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Effectiveness of Food Fortification to Anemia in Adolescents: A Systematic Review and Meta-Analysis

Efektivitas Fortifikasi Pangan terhadap Kadar Hemoglobin pada Remaja: Tinjauan Sistematis dan Meta-Analisis

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Iron Fortification, Adolescent, Anemia, Hemoglobin, Meta-Analysis

ABSTRACT

Background: Anemia is still a global problem with nearly 2 billion people worldwide experiencing anemia by 2021. The population most vulnerable to anemia is adolescent girls. Anemia is prevalent in low- and middle-income countries. Food fortification is an anemia prevention strategy that is considered the most effective, economical, and able to reach the wider community.
Objectives: To assess the effectiveness of iron (Fe)-fortified foods, whether or not supplemented with other micronutrients, on adolescent anemia in low- and middle-income countries.
Methods: This research follows the PRISMA protocol and PICO rules. The databases used were PubMed, Scopus, Science Direct, and Cochrane. Study participants were adolescent girls aged 10-18 who received Fe-fortified food intervention. The comparison was adolescents who were given non-fortified food or a placebo. The outcome of interest was hemoglobin (Hb) level.
Discussions: Of the 482 studies obtained, 10 studies were eligible, and eight studies proceeded to meta-analysis. The results of the meta-analysis showed that the mean change in Hb was higher in the intervention group compared to the control group. However, the variation between studies was heterogeneous (I^2=97%, p-value<0.01). The highest mean difference value was fortification in soy sauce with 40 mg NaFeEDTA with Standardized Mean Difference (SMD)=2.88 mg/dL, while the lowest was rice fortification with SMD=0.01 mg/dL.
Conclusions: This study can serve as a reference for creating intervention programs for fortification of foodstuffs to prevent anemia in adolescent girls in developing countries and upper-middle-income countries.

INTRODUCTION

Anemia is a global problem with almost 2 billion people in the world experiencing anemia in 2021. Anemia is more common in women than men[1]. Anemia is generally caused by Iron Deficiency Anemia (IDA), which affects 30% of the population. The causes of IDA include gastrointestinal disorders that cause bleeding, menstruation in women, lack of iron intake in the diet, and impaired iron absorption in the body[2]. Anemia is a major contributor to maternal mortality. In addition, individuals who are anemic can reduce work productivity due to fatigue and shortness of breath during activities[3].

Populations that are prone to anemia are women of childbearing age and adolescent girls. Anemia is prevalent in low-income and middle-income countries[4]. There are four main strategies to address anemia according to the World Health Organization in 2006, namely iron supplementation, fortification, nutrition education, and food diversity. Food fortification is the strategy that is considered the most effective, economical, and able to reach a wide population[5]. Food fortification is the process of adding micronutrients to processed foods[6]. Iron compounds selected for food fortification are usually the most widely available compounds in nature such as *Ferric Sodium Ethylenediaminetetraacetic Acid* (NaFeEDTA), *ferrous sulfate*, *ferrous fumarate*, and elemental iron powder. Foodstuffs used for fortification are staple foodstuffs that are often consumed by the community such as wheat flour, corn flour, rice, dairy products, salt, and sugar[7].

Currently, reviews related to the effect of fortification of various food ingredients on anemia in adolescent girls are limited. Some reviews examine the effect of specific fortification of certain food ingredients on anemia in the entire population or certain populations such as pregnant women[8]. The results of fortification

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practices may vary from country to country depending on local dietary patterns and regulations related to fortification in the country[9]. Therefore, the authors are interested in examining the effect of fortification of various types of food ingredients associated with anemia conditions in adolescents through a systematic review and meta-analysis approach. It can be used as a recommendation for food fortification programs to reduce the prevalence of anemia in adolescent girls in developing countries and low and middle-income countries.

METHODS

This systematic review and meta-analysis refer to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. The databases used were PubMed, Scopus, Science Direct, and Cochrane. The keywords used in each database are listed in Table 1.

Inclusion Criteria

The participants involved in this study were adolescent girls 10-18 years old. If there were studies involving school children under the age limit, they were included in this review. This is based on several studies that found a wide age range of respondents, not specific to the age of 10-18 years. There was a younger age range below 10 years, or older than 18 years. However, when the age of 10-18 years was included, the article was still included. Some studies were also limited; there was no division of fortification effectiveness in various age categories involved. In addition, research related to fortification especially in low and middle-income countries is still rare. Therefore, the author included the age category with the aim of capturing articles related to the effectiveness of food fortification in the adolescent age range. The intervention was the provision of Fe-fortified foodstuffs. The food ingredients included rice, biscuits, flour, snacks, and others. The duration of the intervention was at least 12 weeks. There was no year restriction in this review. All articles that met the inclusion criteria, even those from previous years, were retrieved. The control group was participants who were given unfortified food or a placebo. The outcome measured was the Hemoglobin (Hb) level. The type of research included in this study were experimental research such as Randomized Control Trials (RCT) and quasi-experimental. The study sites selected were low and middle-income countries (LMICs) and upper-middle-income countries (UMICs). The language chosen was English. Articles are in full text and open access.

