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IRON WITH FOLIC ACID SUPPLEMENATION AND BIRTH WEIGHT IN ETHIOPIA SYSTEMIC REVIEW AND META ANALYSIS

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ABSTRACT

REVIEW ARTICLE

Objective: The aim of this systemic review and meta-analysis was to examine the relationship between iron with folic acid supplementation and low birth weight in Ethiopia Previous studies on iron with folic acid supplementation and low birth weight indicated different findings. We include 24 studies in different regions of Ethiopia. We have done this study focusing on iron with folic acid supplementation

Materials and Methods The databases searched were PUBMED and Advanced Google Scholar. on reference manager software reporting iron with folic acid supplementation and low birth weight. Three researchers were carried out the data extraction and assessed independently the articles for inclusion in the review using risk-of-bias tool guided by PRISMA checklist. The combined adjusted Odds ratios (OR)) and 95% confidence intervals were calculated using random effect model

Results: Twenty-four observational studies involving 10 989 participants, 2348 newborns have low birth weight were included. The combined effect size (OR) for low birth weight r comparing women who have iron with folic acid supplementation versus women who did not have iron with folic acid supplementation was 0.37 (95%CI 0.25 to 0.55), $p<0.00001$, I^2 = 91 %). There was significant heterogeneity (Q = 264.75. I^2 =91 %). $p<0.00001$) No publication bias was observed (Egger's test: p = 0.621, Begg's test: p = 0.254). 71.11% (7815), women reported iron with folic acid supplementation during current pregnancy in all studies, the proportion of low birth weight among women reported iron with folic acid supplementation during current

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pregnancy was 1392 (17.85%).
Conclusions: Women who take iron with folic acid supplementation during pregnancy have a 67% decreased of delivering low birth weight new born in Ethiopia.

INTRODUCTION

The World Health Organization (WHO) defines Low Birth Weight (LBW) as having a birth weight (BW) of less than 2500 gram irrespective of the gestational age of the neonate [1]. An estimated 18 million babies worldwide are born each year with LBW [1].

The prevalence of low birth weight in developing countries (16.5%) (2)

Previous studies done in Ethiopia have shown that low birth weight prevalence was ranged from 22.5%, in Southwest and 17.5%, in Northwest [3, 4.].

Low birth weight can be prevented by services during ANC and educating mother about reproductive health [5]

Some of the variables that are found to be predicator of LBW in one study may not necessarily be factor in another study. Supporting the argument on possible determinants of LBW vary across the geographical location. (6)

Previous studies in Ethiopia (7-11) have showed a relationship between Iron with folic acid supplementation and low birth weight and other studies in Ethiopia shows the absence of association between Iron with folic acid supplementation and low birth weight (12- *19)*

In Ethiopia studies reported inconsistent results. Now a days using study result from meta-analysis can provide concrete evidence and have got due attention worldwide. (20)

In Ethiopia, no meta-analysis was conducted to show the effect of Iron with folic acid supplementation on low birth weight. Therefore, the purpose of this meta-analysis was to determine the pooled effect size of Iron with folic acid supplementation on low birth weight by reviewing a collection of evidences from limited studies conducted in Ethiopia.

METHODS

Search approach and appraisal of studies

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

The databases searched were PUBMED and Advanced Google Scholar, References of studies that meet eligibility criteria were used to identify similar articles

Inclusion criteria

1. All Studies that were assessed the relationship between iron with folic acid supplementation and birth weight.
2. The outcome of interest was low birth weight
3. The study reported the percentage of low birth weight according to iron with folic acid supplementation
4. Meet quality assessment

Exclusion criteria

1. Studies that were published in languages other than English,
2. included participants with birth weight not dichotomized as low and normal,
3. included participants with iron with folic acid supplementation not dichotomized as yes and no
4. studies conducted not in Ethiopia were also excluded to avoid the combination of studies that were not comparable.

Data Extraction

Three researchers were carried out the data extraction The extracted information were the name of the author, study design, sample size, study area, the number and percentage of low birth weight, 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 bias), 4) blinding of outcome assessment (detection bias), 5) incomplete outcome data (attrition bias), 6) selective reporting (reporting bias) 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 (21).

Three reviewers assessed independently the articles for inclusion in the review using risk-of-bias tool and guided by PRISMA checklist.

