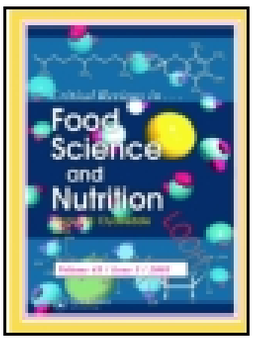

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Effects of iron supplementation versus dietary iron on the nutritional iron status: Systematic review with meta-analysis of randomized controlled trials

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Abstract

This meta-analysis compared the effects of dietary intervention *versus* iron supplementation on biochemical parameters related to the iron nutritional status in humans. The PubMed, CENTRAL, LILACS, SCIELO, OPENGREY.EU and ClinicalTrials.gov databases were searched for randomized clinical trials that assigned individuals to a dietary intervention or to an iron supplementation regimen, for 12 weeks or more. The primary outcome was the hemoglobin concentration, and secondary outcomes were ferritin, RDW, mean corpuscular volume, soluble transferrin receptor, total iron binding capacity, serum iron, and transferrin saturation. From the 6095 records identified, twelve studies were included, six with children, five with adolescents/adults, and one with pregnant women. In the subgroup of studies that included anemic/iron deficient children, supplementation significantly increased the hemoglobin concentration (weighted mean difference (WMD): 3.19 g/L [95% CI: 1.31, 5.07]) and induced a significantly greater reduction of the soluble transferrin receptor (WMD: -0.46 mg/L [95% CI: -0.70, -0, 21]), when compared to dietary intervention. It also induced a greater reduction of the total binding capacity of iron in adolescents/adults (WMD: -6.96 µmol/L [95% CI: -12.70, -1.21]). Supplementation showed a better effect on hemoglobin recovery in anemic/iron deficient children, while no differences were observed between supplementation and dietary intervention in treating adolescents/adults.

Keywords

Anemia. Hemoglobin. Diet. Ferrous sulfate.

INTRODUCTION

Anemia remains a public health problem throughout the world. According to data from the World Health Organization (WHO), approximately 25% of the world's population is affected by this disease, with prevalence ranging from 23% to 52% in developed and underdeveloped countries, respectively (WHO 2008; WHO 2001). It is estimated that about 50% of the cases of anemia are due to iron deficiency, also known as iron deficiency anemia (IDA) (WHO 2015, Stevens et al. 2013), with the main causes being insufficient intake of food sources of iron, poor absorption, intestinal parasitosis and blood loss (Okuturlar et al. 2016). IDA, especially of long duration, has serious health consequences, especially in childhood, associated with complications in growth and development, decreased working capacity in adult life, increased susceptibility to infections, and cognitive and motor impairment. For these reasons, IDA should be strongly countered, especially in the first years of life (Gupta et al. 2016; Wieringa et al. 2016). In adulthood, anemia leads to a decline in academic and professional performance, influencing productivity, with repercussions on family income (Bishwajit et al. 2016).

There are a number of strategies for preventing and combating IDA worldwide, with iron salt supplementation being the most widespread, with less attention being given to dietary approaches, which are, usually, more widely accepted by the population. Although the effectiveness of iron supplementation is already proven, the prevalence of anemia has remained high, especially in the less developed countries. One of the justifications for this situation is the low adherence to the use of the supplement, mainly due to its side effects, such as nausea, vomiting, colic and diarrhea, causing the treatment to be discontinued, decreasing its effectiveness (Azeredo et al. 2013; Cançado, Lobo and Friedrich 2010; Souza et al. 2009).

Regarding the dietary approach, a meta-analysis by Gera, Sachdev and Boy (2012) reported that the consumption of iron-enriched foods, compared to similar foods without iron fortification, results in improved biochemical parameters, especially hemoglobin and ferritin, reducing the risk of the individual remaining iron deficient or anemic. The authors emphasized the important role of food as a strategy for prevention/treatment of IDA. It is worth noting that the consumption of fortified foods does not trigger the appearance of the side effects caused by the supplementation.

In this context, the present meta-analysis of randomized clinical trials aimed to compare the effects of a dietary intervention versus iron supplementation on the hemoglobin and other serum biochemical parameters related to the iron nutritional status of humans, in a standard treatment period (defined as 12 weeks or more follow-up). The dietary intervention of studies should focus either on the supply of iron naturally present in food or supplied through fortified food.

