

Original Article



Effect of NaFeEDTA-Fortified Soy Sauce on Anemia Prevalence in China: A Systematic Review and Meta-analysis of Randomized Controlled Trials*

HUO Jun Sheng^{1, #}, YIN Ji Yong¹, SUN Jing¹, HUANG Jian¹, LU Zhen Xin², REGINA Moench-Pfanner², CHEN Jun Shi¹, and CHEN Chun Ming¹

1. Key Laboratory of trace element nutrition of Ministry of health, National Institute for Nutrition and Health, Chinese Center for Disease Control and Prevention. Beijing 100050, China; 2. Global Alliance of Improved Nutrition, Singapore 247672, Singapore

Abstract

Objective To assess the effect of sodium iron ethylenediaminetetraacetate (NaFeEDTA)-fortified soy sauce on anemia prevalence in the Chinese population.

Methods A systematic review was performed to identify potential studies by searching the electronic databases of PubMed, Cochrane Library, WHO Library, HighWire, CNKI, and other sources. The selection criteria included randomized controlled trials that compared the efficacy of NaFeEDTA-fortified soy sauce with that of non-fortified soy sauce. Anemia rates and hemoglobin levels were the outcomes of interest. Inclusion decisions, quality assessment, and data extraction were performed by two reviewers independently. A total of 16 studies met the inclusion criteria for anemia rate analysis, of which 12 studies met the inclusion criteria for hemoglobin analysis. All included studies assessed the effect of NaFeEDTA-fortified soy sauce on anemia rates and hemoglobin concentrations.

Results After the intervention, the hemoglobin concentration increased and anemia rates decreased significantly as compared with the non-fortified soy sauce groups. For anemia rates, data from 16 studies could be pooled, and the pooled estimate odds ratio was 0.25 (95% CI 0.19-0.35). For hemoglobin concentrations, data from 12 studies could be pooled, and the pooled weighted mean difference was 8.81 g/L (95% CI 5.96-11.67).

Conclusion NaFeEDTA-fortified soy sauce has a positive effect on anemia control and prevention in the at-risk population.

Key words: Sodium iron ethylenediaminetetraacetate; NaFeEDTA; Anemia; Hemoglobin; Iron deficiency; Meta-analyses; Food fortification

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INTRODUCTION

Iron deficiency and iron deficiency anemia are the most widespread micronutrient deficiencies in China as well as in other

countries of the world, with about one-fifth of the world's population suffering from iron deficiency anemia and the prevalence rates being 18.1% in children (<5 years) and 19.2% in pregnant women^[1]. The 2002 National Nutrition Survey showed that the

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#Correspondence should be addressed to: HUO Jun Sheng, Tel: 86-10-83132383, Fax: 86-10-83132317, E-mail: jshuo@263.net.cn

Biographical note of the first author: HUO Jun Sheng, male, born in 1962, researcher fellow/PhD, majoring in nutrition and public health.

average prevalence of anemia in the whole population was 20.1%, among which the anemia rate in the high-risk group could be even higher; for example, among women of childbearing age, the prevalence rates were 28% in urban areas and 41% in rural areas^[2-3]. It has been widely recognized that iron deficiency and iron deficiency anemia have adverse effects on health, including impaired cognitive development in children, increased susceptibility to infectious diseases, and reduced productivity in adults^[4]. Ross et al.^[5] estimated that the loss of productivity due to childhood and adult anemia in 2001 accounted for 3.6% of the Chinese national gross domestic product. Therefore, the development and implementation of effective measures for controlling iron deficiency and iron deficiency anemia is an important public health issue that is relevant to the further development of the national economy in China. Food fortification is recognized as an important strategy for controlling micronutrient deficiencies. Its advantages include effectiveness, low cost, potential for rapid implementation, and the possibility of covering wide geographic areas and most subpopulations^[6-7].

Soy sauce is produced through a complicated fermentation process using soy bean and other raw materials. It is a dark, salty liquid condiment and has been evaluated as a suitable food carrier for iron fortification. Soy sauce is a commonly used traditional condiment in all parts of China, with quite a less variation in consumption across regions. Consumption of soy sauce is unlikely excessive because of the self-limitation from the heavy salty taste in terms of daily intake^[8]. Previous observations have shown that the quality of sodium iron ethylene diaminetetraacetate (NaFeEDTA)-fortified soy sauce (IFSS) remains almost the same as that of the non-fortified soy sauce, although fortified soy sauce tastes metallic and precipitates heavily in a packed bottle, compared with other iron fortificants^[9]. Iron absorption of IFSS was reported to be more than twice that of ferrous sulfate in adult females in a study using stable isotopes^[10]. Two studies were conducted in 1998 and 2001 to evaluate the efficacy and effectiveness of IFSS on anemic school students and in poor rural villages. Both studies showed a positive effect on hemoglobin (Hb) levels and anemia rates of the study subjects with IFSS intervention^[11-12]. Based on these results, the Ministry of Health approved the project 'Use iron fortified soy sauce to control and prevent iron deficiency and iron deficiency anemia in China' in