Exclusion Criteria

Articles were excluded if they were not open access or if they required payment, as well as if they were thesis or dissertation articles, proceedings, review articles such as systematic reviews, meta-analyses, or if the results did not answer the research question. Interventions in the form of micronutrient powders were excluded. Populations with critical illness or comorbidities were also excluded.

Literature Search Strategy

Population, Intervention, Comparison, Outcome (PICO) rules were used to facilitate the literature search. The research question in this systematic review was "What is the effectiveness of iron fortification in food on anemia in adolescent girls?". The literature search and review writing process were conducted between 15th October and 22nd December 2023. The literature search process is listed in Figure 1.

Selection, Extraction, and Analysis Process

The article screening process was carried out by two people independently using the Rayyan application. The stages of the screening process began with checking the duplication of articles. After that, the title and abstract were screened. The next stage was full-text screening. If there were differing results, the two authors discussed to determine the decision of the article. Articles selected according to the inclusion criteria were then extracted. Extracted data included author name, year the study was published, study location, study design, population, intervention type, fortified food ingredients, fortified substances, research results, and risk of bias. The risk of bias assessment was carried out according to the study design used, if the study design was a Randomized Controlled Trial, the Cochrane Risk of Bias Tool instrument was used, if the study design was quasi-experimental then the MINORS instrument was used. The risk of bias assessment was conducted by one person. The results of the risk of bias assessment are listed in Table 2. Meta-analysis of treatment effects presented as mean difference, 95% Confident Interval (CI). Analysis using R Studio 4.2.2 software. Results were presented in the forest plot. Funnel plots were performed to see the presence of publication bias. Random effect was used when heterogeneity was high (Chi Square p-value<0.1 and I^2 > 30%)[9]. Subgroup analysis was conducted to look for heterogeneous sources.

Table 1. Keywords used when searching for articles in the database

Database	Keyword	Total Study
PubMed	Adolescent* AND "Food, Fortified"[Mesh] AND "Anemia"[Mesh]	153
Science Direct	Adolescent* AND Food, Fortified AND Anemia AND Randomized Controlled Trial	9
Scopus	Adolescent* AND "food fortified" AND anemia AND "Randomized Controlled Trial"	174
Cochrane	Adolescent* AND (Iron Food Fortified) AND Hemoglobin* AND Randomized Controlled Trial	46

*Truncation symbol was used to capture all possible variations of a word
“..” ensure the search result containing the exact phrase