METHODS

This meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) Statement (Moher et al. 2009). A protocol was published in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO), under registration number CRD42018082542.

Search strategy

The following databases were searched: MEDLINE (via PubMed), CENTRAL, LILACS, SCIELO, OPENGREY.EU and ClinicalTrials.gov. There was no manual search in the references of the included articles and experts of the area were not contacted, to avoid the risk of citation bias (Sterne, Egger and Moher 2011). The search strategy consisted of terms related to intervention (dietary treatment), comparison (iron supplementation), including a strategy with terms intended to improve the sensitivity of the search for randomized clinical trials (Lefebvre, Manheimer and Glanville 2011). Search was not restricted to year or language of publication. The complete search strategy is found in the supplementary material.

Eligibility criteria

Only randomized clinical trials that met the following criteria were included: (1) study participants were allocated to a dietary intervention group (i.e. an intervention that provided a fortified food product or a dietary plan offering at least half of daily Recommended dietary allowances/Adequate Intake (Institute of Medicine 2001); or participants were allocated to a medical supplement group (i.e. iron supplement only); (2) the follow-up period was 12 weeks or longer; and (3) interventions in both groups have occurred at least five times a week. There were no restrictions based on the participants' sex, age or race.

The studies needed to have evaluated at least one serum biochemical parameter that had an interface with the iron nutritional status (hemoglobin, ferritin, serum iron, among others), presenting mean values of the end of the intervention or the differences between the final and initial mean values, for each group. The exclusion criteria were as follows: (1) Studies with dietary intervention and iron supplementation in the same group; (2) Studies conducted exclusively with participants with chronic diseases that interfere with the nutritional iron status (eg. Acquired Immunodeficiency Syndrome (AIDS), cancer or kidney disease); and (3) duplicate publications of included trials.

Data extraction

Two authors, who were not masked by the authors or titles of the journals, independently evaluated the titles and abstracts of articles obtained with the search. Subsequently, the full texts of potentially eligible articles were acquired for further evaluation. The primary outcome sought in the studies was the final concentration or the difference between the final and the initial serum hemoglobin concentration, associated with a measure of dispersion. As secondary endpoints, any other biochemical parameters related to nutritional status in iron were observed. In addition, the final prevalence of anemia was also evaluated.

The necessary information was extracted from the selected articles, protocols and comments related to each study, and when necessary, the authors were contacted for additional information. In studies that presented more than two experimental groups, the two most suitable groups were chosen by consensus. A standard form for data storage was created based on the Cochrane collaboration model (Higgins and Deeks 2011).

Risk of bias assessment

The risk of bias of included studies was assessed at the level of the primary outcome only and followed the recommendations of the Cochrane Collaboration (Higgins, Altman and Sterne 2011). Two investigators independently assessed the quality of the studies in five categories: adequate sequence generation, allocation concealment, blinding of outcome assessors, management of missing data (using intention-to-treat analysis or per-protocol analysis), and selective reporting of results.

Data analysis

Due to the physiological heterogeneity of the different phases of life, it was decided that the studies would be analyzed in two separated groups: studies with children and studies with adolescents/adults. Despite the differences between adolescents and adults, it was understood that clustering would be feasible, due to the fact that the minimum age of inclusion found in the studies was 16 years, which makes the cutoff point for hemoglobin levels classification the same for all individuals in the cluster (WHO 2011).

The absolute value of each parameter, presented as the final arithmetic means after the intervention or the difference between the final and the initial mean, was evaluated for each group, as well as the prevalence of anemia after the end of the interventions, when applicable. The magnitude of the effect of each parameter was computed as the difference between the final means or between the change between the two groups. The weights of the studies were assigned according to the inverse of the variances method (Deeks, Higgins and Altman 2011), and the calculations were based on a random effects model (Dersimonian and Laird 1986). The value of α adopted was 5%. When it was not possible to obtain the necessary data, imputations were performed (Higgins, Deeks and Altman 2011).