2003, which was funded by the Global Alliance of Improved Nutrition (GAIN). The project has been implemented in two phases: the first phase was from 2003 to 2008 and the major target was to promote the manufacture of IFSS in the soy sauce industry and awareness of consumers in both rural and urban consumers in nine provinces. The second phase was from 2010 to 2014 and the target was to explore a sustainable model for IFSS in China. During both phases, studies have been conducted to assess the effect of IFSS on anemia prevalence in different regions and different population groups.

In the present study, a systematic review was conducted with a meta-analysis method to evaluate the effect of IFSS on anemia prevalence based on scientific studies on the effect of IFSS with different iron dosages on populations with different age groups in different regions in China.

METHOD

Inclusion and Exclusion

Anemia rate and Hb concentrations were used as the measured outcome, which are reported according to WHO-defined cut-off values for different populations^[13]. Randomized controlled trials were screened and included. Controlled before-and-after studies, self-controlled before-and-after studies, interrupted time-series studies, cohort studies, case-control studies, and cross-sectional studies were excluded. Participants included were any population in which anemia is a public health problem. Studies comparing IFSS vs. non-IFSS as control were included. Studies on fortified soy sauce consisting of other iron fortificants or iron supplements or iron absorption enhancers such as vitamin C or other anti-anemic drugs being simultaneously administered were excluded.

Search Strategy

Published original research papers were retrieved by searching PubMed (1997 to June 2014), Cochrane Library (issue 2, 2014), Highwire (1997 to June 2014), WHO Library (WHOLIS), and China National Knowledge Infrastructure (CNKI) (1997 to 2014). As research on IFSS was initiated in 1997 in China, we searched all the databases after 1997 until May 2014. We also hand searched conference proceedings and reference lists and contacted specialists in the field.

Selection of Eligible Studies and Quality Assessment

Randomized controlled trials were identified by abstract evaluation. Based on the inclusion and exclusion criteria, eligible studies were included through full-text overview. Two reviewers (Yin JY and Huo JS) independently assessed the quality of the included studies using the quality assessment criteria for randomized controlled trials, which were established by the Cochrane Effective Practice and Organisation of Care Group (EPOC)^[14].

Data were extracted independently by the two reviewers, and any differences of opinion were resolved by discussion and consensus was reached by discussion and by seeking the opinion of a third reviewer (J Huang). The reviewers collected information about methodological (study design, blinding, follow-up, allocation concealment, protection against contamination, baseline comparability, levels of allocation, and analysis) and study characteristics (intervention measures, control measures, location and setting, inclusion criteria, interested outcomes, and important results). RevMan version 5 (Update Software Ltd, Oxford, Oxon, UK) was used to perform risk evaluation of studies, heterogeneity tests, and meta-analysis. The heterogeneity test was used to decide whether to use the fixed effect model or the random effect model, and as the result was significant in this study, the random effect model was used^[15]. For one study with more than one intervention group, we divided the control group evenly according to the number of intervention groups^[16]. Publication bias was examined using the risk of bias table in Revman version 5. For quality assessment, the RevMan version 5 lists seven items as the assessment standard: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. If more than three items in one study were regarded as 'high risk' or 'unclear,' then this study was defined as 'unacceptable' in terms of methodological quality and was not included in the analysis.

RESULTS

Included Studies

The selected eligible studies are depicted in Figure 1. Through comprehensive searching, we

found 156 articles related to randomized controlled trials on anemic population with the intervention of NaFeEDTA-fortified foods and supplements. Among them, 29 articles were identified as IFSS- and iron-fortified fish sauce intervention studies. According to the inclusion and exclusion criteria, we excluded 5 articles from the 29 articles, in which either iron-fortified fish sauce was used or the description on data was not enough to support further analysis. From the remaining 24 articles, 8 were excluded because of similar or repeated results, and finally 16 studies were included for anemia as the major outcome^[17-32]. Four articles were again excluded because of no Hb data, and finally 12 articles were selected for Hb level as the major outcome. However, the authors chose to retain the four articles without Hb data because of the accepted quality and inclusion of pregnant women as the observed groups. Important excluded studies included three NaFeEDTA-fortified fish sauce studies conducted in other countries. One study did not list anemia rates at baseline and after intervention survey but listed out only the difference of the anemia rates between baseline and after intervention. Another study used randomized sampling design but without the description of the control group. All eligible studies were implemented in the Chinese population: five studies in poor rural villages, eight in schools, and three in hospitals. The eligible studies included seven individual randomized controlled trials and eight cluster randomized controlled trials. All the participants of the included studies were from anemia-risk populations: two studies focusing on 3- to 6-year-old children, nine studies focusing on teenagers, three studies on pregnant women, and one study covered all groups of children >3 years. The intervention dose of iron in NaFeEDTA ranged from 2.3 to 20 mg/day/person. Iron dosages were <4 mg/day in eight studies and ≥4 mg/day in seven studies. The intervention duration ranged from 3 to 18 months. Twelve studies reported Hb concentration and four studies reported only on anemia rates. One study reported one dropout subject due to less intent of fortified soy sauce, and all the other studies did not report about any adverse impact of the taste of the fortified soy sauce.