A discrepancy that would face 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) as having a birth weight (BW) of less than 2500 gram irrespective of the gestational age of the neonate. If low birth weight 1 and if not low birth weight 0 [1].

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 low birth weight 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 = 91%, Q = 264.75. p<0.00001) the Random effects model was used to estimate the DerSimonian and Laird's pooled effect.

Assessment of Heterogeneity.

To examine the magnitude of the variation between studies, we will quantify the heterogeneity by using the I^2 measure and its p value. To identify the possible source of heterogeneity, Meta regression was undertaken by taking low birth weight and iron with folic acid supplementation

Assessment of *Publication Bias*

Funnel plot asymmetry and Egger's test was used to check the 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)

Characteristics of Included Studies

Twenty-four (24) studies, 10 989 participants, 2348 newborns have low birth weight were included.

Table 1 shows description of original studies included (n=24), (Table 1)

The studies constitutes populations from five regions of Ethiopia. Two studies from the Tigray region, another 7 from Amhara region, the 3 studies from the Oromia region and 9 studies from Southern region, 1 national Ethiopia study and 2 study from Addis Ababa city.

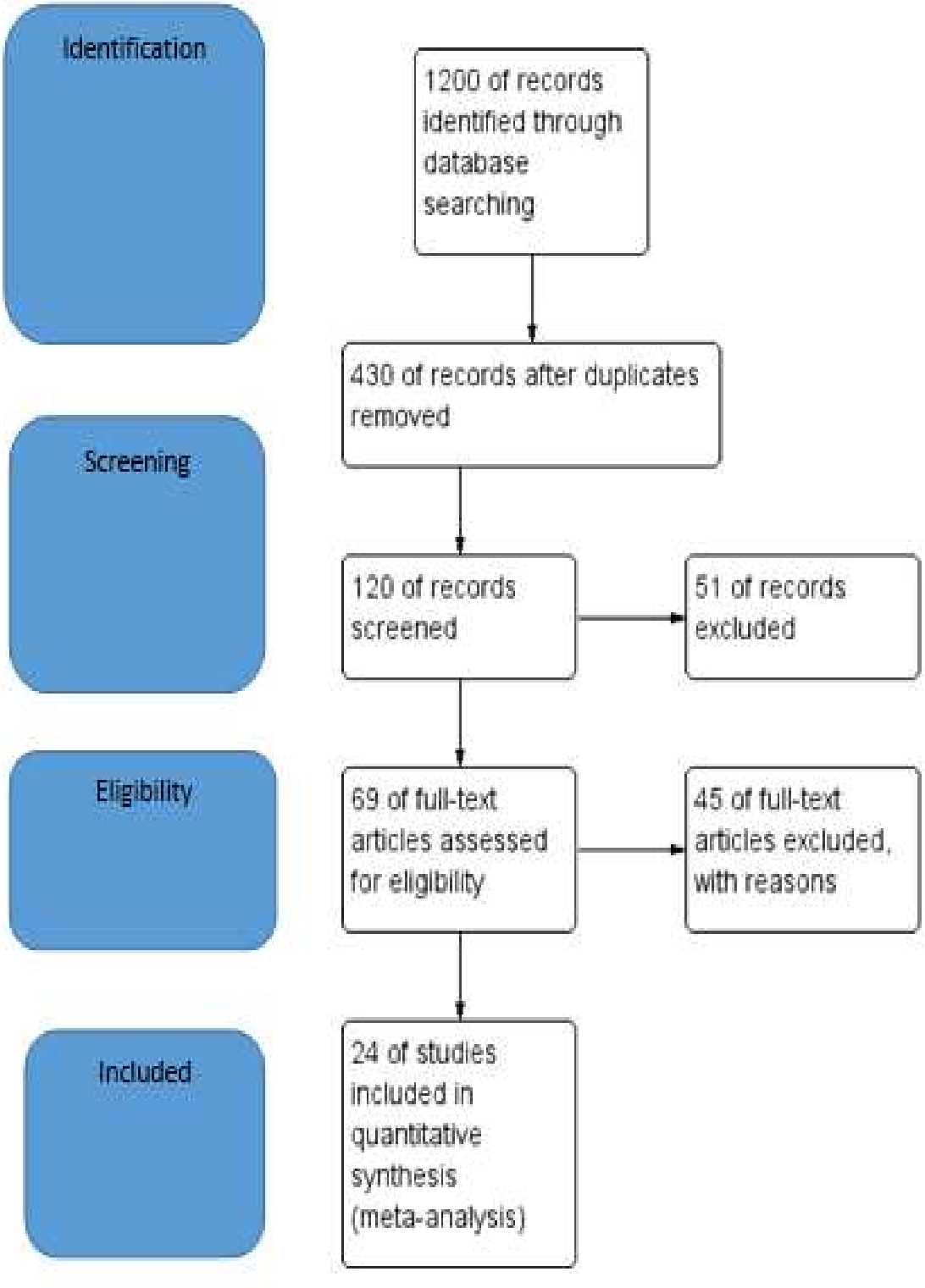

Figure 1: PRISMA flow chart of the included studies selection process

Table 1 Characteristics of studies for Iron/folate supplementation and Birth weight Ethiopia, 2020(n=24)

S. No.	Articles	SS	Tittle / study design	Iron-folate supplementation	Birth weight	
					Low	Normal
1.	Aynie	292	Prevalence of Low Birth Weight and Its Determinants in Bahirdar City, Amhara Region, North West Ethiopia: Health Facility Based Cross-Sectional Study	Yes	39	221
				No	15	17
2.	Alemneh Mekuriaw Liyew	1502	Spatial distribution and factors associated with low birth weight in Ethiopia using data from Ethiopian demographic and health survey 2016: spatial and multilevel analysis.	Yes	108	745
				No	90	559
3.	Lema Desalegn	441	Determinants Of Low Birth Weight In Debre Berehan Referal Hospital, North Shoa Zone, Amhara Regional State, Ethiopia (A Case – Control Study)	Yes	18	43
				No	129	251
4.	Hirut Mulatu,	457	Magnitude and Factors Associated with Low Birth Weight among New Born in Selected Public Hospitals of Addis Ababa, Ethiopia, 2016	Yes	17	258
				No	23	159