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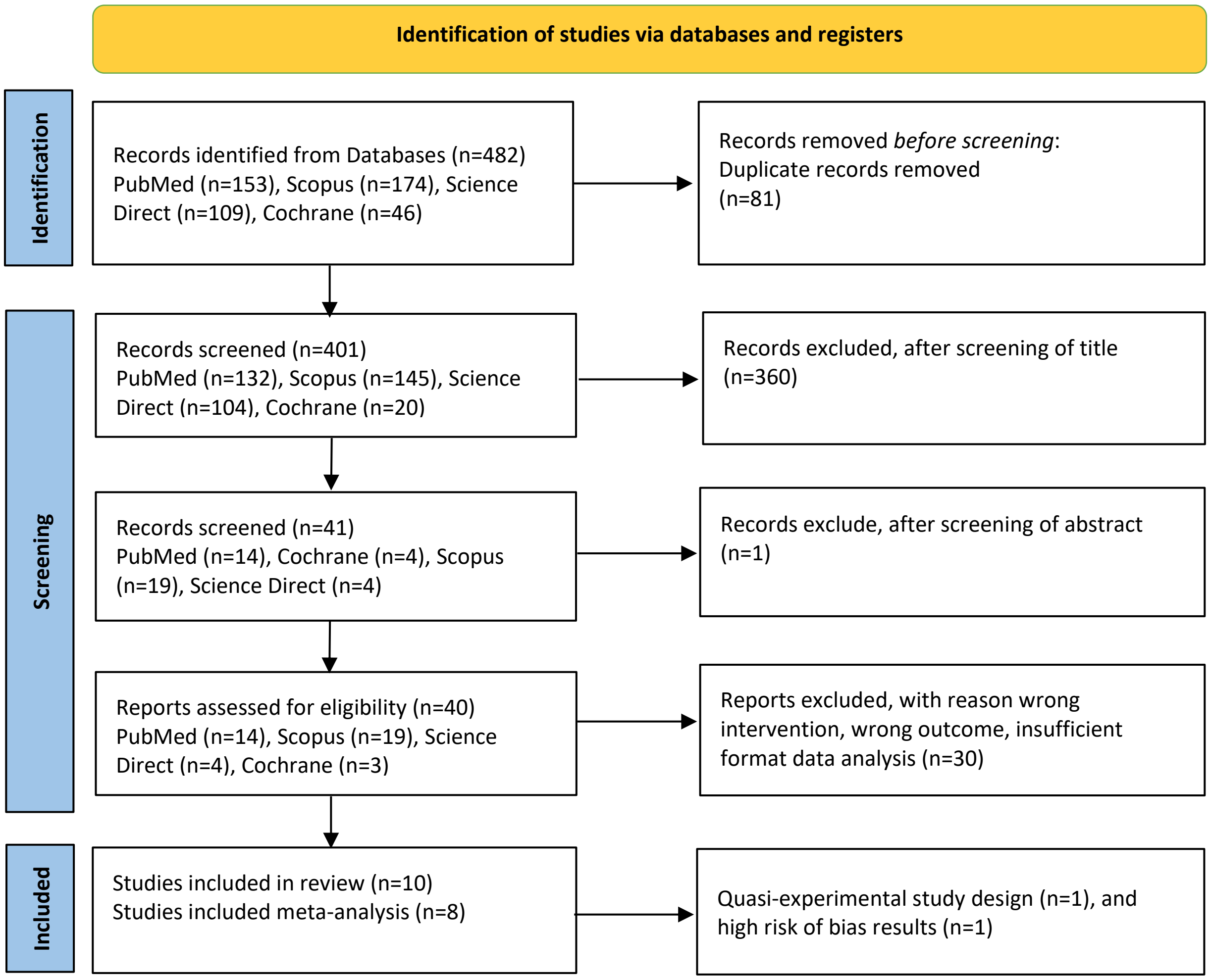

Figure 1. Flow diagram of articles selection process

DISCUSSIONS

Based on the results of the literature search, ten studies were obtained that met the inclusion criteria. Of the ten studies, the study locations were India (n=2), Haiti (n=1), Cambodia (n=2), Bangladesh (n=1), Brazil (n=1), and China (n=3). The study design was a Randomized Control Trial (RCT) with nine studies (90%) and quasi-experimental with one study (10%). The youngest population is 6 years old and the oldest is 21 years old. The length of intervention varied from study to study. The earliest duration was 12 weeks, while the longest was 72 weeks. The intervention involved providing fortified foodstuffs to adolescent girls. Food ingredients used in the studies included peanut butter, rice, soy sauce, fish sauce, flour, corn, and beverages. Fe (iron) fortification was given in the form of elemental, kernels, NaFeEDTA, electrolyte iron, and FeSO4. Details of eligible studies are summarized in Table 2.

The selected studies after extraction were then analyzed. Before analysis, a risk of bias assessment was conducted. Nine studies used the Cochrane Risk of Bias Tool which was classified into low, some concerns, and high risk of bias. Meanwhile, one study used the Minors tool because the study design was quasi-experimental. The results of the nine studies' risk of bias assessment are listed in Figure 2 and 3. Ten studies were assessed for risk of bias, there were four studies with low risk of bias results (one quasi-experimental design study), five studies with moderate risk of bias, and one study with high risk of bias results. Therefore, only eight studies were meta-analyzed.

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Table 2. Characteristics of the research study included in systematic review and meta-analysis obtained from the literature search database