Methodological Quality of Included Studies

According to the risk of bias table, the quality of the included studies was assessed in terms of six aspects: allocation concealment, follow-up, baseline

measurement, blinded assessment of outcomes, reliable outcome measure, and protection against other possible effects. All controlled trials had adequate follow-up, good comparability in baseline measurement between intervention and control groups, blinded assessment of outcome, reliable outcome measures, and measures to protect against contamination. Allocation concealment was at low

risk in 13-studies^[17-24,27-28,30-32], at high risk in three studies^[25-26,29], and no study at unclear. All the included studies were regarded as generally 'low risk' in terms of methodological quality, and thus 16 studies for anemia rates and 12 studies for Hb levels were included in the analysis. Risk graph and risk summary of 16 studies are listed in Figures 2 and 3, respectively.

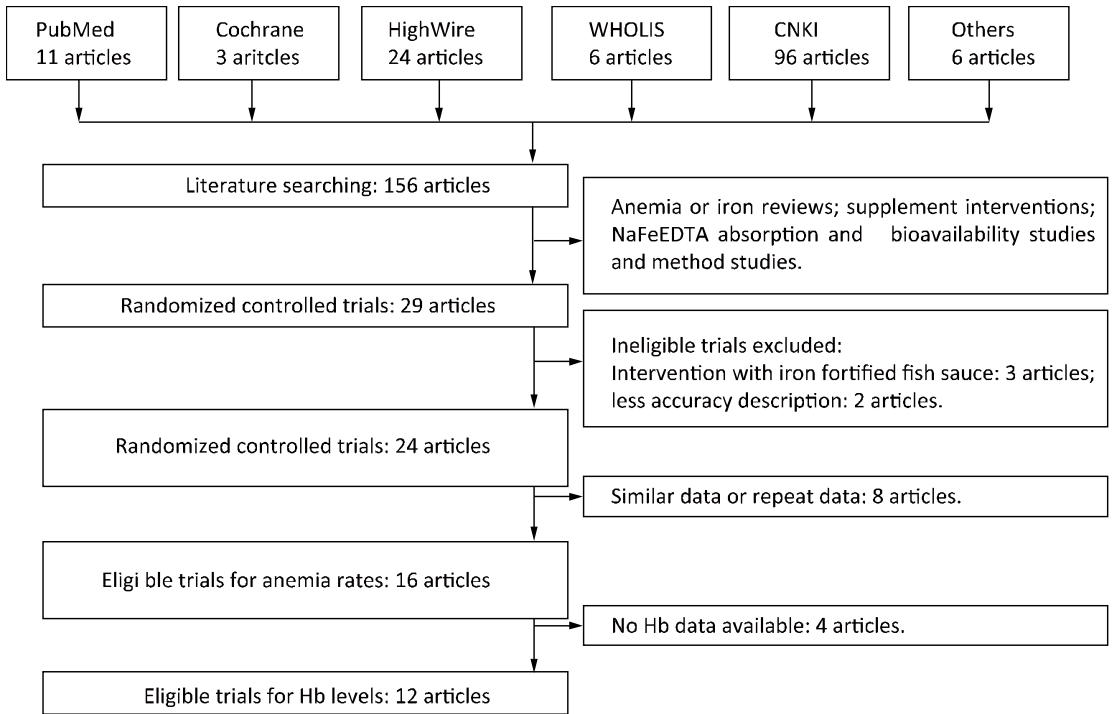


Figure 1. Selection of eligible studies on the effect of IFSS.