5.	Eyasu Alem Lake	304	Low Birth Weight and Its Associated Factors among Newborns Delivered at Wolaita Sodo University Teaching and Referral Hospital, Southern Ethiopia, 2018	Yes	24	1 89
				No	24	67
6.	Tigistu Toru	196	Assessment of Low Birth Weight and Associated Factors Among Neonates in Butajira General Hospital, South Ethiopia, Cross Sectional Study, 2019	Yes	5	125
				No	12	42
7.	Habtamu Chane	243	Prevalence of LBW In Deberemarkose Referal Hospital	Yes	50	163
				No	14	16
8.	Alemu Basazin Mingude	300	Determinants of low birth weight among live birth newborns delivered at public hospitals in Gamo Gofa Zone, South Ethiopia: Unmatched case control study	Yes	33	202
				No	27	38
9.	GetnetAsmare	453	Determinants of low birth weight among neonates born in	Yes	95	244

			Amhara Regional State Referral Hospitals of Ethiopia: unmatched case control study	No	48	42
10.	Tewelde Gebrehawerya	287	Determinants of Low Birth Weight among Mothers Who Gave Birth in Debremarkos Referral Hospital, Debremarkos Town, East Gojam, Amhara Region, Ethiopia	Yes	74	175
				No	22	16
				No	7	49
11.	Shimelis Girma	279	Factors associated with low birthweight among newborns delivered at public health facilities of Nekemte town, West Ethiopia: a case control study	Yes	64	166
				No	29	20
12.	Tigistu Yemane	403	Low Birth Weight and Associated Factors In Public Health Facilities In Diredawa Town, Ethiopia	Yes	33	317
				No	20	33
13.	Getaneh Baye Mulu et al	279	Determinants of Low Birth Weight Among Newborns Delivered in Public Hospitals in Addis Ababa, Ethiopia: Case-Control Study	Yes	65	145
				No	25	35
14.	Muse Bututa Bekela	354	Determinants of Low Birth Weight among Newborns Delivered at Public Hospitals in Sidama Zone, South Ethiopia: Unmatched Case-Control Study	Yes	15	104
				No	90	112
15.	Helen Tsehaye Hailemichael	405	Determinants of adverse birth outcome in Tigrai region, North Ethiopia: Hospital-based case-control study	Yes	89	239
				No	46	31
16.	Berhanu Gizaw	470	Factors associated with low birthweight in North Shewa zone, Central Ethiopia: case-control study	Yes	26	159
				No	68	217
17.	Desalegn Abebaw Jember	358	Low Birth Weight and Associated Factors Among Newborn Babies in Health Institutions in Dessie, Amhara, Ethiopia	Yes	40	261
				No	16	41
18.	Melese Siyoum	330	Factors associated with low birth weight among babies born at Hawassa University Comprehensive Specialized Hospital, Hawassa, Ethiopia	Yes	47	169
				No	63	51
19.	Feleke Gebremeskel	420	Determinants of Adverse Birth Outcome among Mothers who Gave Birth at Hospitals in Gamo Gofa Zone, Southern Ethiopia: A Facility Based Case Control Study	Yes	144	130
				No	14	131