Statistical heterogeneity among the studies was assessed using the Cochran Q test, and the inconsistency was measured using the I^2 statistic. A P-value of less than 0.10 was considered statistically significant for this analysis. Whenever one result showed heterogeneity ($P < 0.1$), the analysis was repeated, with the removal of one study at a time, in order to assess whether a particular study explained heterogeneity. Some subgroups were considered for analysis, considering the methodological characteristics of the studies: type of supplement used (syrup/capsules or multiple micronutrients powder); iron status of the participants (studies that included anemic or iron deficient individuals, and those who did not report this, or only included individuals without iron deficiency or anemia); and risk of study bias. All analyzes and charts were performed in the RevMan 5.3 program (Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Included studies

The searches conducted in the databases resulted in 6095 potentially eligible records; after the removal of the duplicate occurrences, there were 4259 references, which were submitted to the title and abstract reading. Of these references, 26 potentially met the selection criteria, and their complete texts were

acquired for further evaluation. After a detailed review, 12 articles were included in the qualitative analysis. One of these included articles was conducted with pregnant women; hence, it was not included in the quantitative analysis, due to the physiological heterogeneity of this group. Therefore, 11 articles were included in the quantitative analysis. The characteristics of the included studies and samples are shown in Table 1. The flowchart of the search and selection of the studies, including their respective reasons for exclusion, are presented in Figure 1.

Among the included studies in the qualitative analysis, six were performed with children, four with adolescents and adults and two with adults only. After accounting for the losses of participants, the six studies with children totaled 730 individuals randomized to one of the groups (369 for the dietary intervention group and 361 for the supplement group); the six that included adolescents/adults totaled 249 randomized individuals to one of the groups (132 for the dietary intervention group and 117 for the supplement group). Among the studies analyzed, seven had more than two intervention groups, being determined which would best fit the eligibility criteria by consensus. The description of the experimental groups of the analyzed studies is found in the supplementary material.

The articles included in this study employed different types of dietary interventions and iron supplements. In the dietary intervention, seven studies offered some fortified food, such as milk, pasta and porridge (Hoa et al. 2005; Hoppe et al. 2013; Rosado et al. 2010; Sazawal et al. 2014; Thi Le et al. 2006; Ziegler et al. 2009; Ríos L. et al. 1999); two studies conducted dietary counseling, delivering a food list, classified according to iron content (Patterson et al. 2001), or encouraging the daily consumption of food products that were sources of heme iron (Rajaram et al. 1995); one study offered a food of plant origin, amaranth (Macharia-Mutie et al. 2012); a study promoted the delivery of a menu that should be followed by the participant, focusing on the greater supply of iron (Lyle et al. 1992); and a study encouraged daily consumption of a minimal portion of meat (Heath et al. 2001). Regarding the supplementation, the iron types used were: ferrous sulfate (Hoa et al. 2005; Patterson et al. 2001; Rosado et al. 2010; Ziegler et al. 2009; Ríos L. et al. 1999); elemental iron (Sazawal et al. 2014; Macharia-Mutie et al. 2012); ferrous fumarate (Hoppe et al. 2013; Thi Le et al. 2006), and iron bisglycinate (Heath et al. 2001), in the form of multi-micronutrient capsules, syrups, or sachets. The study by Lyle et al. (1992) did not report the type of iron used in the supplementation.

Risk of bias assessment

The risk of bias of each study at the primary outcome level is shown in Table 2. In the final result, seven of the included studies were assessed as being at high risk of bias and only five were at low risk of bias.

Data analysis

Studies conducted with children

Hemoglobin. Six studies (730 individuals) were evaluated (Figure 2). There was no significant difference between individuals allocated for a dietary intervention compared to individuals allocated for supplementation (-1.43 g/L [95% CI: -6.02, 3.16]; P = 0.54, I^2, 89%, P <0.01). In the subgroup analysis of the studies that reported having included individuals with iron deficiency/IDA, the heterogeneity was reversed, showing a significant difference between groups, with a higher concentration of hemoglobin in the individuals allocated for supplementation when compared to the dietary intervention group (3.19 g/L [95% CI: 1.31, 5.07]; P <0.01, I^2, 0%, P = 0.41). When analyzing the subgroup of studies that reported not having included individuals with iron deficiency/IDA, or which did not show this information, the heterogeneity was not reversed, however, there was a significant difference between groups, with a lower hemoglobin concentration in the supplementation group (-6.58 g/L [95% CI: -11.52, -1,64), P <0.01, I^2, 78%, P = 0.01). Other subgroups were tested: type of supplement used (syrup/capsule or multiple micronutrients powder); and studies with low risk of bias. However, in these analyzes, the heterogeneity remained high, and the comparison between the groups did not present statistical significance (data not shown).