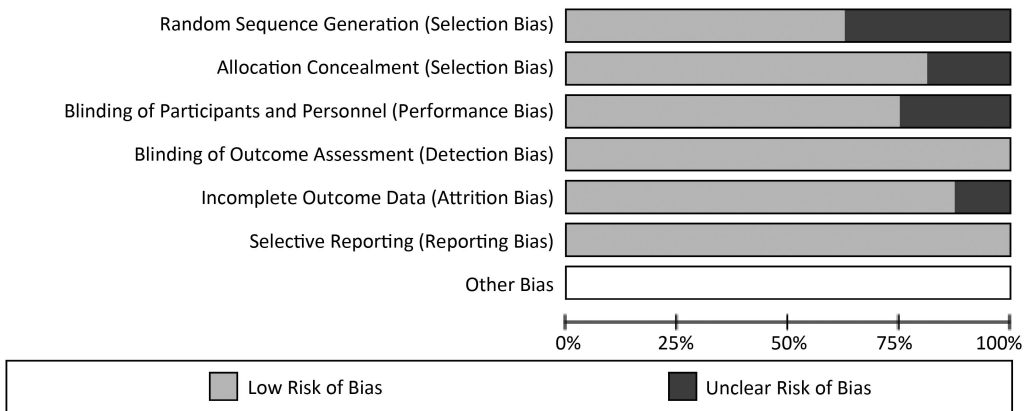


Figure 2. Risk graph of bias: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Summary of Effect of IFSS on Anemia Prevalence

All included trials were evaluated for anemia rates as the major outcome. The number of subjects, aged from 3 to >55 years and from different provinces, totaled 8411 in the IFSS intervention groups and 8408 in the non-IFSS control groups. The heterogeneity of included studies is τ^2 0.29, χ^2 148.54, $P < 0.00001$, and I^2 90%, which indicates a significantly higher heterogeneity, and hence the random effect model was used for the analysis. The

IFSS intervention group compared with the non-IFSS group showed significant difference for odds ratio and favors the IFSS group to likely have lower anemia rates at follow-up than those receiving non-IFSS treatment [average odds ratio 0.25; 95% confidence interval (CI) 0.19-0.35] (Figure 4). This result indicated that the IFSS interventions were effective in populations with different anemia prevalence rates and among all age groups with different intervention time from 2 to 18 months. Funnel plot for anemia rate analysis showed a remarkable bias of anemia rates existing among studies, which could have arisen due to differences in age, dosage, and intervention time or economic status among the different observed groups (Figure 6).

Summary of Effect of IFSS on Hb Levels

A total of 12 eligible studies analyzed 4037 subjects from the intervention groups and 4034 from the control groups with an age group from 3 to >55 years and from different provinces. Assessment showed significant heterogeneity (τ^2 23.5, χ^2 352.84, $P < 0.00001$, and I^2 97%), and hence the random effect model was used. The weighted mean difference was 8.81 g/L with 95% CI 5.96-11.67 between the IFSS and non-IFSS groups (Figure 5). This result significantly favored IFSS, suggesting that the IFSS group was likely to have higher Hb concentrations in all age groups with different intervention time from 2 to 18 months. Funnel plot from the analysis (Figure 7) showed remarkable bias among studies, as the observed groups were different in several respects as mentioned above.

DISCUSSION

Bias Control

It is fully aware that bias may be induced in each step of the review analysis. The authors tried to minimize the bias in every critical process. Independent reviewers evaluated the quality of the articles and contacted the original authors of the articles to collect more detailed information of the studies. The six quality assessment criteria in Revman 5 were used to evaluate the qualities of retrieved studies. In the present analysis, it was defined that trials with more than three 'high risk' or 'unclear' are to be regarded as unacceptable and could not be included in the analysis. A total of 16 studies were analyzed as eligible articles for anemia rate analysis and 12 studies for Hb level analysis. Baseline and final values of anemia rates and Hb levels

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen JS et al. 2005[23]	+	+	+	+	+	+	
Fang ZF et al. 2008[27]	-	+	-	+	+	+	
He SL et al. 2008[28]	+	+	+	+	+	+	
Huang YK et al. 2006[24]	-	+	+	+	+	+	
Huo JS et al. 2001[17]	-	+	+	+	+	+	
Li LJ et al. 2008[29]	-	+	+	+	+	+	
Li ZJ et al. 2006[25]	+	-	-	+	+	+	
Li ZJ et al. 2008[30]	+	-	-	+	+	+	
Qi FS et al. 2011[32]	-	+	+	+	+	+	
Sun J et al. 2003[19]	-	+	+	+	+	+	
Wang MI et al. 2006[26]	+	-	-	+	+	+	
Wang SS et al. 2002[18]	+	+	+	+	+	+	
Wang SS et al. 2004[20]	+	+	+	+	-	+	
Wang SS et al. 2004[21]	+	+	+	+	+	+	
Xu QH et al. 2010[31]	+	+	+	+	+	+	
Zhao XF et al. 2004[22]	+	+	+	+	-	+	

Figure 3. Risk summary of bias: review authors' judgments about each risk of bias item for each included study.