20.	Omer Seid Adem	464	Determinants of Low Bir th Weight Infants in Mekelle Zone, Tigray Region, Nor thern Ethiopia- Case-Control Study	Yes	82	279
				No	34	51
21.	Simegn Alemu	282	Determinants of low birth weight in public health facilities, of Kambata Tembaro Zone, South Ethiopia	Yes	38	204
				No	19	21
22.	Daniale Tekelia Ekubagewargies	240	Maternal HIV infection and preeclampsia increased risk of low birth weight among newborns delivered at University of Gondar specialized referral hospital, Northwest Ethiopia, 2017	Yes	20	189
				No	12	19
23.	Emebet Dendir	347	Substance use and birth weight among mothers attending public hospitals: A case control study	Yes	205	93
				No	30	19
24.	Tesfaye Abera Gudeta	1980	Magnitude And Factors Associated With Low Birth Weight Among Women Delivered In Public Hospitals Of Bench Maji, Keffa And Sheka Zones South West Of Ethiopia, 2018	Yes	64	1600
				No	84	232

71.11% (7815), women reported iron with folic acid supplementation during current pregnancy, 21.37% (2348) newborns have low birth weight in all studies, the proportion of low birth weight among women reported iron with folic acid supplementation during current pregnancy was 1392 (17.85%).

Pooled effect size

The pooled effect size of low birth weight among women with iron/folic acid supplementation in the form of odds ratio (OR) was 0.37 (95%CI 0.25 to 0.55), *p<0.00001*. I^2= 91% %) as compared to those without iron/folic acid supplementation