Ferritin. Five studies (586 subjects) were evaluated (Figure 3). No significant difference was observed between the individuals allocated to the dietary intervention group compared to the individuals allocated to the supplement group (44.81 pmol/mL [95% CI: -7.58, 97.19], P = 0.09; I^2, 96%, P <0.01). The heterogeneity was reversed when the study by Thi Le et al. (2006) was excluded, with no significant change in results (3.26 pmol/mL [95% CI: -6.21, 12.73], P = 0.50; I^2, 9%, P = 0.35).

RDW - Red Cell Distribution Width. Two studies were included, Sazawal et al. (2014) and Ziegler et al. (2009), (208 individuals). No significant difference was observed between groups (0.21% [95% CI: -0.22, 0.64], P = 0.33, I^2, 0%, P = 0.33).

Mean corpuscular volume (MCV). Two studies were included, Sazawal et al. (2014) and Ziegler et al. (2009), (208 individuals). No significant difference was observed between groups (-1.96 fL [95% CI: -6.16, 2.24]; P = 0.36, I^2, 84%, P = 0.01).

Soluble transferrin receptor. Two studies were included, Macharia-Mutie et al. (2012) and Thi Le et al. (2006), (334 individuals). There was a significant difference between groups, with a lower concentration in the individuals allocated to the supplement group, when compared to those allocated to the dietary intervention group (-0.46 mg/L [95% CI: -0.70, -0, 21], P <0.01, I^2, 0%, P = 0.47).

Final prevalence of anemia. Three studies were included. Macharia-Mutie et al. (2012) observed that the prevalence of iron deficiency anemia in the supplement group was 4.3%, whereas, in the group that underwent dietary intervention, the prevalence was 9.7%. In the studies by Rosado et al. (2010) and Thi Le et al. (2006), the final prevalence of anemia in the supplement and dietary intervention were 42.5% vs 54.9% and 6.6% vs 9.7%, respectively.

Studies with adolescents and adults

Hemoglobin. Five studies (165 subjects) were evaluated (Figure 4). No significant difference was observed between the individuals allocated to the dietary intervention group, compared to those allocated to the supplement group (0.04 g/L [95% CI: -2.50, 2.58], P = 0.98, I^2, 0%, P = 0.43). The subgroup of anemic vs. non-anemic individuals did not show any difference when compared the main result, considering the absence of heterogeneity (data not shown).

Ferritin. Four studies (136 subjects) were evaluated (Figure 5). There was no significant difference between groups (12.53 pmol/mL [95% CI: -4.11, 29.17]; P = 0.14, I^2, 81%, P <0.01). The presented heterogeneity was reversed when the study by Patterson et al. (2001) was excluded, with no significant change in results (5.95 pmol/mL [95% CI: -0.38, 12.27], P = 0.07, I^2, 0%, P = 0.84).

Total iron binding capacity. Two studies were included, Lyle et al. (1992) and Patterson et al. (2001), (67 individuals). A significant difference was observed between the individuals allocated to the dietary intervention group, compared to those allocated to the supplement group, which presented the lowest concentrations (-6.96 μmol/L [95% CI: -12.70, -1.21]; P = 0.02, I^2, 0%, P = 0.80).

Serum iron. Two studies were included, Lyle et al. (1992) and Patterson et al. (2001), (67 individuals). No significant difference was observed between groups (2.40 μmol/L [95% CI: -1.32, 6.12]; P = 0.21, I^2, 53%, P = 0.15).

Transferrin saturation. Two studies were included, Lyle et al. (1992) and Rajaram et al. (1995), (52 individuals). No significant difference was observed between groups (8.12% [95% CI: -1.77, 18.01], P = 0.11, I^2, 63%, P = 0.10).

Study conducted with pregnant women

Due to the physiological heterogeneity of pregnancy, the study by Hoa et al. (2005) was not included in the adolescents/adults analysis. In this study, hemoglobin and transferrin saturation were analyzed. It was observed that the group that received iron supplementation presented higher mean of both hemoglobin and transferrin saturation when compared to the group that received dietary intervention, 113.3 ± 8.8 (g/L) vs 112.1 ± 8, 4 (g/L) and 28 ± 9 (%) vs 23.7 ± 6.7 (%), respectively.