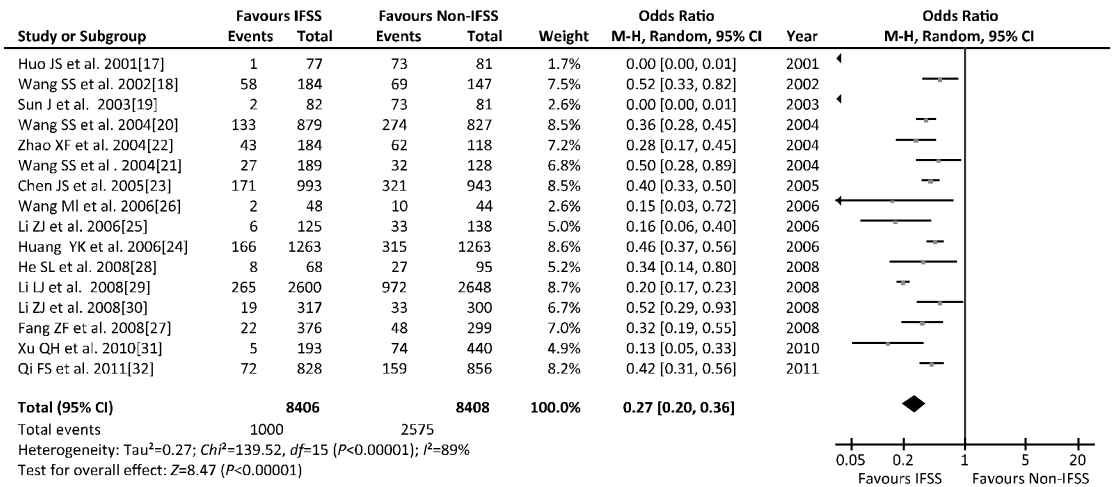


Figure 4. Analysis of IFSS effect on anemia rates from included studies. Event: the number of anemic cases; Total: the research number; Weight: the reciprocal of sum of variance interior research and between studies.

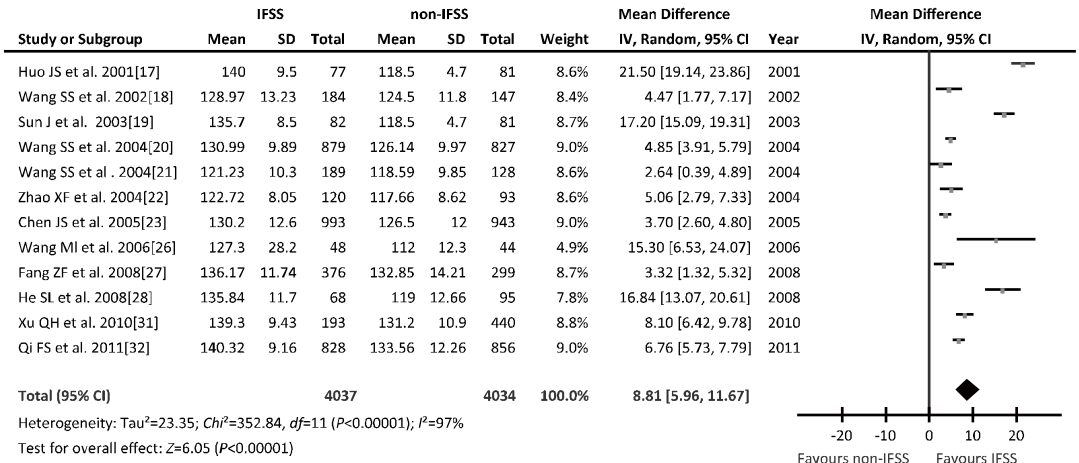


Figure 5. Analysis of IFSS effect on Hb concentration from included studies. Weight: the reciprocal of sum of variance interior research and between studies.

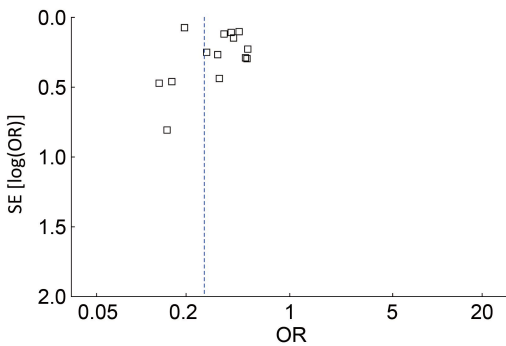


Figure 6. Funnel plot for anemia rate analysis with 16 eligible studies.