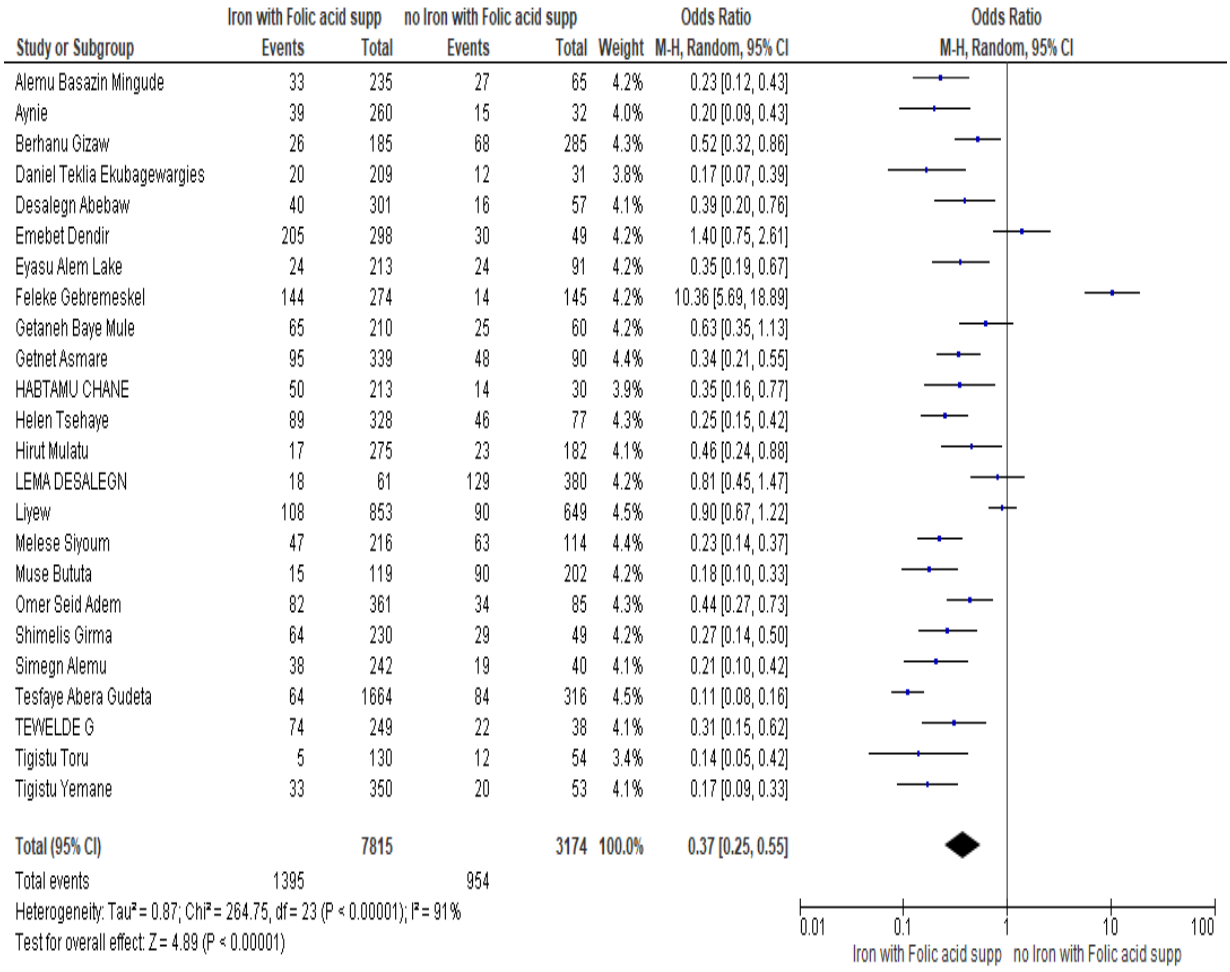

Figure 2 Forest plot for the association between iron with folic acid supplementation ad low birth weight in Ethiopia

The I^2 test for heterogeneity showed significant difference among studies (I^2 = 91 %, p<*0.00001*)). So, 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.

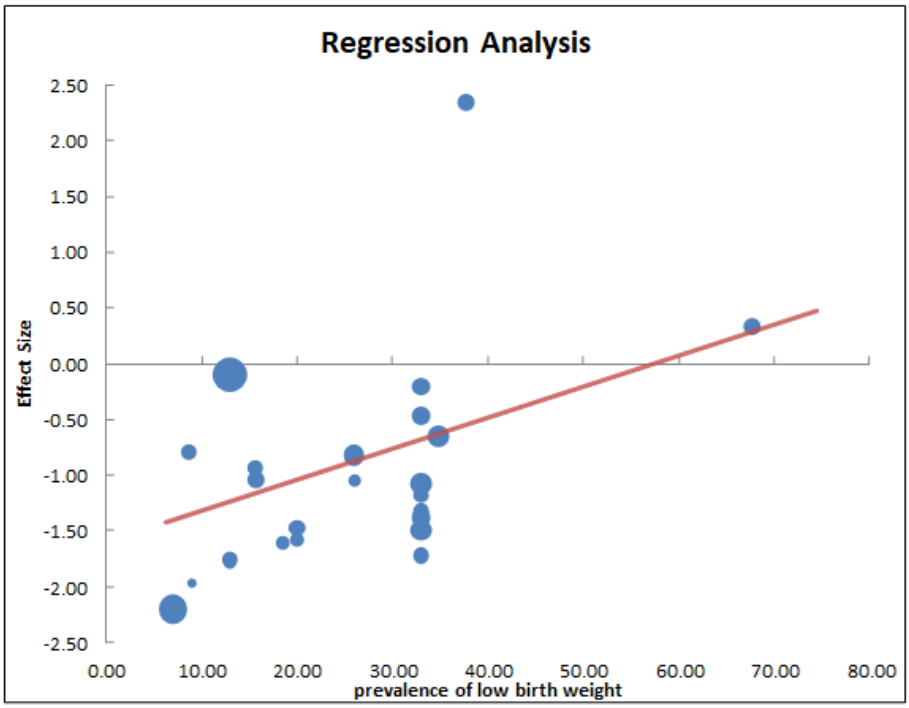

Figure 3 Prevalence of low birth weight and effect size in Ethiopia (B=0.03. p<*0.00001*)

Similarly, as iron/folic acid supplementation decrease the odds of low birth weight increases.