No	First Author, Year	Country	Study design	Target Group	Intervention type	Food Based	Iron compounds, Iron per 100 g raw	Duration and Frequency	Results	Risk of Bias
1	Lakshmi, 2016[10]	India	Double-blind placebo control randomized trial	Adolescent (12–18) years N=80	Iron (Fe)	Beverage	Unknown	Duration: 12 weeks Frequency: on alternate days	Fortified beet-root extract had a high impact on Hb concentration (p-value<0.0001)	High risk
2	Lannotti, 2016[11]	Haiti	Cluster, randomized longitudinal study	Children (3-16) years N=321	Iron + vitamins and minerals (Fe, Ca, Co, I, Mg, Mn, K, Se, Na, Zn, Vit A, Vit B complex, Vit C, D, E, K)	Peanut butter	Unknown 22 mg	Duration: 26 weeks Frequency: once per school day	A fortified snack (Vita Mamba) showed a positive effect on increasing Hb concentration	Low risk
3	Perignon, 2016a[12]	Cambodia	Double-blind, cluster-randomized, placebo-controlled trial	Schoolchildren (6–16) years N=445	Iron + vitamins and minerals (Fe, Zn, Vit B1, Vit B9)	Rice	Unknown 10.67 mg	Duration: 24 weeks Frequency: Six days/week	Fortified rice (URO) had no increased Hb	Some Concern
4	Perignon, 2016b[12]	Cambodia	Double-blind, cluster-randomized, placebo-controlled trial	Schoolchildren (6–16) years N=464	Iron + vitamins and minerals (Fe, Zn, Vit B1, Vit B9, Vit A, Vit B3, Vit B12)	Rice	Unknown 7.55 mg	Duration: 24 weeks Frequency: Six days/week	Fortified rice (NutriRice) had no increased Hb	Some Concern
5	Perignon, 2016c[12]	Cambodia	Double-blind, cluster-randomized, placebo-controlled trial	Schoolchildren (6–16) years N=454	Iron + vitamins and minerals (Fe, Zn, Vit B1, Vit B9, Vit A, Vit B3, Vit B12, Vit B6)	Rice	Unknown 7.46 mg	Duration: 24 weeks Frequency: Six days/week	Fortified rice (URN) had significantly increased Hb	Some Concern
6	Muthayya, 2012[13]	India	Randomized, double-blind, controlled	Student (6-15) years N=379	Iron (Fe)	Flour	NaFeEDTA 6 mg	Duration: 28 weeks Frequency: Six days/week, every lunch meal (except on school holidays)	Fortified wheat flour significantly increases Hb	Low Risk

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No	First Author, Year	Country	Study design	Target Group	Intervention type	Food Based	Iron compounds, Iron per 100 g raw	Duration and Frequency	Results	Risk of Bias
7	Lu´cia HS, 2008[14]	Brazil	Quasi-experimental	Adolescent (7-14) years N=362	Iron + Vitamin (Fe, B9)	Flour	Elemental Fe powder 9,8 mg	Duration: 16 weeks Frequency: Six days/week, every lunch meal (except on school holidays)	Corn Flour fortification had increased Hb	High Quality (MINORS)*
8	P Longfils, 2008a[15]	Cambodia	Randomized double-blinded, placebo-controlled, longitudinal intervention trial	Students aged (6-21) years N=46	Iron (Fe)	Fish Sauce	FeSO4+citrate 10 mg	Duration: 21 weeks Frequency: Six days/week Totaling 114 dosing days	Fortified fish sauce increased Hb concentrations	Some Concern
9	P Longfils, 2008b[15]	Cambodia	Randomized double-blinded, placebo-controlled, longitudinal intervention trial	Students aged (6-21) years N=47	Iron (Fe)	Fish Sauce	NaFeEDTA 10 mL	Duration: 21 weeks Frequency: Six days/week Totaling 114 dosing days	Fortified fish sauce increased Hb concentrations	Some Concern
10	S. M. Ziauddin Hyder, 2007[16]	Bangladesh	Randomized, double-blind, placebo-controlled trial	Adolescent (9-18) years N=482	Iron + vitamins and minerals (Fe, Vit A, I, Zn, Vit C, B12, B9, Vit B 12, Vit B 6, Vit E, B3)	Beverage	Elemental 3,5 mg	Duration: 48 weeks Frequency: six days/week	Fortified beverages increased Hb concentrations (p-value<0.01)	Low Risk
11	Jing Sun BD, 2007a[17]	China	Control Trial	Student aged (11-18) years N=106	Iron (Fe)	Flour	Elemental 6 mg	Duration: 24 weeks Frequency: every day	Flour-fortified increased hemoglobin level (p-value<0.05)	Some Concern
12	Jing Sun BD, 2007b[17]	China	Control Trial	Student aged (11-18) years N=107	Iron (Fe)	Flour	NaFeEDTA 2 mg	Duration: 24 weeks Frequency: every day	Flour-fortified increased hemoglobin levels significantly (p-value<0.01)	Some Concern
13	Jing Sun BD, 2007c[17]	China	Control Trial	Student aged (11-18) years N=96	Iron (Fe)	Flour	FeSO4 3 mg	Duration: 24 weeks Frequency everyday	Flour-fortified increased hemoglobin level (p-value<0.01)	Some Concern

