with folic acid supplementation and low birth weight could be the seasonal variations of LBW and differences in sample characteristics, study design, sample size, study time, study area and due to various intervention undertaken between these study time.

The result of this systematic review and meta-analysis should be interpreted in line with its limitations. Firstly, the dataset was not complete due to some restrictions of accessing to full texts. Secondly, due to all of the studies included were done by case–control and cross-sectional study design the result might potentially affected by confounding variables and selection bias. The observed high heterogeneity among studies was also considered as limitation of this review. Due to the above reasons the investigators recommend longitudinal national studies to assess association between IFA supplementation and LBW.

## Conclusion

Women who take IFA supplementation during pregnancy have a 61% decreased odds of delivering low birth weight new born in Ethiopia. The prevalence of LBW was higher among women with no IFA supplementation when compared to women who have taken IFA supplementation. Therefore, continued efforts are needed in enhancing universal access to IFA supplementation to improve neonatal health in Ethiopia.

### Abbreviations

AA: Addis Ababa; CI: Confidence interval; DHS: Demographic and health survey; IFA: Iron and folic acid; LBW: Low birth weight; OR: Odds ratio; UNICEF: United Nations Children's Fund; WHO: World Health Organization.

### Acknowledgements

We would like to thank all the primary authors of the included articles.

### Authors' contributions

AZ, KTT, BB and AAA contributed to the idea of the study and study design. AAA, KTT and BB established the search strategy. AZ, KTT and AAA carried out the data extraction. AZ, KTT, BB and AAA contributed in analysis and interpretation of data and drafting the article for intellectual content. AZ revised the final manuscript, and is the corresponding author. All of the authors read and approved the final manuscript.

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No funding was received for this meta-analysis.

### Availability of data and materials

All analyzed data are included in the article.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interest

The authors declare that they have no competing interest.

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