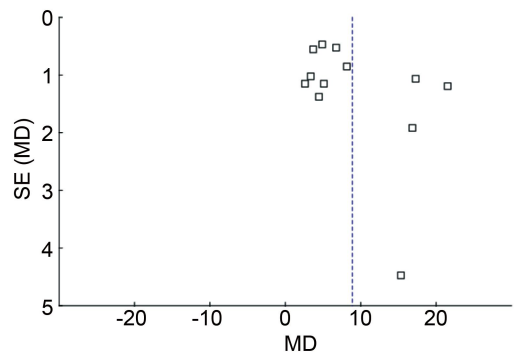


Figure 7. Funnel plot for Hb level analysis with 12 eligible studies.

were used to conduct the meta-analysis^[33].

Effect of IFSS

All studies individually showed positive effects of IFSS by reducing the anemia rates and increasing the Hb levels compared with the non-IFSS groups of different age and at-risk groups in different regions with 2-18 months of interventions. Result from this meta-analysis strongly supported the results shown in Figures 4 and 5. There seemed to be less sufficient research and data available to further support the subgroup analysis, such as age, iron dosage, region, intervention time log or anemia rates, and Hb levels at baseline. Only one of the 16 studies mentioned about complaints of subjects regarding the taste of IFSS, which was not supported by other organoleptic observations on IFSS. No other adverse effects were reported in the selected studies.

Present Situation of IFSS Market

IFSS as a fortified condiment has been accepted in the market. We estimated that the annual output of IFSS is around 80,000 metric tons in recent years, which accounted for about 1.6% of the total soy sauce market. This amount of IFSS could supply approximately 18.9% of the anemic population annually if the average soy sauce consumption is assumed to be 8.9 g and anemic population to be 130 million. Randomized controlled trials and monitoring of data from the GAIN project showed reduced anemia and increased Hb levels in the IFSS promotion provinces. However, the economic development and nutrition knowledge promoted in recent decades have also been considered the reasons for the reduced anemia rates, but this review showed that the continuous IFSS supply in the market along with spread of iron nutrition knowledge to consumers, especially in the at-risk regions, should be one of the factors for the overall decrease of anemia in Chinese population, since the project has been conducted for >10 years^[34].

Limitations of This Review

There are some limitations in this review. First, allocation concealment analysis showed inclusion of some studies with high risk, which is associated with a bias^[35]. However, sensitivity analysis that excluded these three studies suggested that this bias was unlikely to materially alter the primary results of the analysis. Second, the results in this review came from largely heterogeneous data derived from randomized

controlled trials. Actually, these differences in age, dosage, intervention time log, anemia rates, and Hb level at baseline and regional differences in diet and economic status have contributed to the heterogeneity among the included studies. It was appropriate to combine data from heterogeneous studies in the random effect meta-analyses in this review because the eligible studies addressed the effect of IFSS on the outcomes of anemia rates and Hb levels. Third, 16 studies were eligible for anemia rates analysis, of which only 12 reported Hb data (Table 1); however, the sensitivity analysis did not change the result if the four studies without Hb data were excluded. Fourth, because only 4 studies of the 16 eligible studies listed ferritin and other indexes of iron status, this result could reveal only the impact of IFSS on anemia rates, which included all types of anemia. It is difficult to explore the detailed effects of IFSS on specific types of anemia such as iron deficiency anemia. Further systematic reviews should be carried out to compare the effect of IFSS with that of other commonly used iron-fortified food preparations for high-risk iron deficiency groups.

In summary, this systematic review evidently suggested that long-term intervention with IFSS resulted in 8.81 g/L increase of Hb level in the high-risk anemic population and a 25% decrease in the anemia rate compared with that in the non-IFSS population. The newly reported decrease of anemia prevalence has been considered to be due to IFSS promotion jointly conducted by the Ministry of Health and GAIN to a certain degree. Therefore, IFSS should be continuously promoted to be a sustainable approach for iron deficiency and iron deficiency anemia with partnership of the government, NGO, and the soy sauce industry. More studies are needed for a better understanding of the relationship between IFSS and iron status and anemia rates among the intervened population.

DECLARATION OF CONFLICT OF INTEREST

All authors of this review declare that there is no conflict of interest to this study.

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Table 1. Characteristics of the Studies