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No	First Author, Year	Country	Study design	Target Group	Intervention type	Food Based	Iron compounds, Iron per 100 g raw	Duration and Frequency	Results	Risk of Bias
14	Junshi Chen, 2005[18]	China	Randomized, double-blinded, controlled intervention trial	Females (7-18) years N= 381	Iron (Fe)	Soy Sauce	Elemental Fe 29,6 mg/100 ml	Duration: 72 weeks Frequency: six days/week	Fortified soy sauce had significantly higher hemoglobin level (p-value<0.001)	Some Concern
15	Junsheng, 2002a[19]	China	Randomized Trial	Children (11-17) years N=62	Iron (Fe)	Soy Sauce	NaFeEDTA 10 mg	Duration: 12 weeks Frequency: daily at lunch	Fortified soy sauce had significantly increased hemoglobin level (p-value<0.01)	Some Concern
16	Junsheng, 2002b[19]	China	Randomized Trial	Children (11-17) years N=77	Iron (Fe)	Soy Sauce	NaFeEDTA 40 mg	Duration: 12 weeks Frequency: daily at lunch	Fortified soy sauce had significantly increased hemoglobin level (p-value<0.01)	Some Concern

*Study number 7 used the MINORS risk of bias tool because the study design was quasi-experimental while the others used the Cochrane Risk of Bias Tool

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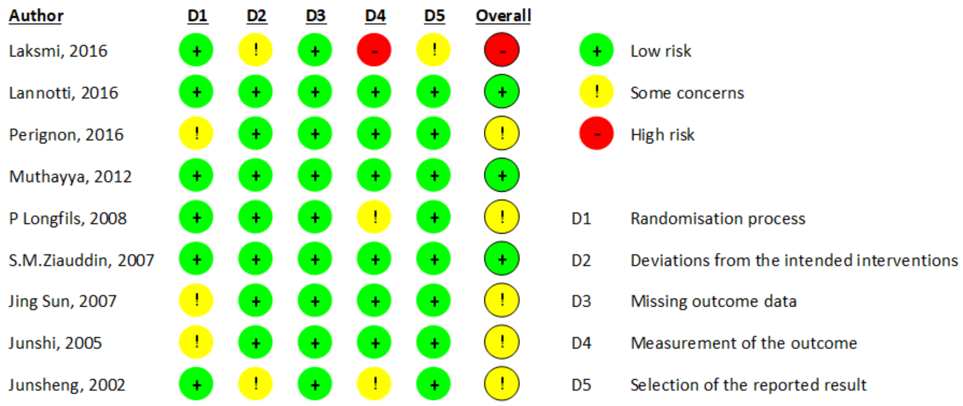

Figure 2. Result of risk of bias assessments for studies of the effectiveness of food fortification to anemia in adolescent used Cochrane Bias Tool

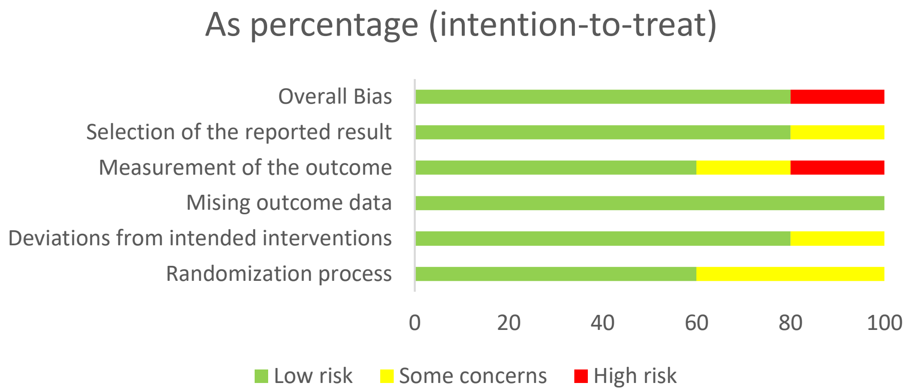

Figure 3. Presentation of risk of bias assessments for studies in a Cochrane review of effectiveness of food fortification to anemia in adolescent

Forest Plot

Eight RCT design studies were conducted that were obtained after data analysis, the Forest Plot was obtained as follows. Figure 3. shows that the variation between studies is heterogeneous, characterized by an I^2 value of 97% and a p-value<0.01, meaning that H_0 is rejected, or the data is not homogeneous. The data obtained was heterogeneous, so a random effect model is used. Therefore, the authors conducted a sub-group analysis to detect the source of heterogeneity. The fortification intervention with the highest mean difference value was obtained from the study of Junsheng et al, 2002b which was the fortification of soy sauce with 40 mg NaFeEDTA with SMD=2.88 mg/dL. The lowest effect size was the study of Perignon, 2016b with SMD value=0.01 mg/dL that was rice fortification.