DISCUSSION

The present meta-analysis found that there were no significant differences in serum hemoglobin, ferritin, RDW and MCV levels between children allocated for a dietary intervention or to an iron supplementation regimen for a follow-up period of 12 weeks or more. A significant difference was found only in soluble transferrin receptor, with lower concentrations in the group that received supplementation. However, this analysis showed a high heterogeneity, which compromises this finding of absence of differences. In the subgroup analysis, with studies involving children with IDA or iron deficiency, a significant difference was observed in hemoglobin levels between groups, with lower concentrations in the group that received a dietary intervention. Overall, it was observed that the supplement presented better

performance in the recovery of these biochemical parameters in children. In the meta-analysis performed with adolescents and adults, there were no significant differences in serum hemoglobin, ferritin, iron and transferrin saturation levels between individuals allocated for a dietary intervention and those allocated for a supplementation regimen, for a follow-up period of 12 weeks or more. A significant difference was observed only in total iron binding capacity, with lower values in the supplementation group. Regarding the risk of bias, seven studies were classified as high risk, and from these, five were performed with adults and adolescents and only two with children. It should be noted that this high risk of bias, *a priori*, did not occur due to a methodological failure of the studies, but due to the lack of information in its reports, thus compromising the evaluation process.

Regarding hemoglobin concentration in children, there was a significant difference in the subgroup of studies that included children with IDA or iron deficiency. Lower values for those allocated for the dietary intervention, when compared to those allocated for a supplementation were found. In a meta-analysis published by Athe, Rao and Nair (2014), without reference to the nutritional iron of the individuals studied, higher hemoglobin was observed in children who consumed fortified food with iron, when compared to a group that received non-fortified food. The results of these authors show that fortification present positive results on the nutritional iron status, as well as potentially contributes to the consumption of other essential nutrients. However, according to the present finding, in situations of deficiency of this mineral, fortification does not seem to be equally effective as supplementation for recovery of hemoglobin concentrations. Regarding this outcome in adolescents and adults, it is noteworthy the fact that, although the amount of iron in the iron supplementation regimen is often higher than the amount of iron delivered by dietary intervention, there was no significant difference between the two groups. Such a result may represent an advantage of dietary treatment over the supplement, in the present conditions, since it is a widely accepted approach, with a reduced risk of side effects, usual in supplementation.

Regarding other outcomes related to the nutritional iron status, there was no significant difference in serum ferritin levels between groups, either in the analyses with children and in the analyses with adolescents and adults. The two studies that increased heterogeneity in these analyzes, Thi Le et al. (2006), involving children, and Patterson et al. (2001), with adolescents and adults, were the only ones that in the analyzes presented significantly lower results for the individuals allocated for dietary intervention, when compared to those allocated for a supplementation regimen. These studies were the only ones that reported having recruited only anemic or iron deficient individuals, offering significantly higher doses of iron by supplementation, when compared to the other studies included in the analyzes, a situation that may justify the high heterogeneity. The analyzes of soluble transferrin receptor, with children, and total iron binding capacity, with adolescents and adults, presented a significant difference between groups, with lower values for the supplement groups, indicating better results when using this type of intervention.

It is noteworthy that the responses in the serum biochemical parameters related to the iron status are associated with the iron dose administered; thus, theoretically, the greater the amount offered, within the recommended limits, the better the observed response (Ulvik, Moller and Hervig 2013). However, even with the use of lower doses, beneficial effects (Ulvik, Moller and Hervig 2013), related to the frequency and time of intervention, are fundamental to reach the expected result (Low et al. 2016).

Only three studies reported the final prevalence of anemia, all of which conducted with children. It was observed that the final prevalence of anemia in the supplementation group was lower than in the dietary intervention group in all three studies. However, Hieu et al. (2012), in a study with children followed-up for six months, found that the group that received daily iron-fortified food presented a lower prevalence of IDA when compared to the group that received weekly iron supplementation, demonstrating that the frequency of treatment is paramount for the achievement of results. It is important to emphasize the adverse effects from the daily use of iron supplements, which most often leads to the discontinuation of the treatment (Zaim et al. 2012).

Despite the contributions of the present work, some limitations can be observed. First, aggregated data from the studies were used, rather than individual patient data. Secondly, it would be ideal that the included studies only began to treat IDA or iron deficiency after anthelmintic treatment, a situation observed only in the study by Thi Le et al. (2006). Thirdly, there was no analysis of the side effects caused by the interventions used, especially gastrointestinal events (Zaim et al. 2012), commonly reported in iron supplementation. Fourth, the non-standardization of the therapies employed in the groups, as well as the disparity between the amounts of iron supplied in the dietary intervention and supplementation groups. All these aspects may decrease the external validity of the present results.