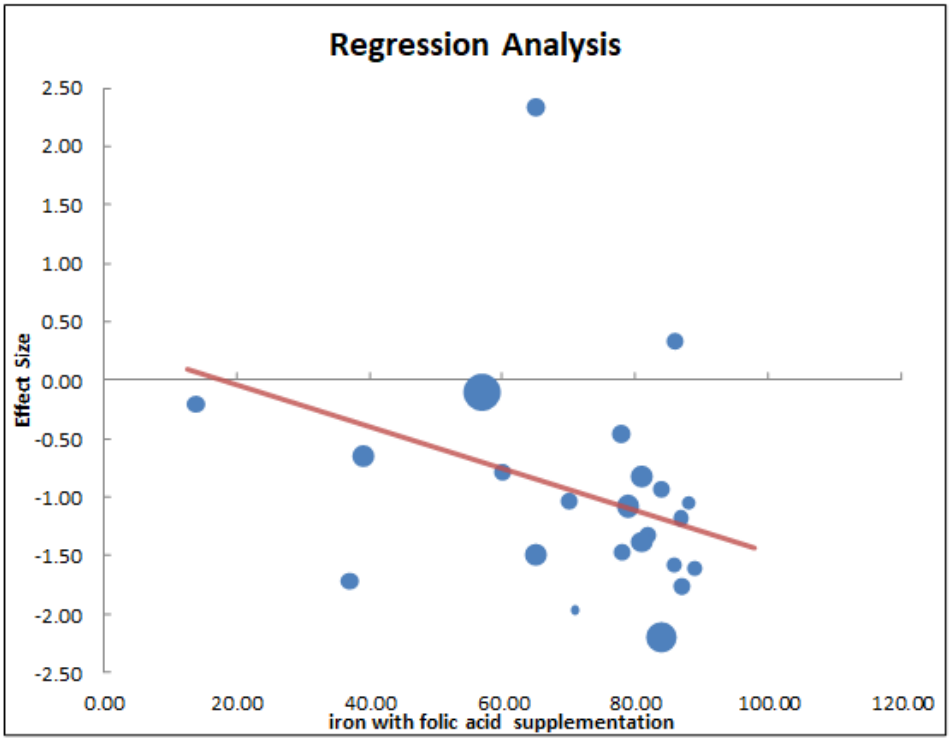

Figure 4 Iron with folic acid supplementation and effect size in Ethiopia (B=-0.02. p<*0.00001*)

No publication bias was observed (Egger's test: $p = 0.621$, Begg's test: $p = 0.254$).