The data that was too heterogeneous can be caused by different food ingredients used for the intervention between studies. Some studies used rice, flour, soy sauce, fish sauce, corn, or even in the form of drinks. In addition, the duration of the study was also suspected to be the cause of heterogeneous data. There were studies whose duration is 12 weeks, 21 weeks, 24 weeks, 28 weeks, 48 weeks, and 72 weeks. The additives were also suspected to affect the interventions. Some interventions used NaFeEDTA, elemental Fe, FeSO4, kernels, and electrolyte iron.

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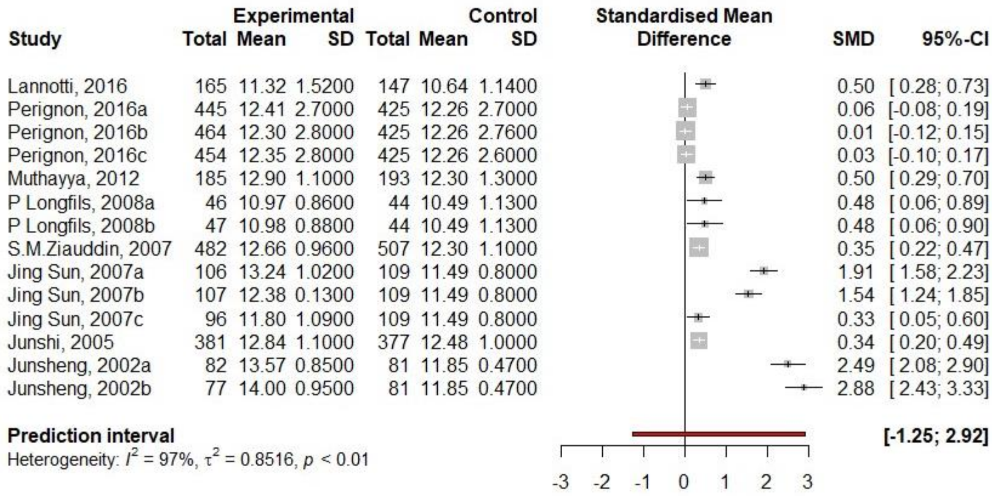
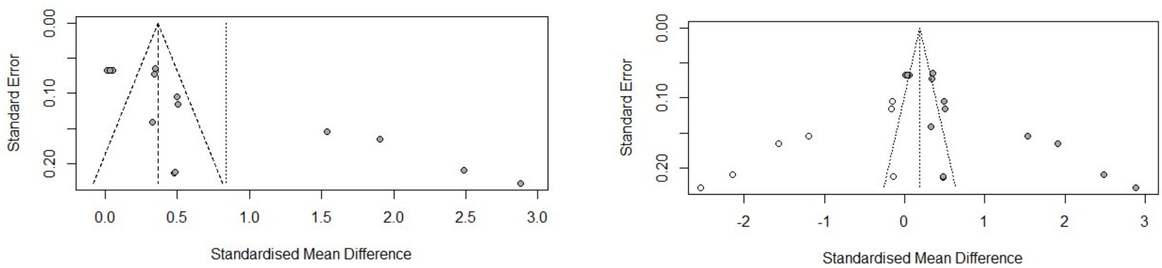


Figure 4. Forest plot of the effect of dietary Fe fortification on Hb increase in eight selected studies. Presentation in the form of mean difference between experimental and control groups. SMD value means that there was a higher Hb increase in the experimental group compared to the control group. Random effect was used because heterogeneity was high (p-value<0.01 and I^2=97%)

Funnel Plot

The presence of publication bias in the study can be seen from the funnel plot. From the funnel plot above, the distribution of studies is not symmetrical, as evidenced by the p-value on Egger's test=0.0010. This indicates the presence of publication bias in the analyzed study. So, the author tries to trim and fill. After doing trim and fill, the results are symmetrical with a p-value=0.91.



(A) **(B)**

Figure 5. Funnel plot of the effect of Fe fortification of foodstuffs on haemoglobin before trim and fill (A). The points are spread and not symmetrical and after trim and fill (B), the points become symmetrical

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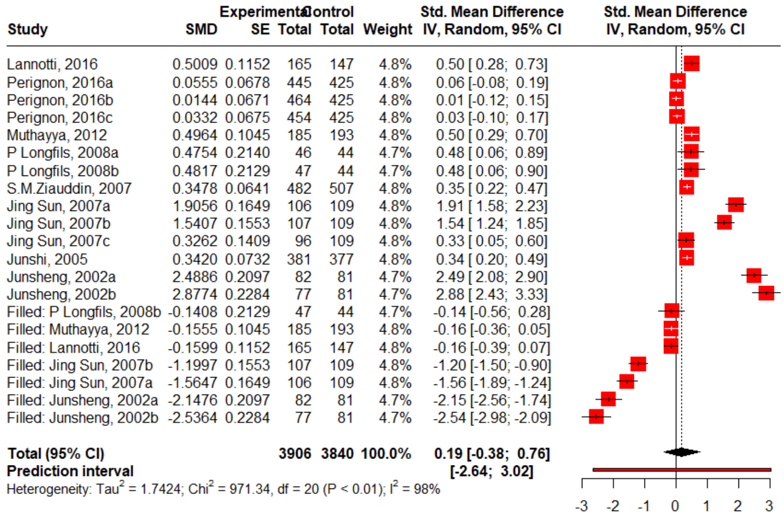