Thus, it is suggested that the next trials seek the standardization of the procedures of the interventions, as well as the analysis and reporting of their findings. The main recommendations would be: to balance the supply of iron between groups, such as in Ziegler et al. (2009) and Ríos L. et al. (1999); to continue to follow study participants after finalization of the protocol, showing which intervention provided better long-term outcome, such as in Patterson et al. (2001) and Ziegler et al. (2009); to perform the analysis of the results by intention-to-treat analysis, such as performed by Macharia-Mutie et al. (2012), preserving the balanced distribution of prognostic factors in the compared groups; to include only anemic or iron deficient individuals in the sample, such as done by Patterson et al. (2001) and Thi Le et al. (2006), or to include only individuals who do not present these situations, as in the studies of Hoppe et al. (2013) and Ziegler et al. (2009), standardizing the sample studied; and finally, to assess the prevalence of IDA at the end of the study, as in Macharia-Mutie et al. (2012), Rosado et al. (2010) and Thi Le et al. (2006).

In conclusion, the low number of included studies and the usually high heterogeneity found across the different analyzed outcomes weakens the findings of the present systematic review with meta-analysis. Nevertheless, the meta-analytical approach was still able to detect significant differences between groups,

without any heterogeneity, despite the low number of included studies, in three different outcomes, as follows: the use of iron supplements, when compared to dietary intervention, significantly increased the hemoglobin concentration and decreased the soluble transferrin receptor of anemic/iron deficient children. Additionally, it decreased the total iron binding capacity in adolescents and adults, when compared to the dietary treatment. Therefore, among the therapeutic options investigated here, the use of supplementation is the strategy of choice in the recovery of hemoglobin from anemic or iron deficient children. Dietary intervention, in turn, may be as useful as the supplementation regimen, with the same recovery power, especially in the serum hemoglobin concentration of adolescents and adults, constituting, in this case, a good approach, with the advantage of presenting reduced risk of rejection and no side effects when compared to the iron supplementation regimen.

Conflicts of Interest

The authors have no conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in this manuscript.

Authors' contribution

Luiz Gonzaga Ribeiro Silva Neto: preparation of the project, first reviewer, data collection and analysis, drafting of the manuscript. João Eudes dos Santos Neto: second reviewer, collection and analysis of the data, preparation of the manuscript. Nassib Bezerra Bueno: elaboration of the project, analysis of the data and preparation of the manuscript. Suzana Lima de Oliveira: elaboration of the project, data analysis and preparation of the manuscript. Terezinha da Rocha Ataide: elaboration of the project, analysis of the data and preparation of the manuscript.

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Table 1. Characteristics of the included studies

Study	Follow-up (months)	Intervention	Iron intake (mg. Diet *vs* Supplement)	Sample (Sex)	Country	Age, in years, Mean (SD)	IDA
Heath et al. (2001)	4	Dietary plan	12.4 *vs* 50	Adolescents/adults (F)	New Zealand	29 (7.9)	Yes
Hoa et al. (2005)	4	Fortified food	15 *vs* 60	Pregnant women (F)	Vietnam	25 (3.7)	Yes
Hoppe et al. (2013)	3	Fortified food	35.4 *vs* 60	Adults (F)	Sweden	24[d]	No
Lyle et al. (1992)	3	Dietary plan	11.8 *vs* 50	Adolescents/adults (F)	USA	18.5 (0.9)	No information
Macharia-Mutie et al.	4	Fortified food	18.9 *vs* 2.5	Children (F/M)	Kenya	3.1 (1.0)	Yes

(2012)							
Patterson et al. (2001)	3	Dietary plan	11.8 *vs* 105	Adolescents/adults (F)	Australia	No information	Yes
Rajaram et al. (1995)	6	Dietary plan	11.1 *vs* 50	Adolescents/adults (F)	USA	20.1 (2.2)	No
Ríos L. et al. (1999)	9	Fortified food	2.5[a] *vs* 2.5[a]	Children (F/M)	Chile	0.25[e]	No information
Rosado et al. (2010)	4	Fortified food	10 *vs* 20	Children (F/M)	Mexico	1.8 (0.7)	Yes
Sazawal et al. (2014)	6	Fortified food	7.9[b]/15.9[c] *vs* 6.25[b]/12.5[c]	Children (F/M)	India	1.4 (0.4)	No information
Thi Le et al. (2006)	6	Fortified food	10.7 *vs* 65	Children (F/M)	Vietnam	7.3 (0.9)	Yes
Ziegler et al. (2009)	5	Fortified food	7 *vs* 7.5	Children (F/M)	USA	0.33[f]	No

F, female; M, male; SD, standard deviation; [a]Each participant was offered 2.5mg / kg / day. [b]Value offered for children under 1 year of age. [c]Value offered for children over 1 year of age. [d]The study does not present the standard deviation, or other measure of dispersion. [e]All children started the study at 3 months of age. [f]All children started the study at 4 months of age.