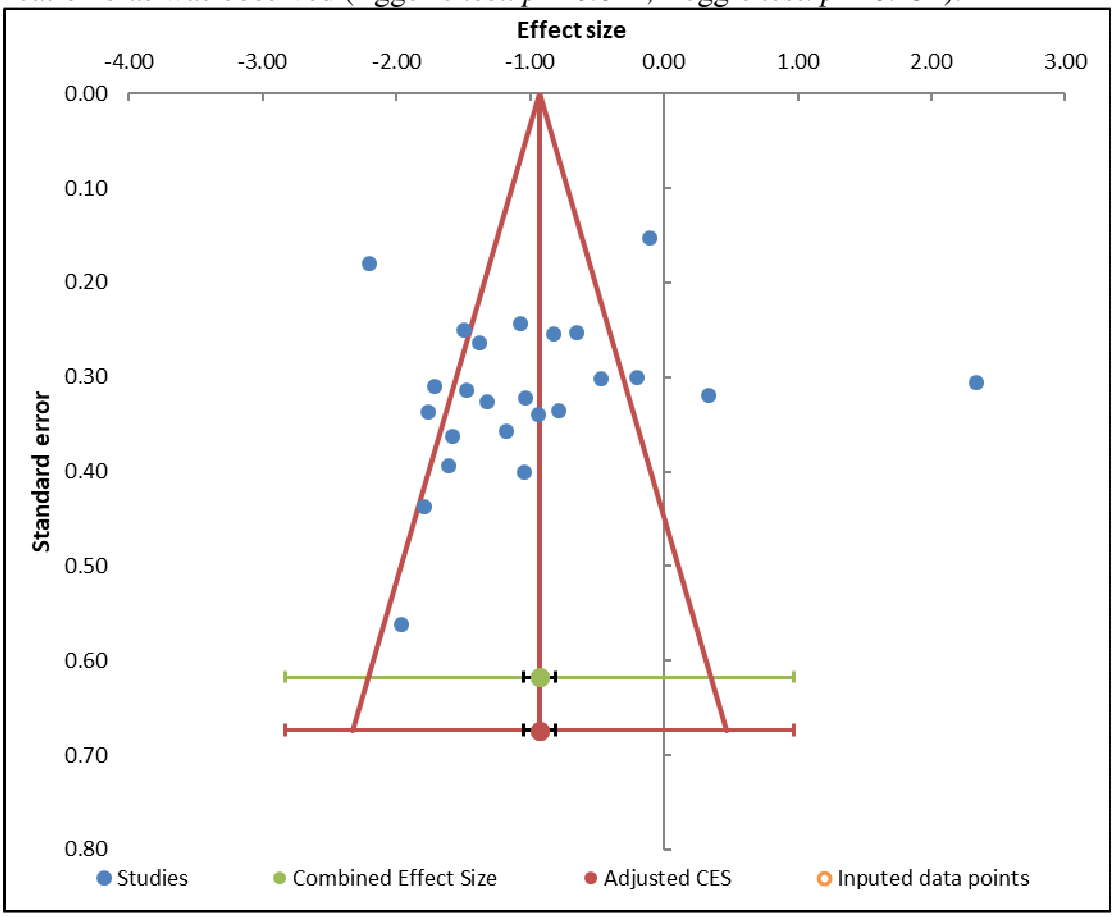

Figure 5 Funnel plot for iron/folic acid supplementation and birth weight in Ethiopia

DISCUSSION

In the present study odds of low birth weight among women who have iron with folic acid supplementation is decreased by 67% compared to women who have not iron with folic acid supplementation (OR=0.37 955CI 0.25-0.55 *p<0.00001*)

This is consistent with previous studies in Ethiopia (7-11), Ghana (22), India [23-24], Bangladesh [25], Nepal (26], America [27] and Mexico) [28].

The physiological mechanism of iron supplementation on birth weight is not understood; however, there are two hypotheses about improvements in birth weight due to iron supplements [27].

First, iron supplementation helps to improve appetite which improves the overall nutritional status of mothers.

Second, iron deficiency anemia leads to change in norepinephrine, cortisol, and corticotrophin that result in oxidative stress to fetal growth which is reduced by iron supplementation [27, 29].

Iron and folic acid 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 [30.].

Women who supplemented with iron were less probable to deliver LBW baby.

It is due to the fact that; the growing fetus shares not only iron but also other

nutrient from mother for its intrauterine development.

But it is different from previous studies in Ethiopia (12- 19) and India (31*)* 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 is 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

CONCLUSION

Women who take iron with folic acid supplementation during pregnancy have a 67% decreased of delivering low birth weight new born in Ethiopia

Conflicts of Interest: The authors declare that they have no conflicts of interest.

Authors' Contributions:

1) Kaleab Tesfaye Tegegne was responsible for conceptualization, project administration, software, supervision, and development of the original drafting of the manuscript.
2) Kaleab Tesfaye Tegegne, Eleni Tesfaye Tegegne, Abiyu Ayalew Assefa, Mekibib Kassa Tessema, Berhanu Bifato and *Andualem Zenebe* were participated in quality assessment of articles, methodology, validation, and screening of research papers
3) All authors contributed with data analysis, critically revised the paper, and agreed to be accountable for their contribution.

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Competing of interest

The authors have declared that there is no competing interest

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