Figure 6. Forest plot of the effect of Fe fortification in foodstuffs on hemoglobin after trim and fill. In the figure, the distribution of SMD values is not only on the right but evenly distributed on the left as well

Subgroup Analysis

Subgroup analysis was conducted based on the duration of the intervention, food ingredients used for fortification, as well as the fortificants substance used and the number of samples. Table 3 showed that the I^2 value after subgroup analysis with various categories obtained an I^2 value of 97% so that even though subgroup analysis was carried out the results remained heterogeneous. However, in the sub-group analysis based on food ingredients, the rice and fish sauce groups have an I^2=0.

Table 3. Subgroup analysis based on food based, the duration of the intervention, the fortificants and the total samples

Subgroup Analysis	I^2	P-diff between subgroup	Total Common/Random Effect Model and 95% CI	Subgroup Difference
Subgroup Analysis (1) based on Food based				
Peanut butter	-	-	0.5 [0.28-0.73]	X1²=42.28 p-value<0.001*
Rice	0	91	0.03 [-0.04-0.11]	
Flour	96	<0.001*	1.06 [0.3-1.82]	
Fish Sauce	0	98	0.48 [0.18-0.77]	
Beverage	-	-	0.35 [0.22-0.47]	
Soy Sauce	99	<0.001*	1.89 [0.33-3.45]	
Subgroup Analysis (2) based on Duration of Intervention				
> 24 weeks	0	42	0.39 [0.31-0.47]	X1²=132.77 p-value<0.001*
13-24 weeks	97	<0.001*	0.6 [0.09-1.1]	
12 weeks	36	21	0.84 [0.35-1.33]	
Subgroup Analysis (3) based on Fortificant				
NaFeEDTA	98	<0.001*	1.42 [0.52-2.32]	X1²=4.33 p=0.04*
Other	93	<0.001*	0.4 [0.06-0.74]	
Sub-group Analysis (4) based on Total Sample				
≥100	96	<0.001*	0.55 [0.15-0.94]	X1²=2.37 p=0.12
<100	97	<0.001*	0.84 [0.35-1.33]	

CI=Confidence Interval, *heterogeneity was high

The results of the random effects meta-analysis showed that fortified foods can significantly increase hemoglobin levels in adolescent girls but study heterogeneity was high. After subgroup analysis with various groups including food ingredients used for fortification, fortificants substances, duration of administration, and number of samples, most of the I^2 values remained above 30%. This shows that the data was heterogeneous. However, in the subgroup analysis based on food ingredients, the rice and fish sauce groups had an I^2 value = 0. It can be concluded that iron fortification in rice can increase Hb levels by 0.03 [-0.04-0.11] mg/dL compared to the control group. While iron fortification in fish sauce can increase Hb levels by 1.89 [0.33-3.45] mg/dL. The same results were also found in the meta-analysis of the study Sadighi, 2018 and the 2019, where iron-fortified flour (wheat, maize, rice, soy, beans) food can increase Hb levels in women, children, infant/

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toddlers and pregnant women when compared to the control group with values of 3.360 g/L, I^2=99.9% and 4.45 g/L, I^2=83%[8,20].

Iron fortification can increase hemoglobin by the same mechanism as iron absorption in other foods. So the increase is gradual unlike iron supplementation which is fast in increasing hemoglobin[21,22]. There are two main sources of iron in the body: iron from food eaten and iron from the recycling of aged erythrocytes. Iron is transported by mitochondria to be synthesized into heme groups while others are stored in the form of ferritin[21]. Fortification takes a longer time, so the fortification approach aims for the long term. Some criteria for fortification to be successful is the selection of food vehicles that include eating habits, eating patterns, geographical conditions and socioeconomic status. Ideally, the selected food does not change people's eating habits so that it can be consumed regularly which has an impact on increasing iron levels in the body[22].