Study	Location	Design	Age group	Sample size before the intervention	Eligibility and exclusion criteria	Baseline measurements of anemia status	NaFeEDTA fortification	Sample size after the intervention	Anemia status after the intervention
Huo JS et al. 2001 ^[17]	Henan, China	Individual RCT	11-17 years	T, n 158 Fe, n 77 PI, n 81	All anemic schoolchildren from two selected middle schools	Hb (g/L), HICN Fe, 116.1±5.1 PI, 116.9±5.5	Fe dose, 20 mg/per/d; Form of intervention, fortified Fe; duration of fortification, 3 months; duration of observation, 3 months	T, n 158 Fe, n 77 PI, n 81	Hb (g/L), HICN Fe, 140.0±9.5 PI, 118.5±4.7
Wang SS et al. 2002 ^[8]	Guizhou, China	Cluster RCT	>55 years	T, n 365 Fe, n 193 PI, n 172	All samples from 9 nature villages	Hb (g/L), HICN Fe, Male 128.5±17.3 Female 119.1±11.9 PI, Male 131.8±14.1 Female 118.8±12.3	Fe dose, 4.0 mg/per/d; Form of intervention, fortified Fe; duration of fortification, 6 months; duration of observation, 6 months	T, n 331 Fe, n 184 PI, n 147	Hb (g/L), HICN Fe, Male 133.7±15.9 Female 124.9±10.4 PI, Male 130.5±11.9 Female 118.9±11.7
Sun J et al. 2003 ^[19]	Henan, China	Individual RCT	11-17 years	T, n 163 Fe, n 82 PI, n 81	All Fe-deficient anemic schoolchildren from two selected middle schools	Hb(g/L), HICN Fe, 115.4±5.1 PI, 116.9±5.5	Fe dose, 5 mg/per/d; Form of intervention, fortified Fe; duration of fortification, 3 months; duration of observation, 3 months	T, n 163 Fe, n 82 PI, n 81	Hb (g/L), HICN Fe, 135.7±8.5 PI, 118.5±4.7
Wang SS et al. 2004 ^[20]	Guizhou, China	Cluster RCT	3-6 years	T, n 364 Fe, n 208 PI, n 156	All samples from 9 nature villages	Hb (g/L), HICN Fe, Male 114.8±11.9 Female 113.9±11.5 PI, Male 116.3±10.1 Female 116.1±12.8	Fe dose, 4 mg/per/d; Form of intervention, fortified Fe; duration of fortification, 6 months; duration of observation, 6 months	T, n 317 Fe, n 189 PI, n 128	Hb (g/L), HICN Fe, Male 120.7±9.9 Female 121.9±10.8 PI, Male 117.9±8.6 Female 119.5±11.3
Wang SS et al. 2004 ^[21]	Guizhou, China	Cluster RCT	7-19 years	T, n 1706 Fe, n 879 PI, n 827	All samples from 9 nature villages	Hb (g/L), HICN Fe, Male 120.2±11.9 Female 118.4±10.9 PI, Male 121.6±10.9 Female 118.2±9.2	Fe dose, 4 mg/per/d; Form of intervention, fortified Fe; duration of fortification, 12 months; duration of observation, 12 months	T, n 1706 Fe, n 879 PI, n 827	Hb (g/L), HICN Fe, Male 132.8±10.7 Female 128.8±8.8 PI, Male 127.8±10.7 Female 123.9±8.9
Zhao XF et al. 2004 ^[22]	Guizhou, China	Cluster RCT	3-6 years	T, n 343 Fe, n 200 PI, n 143	All samples from 9 nature villages	Hb (g/L), HICN Fe, 111.08±11.31 PI, 113.64±9.95	Fe dose, 4 mg/per/d; Form of intervention, fortified Fe; duration of fortification, 18 months; duration of observation, 18 months	T, n 213 Fe, n 120 PI, n 93 High sample loss rate	Hb (g/L), HICN Fe, 122.72±8.05 PI, 117.66±8.62