It is known that the bioavailability of iron in consumed foods depends on its chemical makeup. The two forms of iron that exist are heme and non heme[23]. Meanwhile, food fortification typically involves non-heme iron, so its absorption is maximized when combined with ascorbic acid. Ascorbic acid, also known as vitamin C, can help convert iron from its ferric to ferrous form, making it easier for the body to absorb. Vegetables and fruits are rich sources of vitamin C[24]. Ascorbic acid can also enhance the absorption of less soluble iron compounds, such as ferrous fumarate and elemental iron[23,25]. This indicates that the combination of diets also influences the absorption of iron fortification. Conversely, fortificants such as NaFeEDTA will be inhibited when the consumption is together with phytic acid that is too high. Although NaFeEDTA is good combined in foodstuffs containing phytic acid, its absorption will decrease if phytic acid is very high[26]. This may account for the different effects on hemoglobin levels, even though the food ingredients and fortificants are the same.

The varying effectiveness of fortification in foodstuffs is partly due to the level of bioavailability of the fortificant substance[27]. NaFeEDTA and FeSO4 in fish sauce, iron absorption was 3.3% and 3.1%, while when fortified in soy sauce, the iron absorption rate increased by 6.7% and 7.9%. So it can be seen that the fortificant was higher when given soy sauce than fish sauce[28]. So far, it has been known that NaFeEDTA is suitable as a food additive in cereals and legumes that contain phytic acid. The bioavailability of NaFeEDTA added to rice in other studies also showed high absorption values compared to other Fe compounds[29,30]. However, the disadvantage is that it has a strong odor, so when mixed with rice, it will reduce its acceptability[26]. Therefore, NaFeEDTA is more suitable for adding to soy sauce or fish sauce. In addition, NaFeEDTA also does not cause peptide precipitation. The disadvantage is that NaFeEDTA can often cause discoloration in fortified foodstuffs[5,31]. While food fortification that has the lowest effect size in this study was fortification in rice[12]. Similar results were found in other reviews where fortification of rice with iron alone or in combination with other micronutrients resulted in little or no change in hemoglobin concentration in populations older than 2 years[32]. Another review showed no significant effect on serum ferritin or transferrin levels. This may be due to the duration of the intervention or the lack of Fe fortification in the rice[33]. The characteristics of the food ingredients used for fortification also determine whether or not it is easy for Fe fortification substances to be incorporated. The fortification process in flour is easier than in rice. Micronutrient premixes are only added to flour during milling, while rafeice uses kernels with complex technology[34].

The varied results in this study may also be due to the different characteristics of the subjects. Although the age range is between 10-18 years and some are below and above that age, differences in nutritional status also affect the metabolism of nutrients in the body. Adolescent girls are included in the growth age category, where rapid growth and development at that age is required[35]. This results in the metabolism of food in the body is still good, but it will be different when the nutritional status is excessive or deficient. Adolescents with obesity tend to have impaired iron homeostasis[36]. This is a challenge for the future in providing food fortification but paying attention to the condition of the subject's nutritional status.

The strength of this meta-analysis was there a comparison of the effectiveness of various types of Fe-fortified food ingredients in countries with LMICs and UMICs. The weakness of this study was that sub-group analysis based on the country and age of participants has not been carried out due to the limited number of studies obtained so it did not represent the region and limited age data. In addition, publication bias occurred because in this study all studies showed positive mean differences between the intervention group and the control group. The absence of study findings with negative results indicates a lack of search for studies from various sources or databases. Future research can use various database sources and gray literature so that publication bias does not exist. In addition, to minimize the high heterogeneity in the results of the meta-analysis, further research can focus more on certain food ingredients such as rice, flour or soy sauce in specific populations. Then, if want to take on a wider range of foodstuffs, maybe the fortificants used are more specific and more focused on whether the fortificants only contain iron or a mixture of several microminerals. This could provide a more thorough understanding of anemia prevention strategies. The level of adherence to fortified food is also important to see so that information on the effectiveness of food fortification is obtained based on the level of consumption compliance.

CONCLUSIONS

Food fortification with Fe can increase hemoglobin levels in adolescent. The highest effect size was found in NaFeEDTA fortification in soy sauce. While the lowest effect size was found in Fe fortification in rice. The varying effectiveness of fortification in foodstuffs is partly due to the level of bioavailability of the fortificant substance. This systematic review and meta-analysis can serve as a reference to create a food fortification-based intervention program to prevent anemia in adolescent girls in developing countries and low-middle and upper-middle-income countries.

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AUTHOR CONTRIBUTIONS

UK: formulating the research design, searching for articles, screening articles, analyzed data, writing-review, and editing; NMPKD: assisted in searching for articles, screening articles, and assessing articles; LPP: supervised articles from the beginning of the research design, searching, screening, assessing, writing, and editing.

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