Continued

Study	Location	Design	Age group	Sample size before the intervention	Eligibility and exclusion criteria	Baseline measurements of anemia status	NaFeEDTA fortification	Sample size after the intervention	Anemia status after the intervention
Chen JS et al. 2005 ^[23]	Guizhou, China	Cluster RCT	≥3 years	T, n 1936 Fe, n 993 PI, n 943	All residents of nine selected villages. Exclusion: children aged <3 years	Hb (g/L), HICN Fe, 121.0±13.2 PI, 122.6±12.3	Fe dose, 4.9 mg/per/d; Form of intervention, fortified Fe; duration of fortification, 18 months; duration of observation, 18 months	T, n 1936 Fe, n 993 PI, n 943	Hb (g/L), HICN Fe, 130.2±12.6 PI, 126.5±12.0
Huang YK et al. 2006 ^[24]	Guangxi, China	Individual RCT	3-18 years	T, n 2447 Fe, n 1211 PI, n 1236	All Fe-deficient anemic schoolchildren from 9 selected schools, which included 4 nursery schools, 2 primary schools, 3 middle schools	Hb (g/L), HICN, but no Hb data listed in original paper	Fe dose, 3-4 mg/per/d; Form of intervention, fortified Fe; duration of fortification, 6 months; duration of observation, 6 months	T, n 2499 Fe, n 1263 PI, n 1236	Hb (g/L), HICN No data listed
Li ZI et al. 2006 ^[25]	Hebei, China	Individual RCT	23-38 years, pregnant women	T, n 263 Fe, n 125 PI, n 138	All samples from 2 hospitals. Exclusion: anemic pregnant women.	Hb (g/L), HICN, but no Hb data listed in original paper	Fe dose, 2.3 mg/per/d; Form of intervention, fortified Fe; duration of fortification, 7 months; duration of observation, 7 months	T, n 263 Fe, n 125 PI, n 138	Hb (g/L), HICN No data listed
Wang ML et al. 2006 ^[26]	Zhejiang, China	Individual RCT	21-38 years, pregnant women	T, n 96 Fe, n 50 PI, n 46	All samples from 1 hospital. Exclusion: nonpermanent residents, have disease, a family population of >3; have special eating and drinking habits.	Hb (g/L), HICN Fe, 115.5±27.8 PI, 124.7±14.6	Fe dose, mg/per/d; Form of intervention, fortified Fe; duration of fortification, 7 months; duration of observation, 7 months	T, n 92 Fe, n 48 PI, n 44	Hb (g/L), HICN Fe, 127.3±28.2 PI, 112.0±12.3
Fang ZF et al. 2008 ^[27]	Guangxi, China	Individual RCT	6-12 years	T, n 675 Fe, n 376 PI, n 299	All samples from 2 primary schools	Hb (g/L), Hemoque** Fe, 124.53±12.51 PI, 133.95±14.37	Fe dose, 2.3 mg/per/d according to project recommendation; Form of intervention, fortified Fe; duration of fortification, 4 months; duration of observation, 4 months	T, n 675 Fe, n 376 PI, n 299	Hb (g/L), Hemoque Fe, 136.17±11.74 PI, 132.85±14.21

Continued

Study	Location	Design	Age group	Sample size before the intervention	Eligibility and exclusion criteria	Baseline measurements of anemia status	NaFeEDTA fortification	Sample size after the intervention	Anemia status after the intervention
He SL et al. 2008 ^[28]	Zhejiang, China	Cluster RCT	9-11 years	T, n 163 Fe, n 68 PI, n 95	All samples from 3 districts	Hb (g/L), HICN Fe, 114.36±5.17 PI, 113.83±6	Fe dose, 2.3 mg/per/d according to project recommendation; Form of intervention, fortified Fe; duration of fortification, 2 months; duration of observation, 2 months	T, n 163 Fe, n 68 PI, n 95	Hb (g/L), HICN Fe, 135.84±11.70 PI, 119.0±12.66
Li U et al. 2008 ^[29]	Henan, China	Cluster RCT	11 years	T, n 5248 Fe, n 2600 PI, n 2648	All samples from 12 primary schools. Exclusion: other age students	No original description on Hb method and data	Fe dose, 2.3 mg/per/d according to project recommendation; Form of intervention, fortified Fe; duration of fortification, 2 months; duration of observation, 2 months	T, n 5248 Fe, n 2600 PI, n 2648	No original description on Hb method and data
Li Zi et al. 2008 ^[30]	Hebei, China	Individual RCT	21-38 Years Exclusion: Anemic pregnant women	T, n 617 Fe, n 317 PI, n 300	All samples from 2 hospitals.	No original description on Hb method and data	Fe dose, 2.3 mg/per/d according to project recommendation; Form of intervention, fortified Fe; duration of fortification, 9 months; duration of observation, 9 months	T, n 617 Fe, n 317 PI, n 300	No original description on Hb method and data
Xu QH et al. 2010 ^[31]	Zhejiang, China	Cluster RCT	9-11 years	T, n 664 Fe, n 208 PI, n 456	All samples from 3 primary schools	Hb (g/L), HICN Fe, 139.6±10.52 PI, 135.4±9.57	Fe dose, 2.3 mg/per/d; Form of intervention, fortified Fe; duration of fortification, 10 months; duration of observation, 10 months	T, n 633 Fe, n 193 PI, n 440	Hb (g/L), HICN Fe, 139.3±9.43 PI, 131.2±10.90
Qi FS et al. 2011 ^[32]	Shandong, China	Individual RCT	10-16 years	T, n 1684 Fe, n 828 PI, n 856	All samples from 2 middle schools	Hb (g/L), HICN Fe, 135.25±12.56 PI, 133.18±13.60	Fe dose, 2.3 mg/per/d; Form of intervention, fortified Fe; duration of fortification, 6 months; duration of observation, 6 months	T, n 1684 Fe, n 828 PI, n 856	Hb (g/L), HICN Fe, 140.32±9.16 PI, 133.56±12.26

Note. * : There are no Hb data listed in the articles. ** : Because only one study in the table used Hemocue method, it is not analyzed for the influence of methodology to the result in this review.

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