Table 2. Risk of bias in the included studies

Study	Sequence generation	Allocation Concealment	Blinding	Missing data	Selective Reporting	Overall
Heath et al. (2001)	Unclear	Unclear	Low	High	Low	High
Hoa et al. (2005)	Unclear	Unclear	High	High	Low	High
Hoppe et al. (2013)	Low	Low	Unclear	High	Low	Low

Lyle et al. (1992)	Unclear	Unclear	Unclear	High	Low	High
Macharia-Mutie et al. (2012)	Low	Low	Unclear	Low	Low	Low
Patterson et al. (2001)	Unclear	Unclear	Unclear	High	Low	High
Rajaram et al. (1995)	Unclear	Unclear	Unclear	High	Low	High
Ríos L. et al. (1999)	High	Unclear	Unclear	High	Low	Low
Rosado et al. (2010)	Low	Low	High	High	Low	Low
Sazawal et al. (2014)	Unclear	Unclear	Low	High	Low	High
Thi Le et al. (2006)	Unclear	Low	Unclear	Low	Low	Low
Ziegler et al. (2009)	Unclear	High	Unclear	High	Low	High

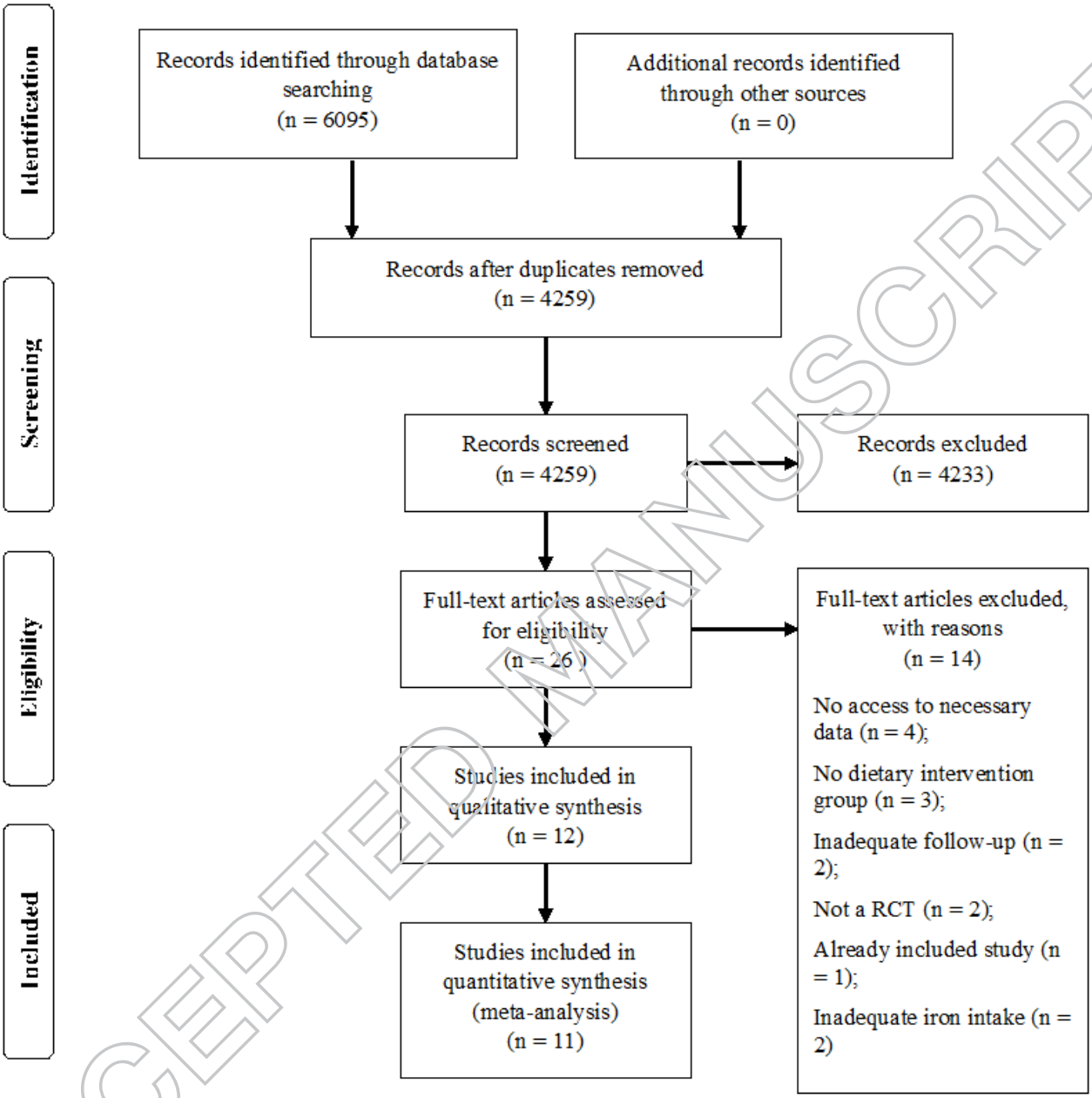

Figure 1. Flowdiagram of study selection

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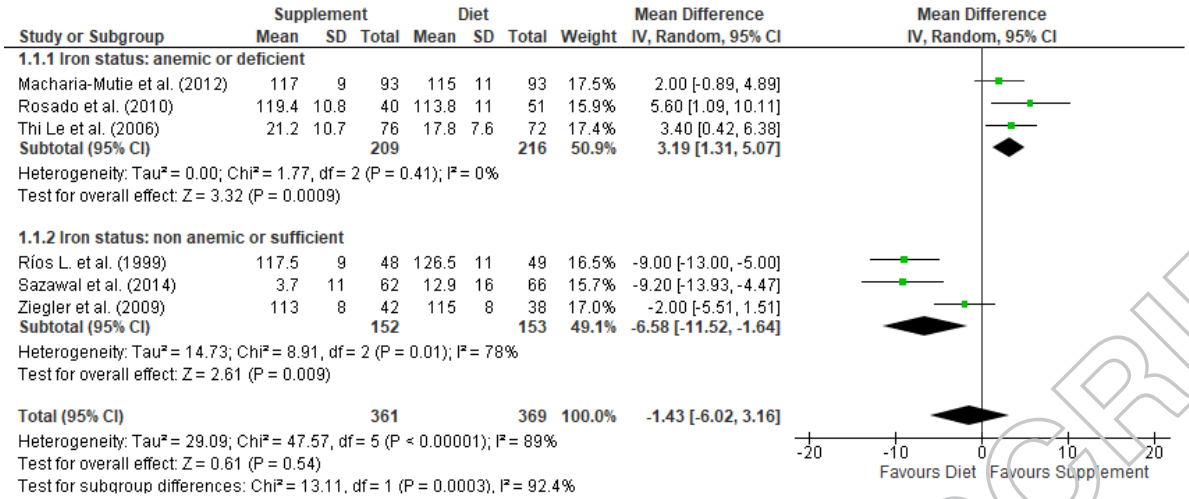

Figure 2. Effect of dietary intervention compared to supplementation on the hemoglobin concentration of children.

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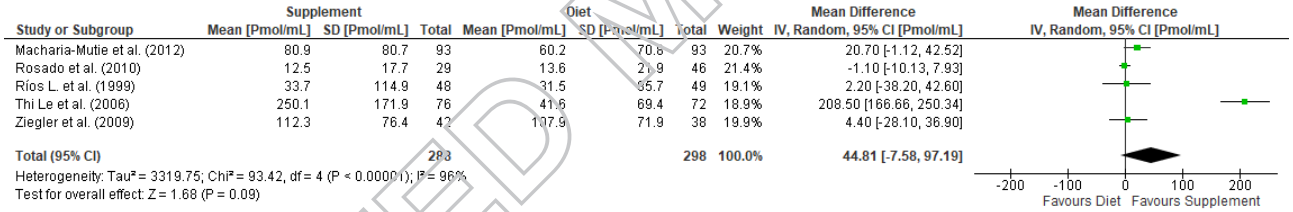

Figure 3. Effect of dietary intervention compared to supplementation on the ferritin concentration of children.

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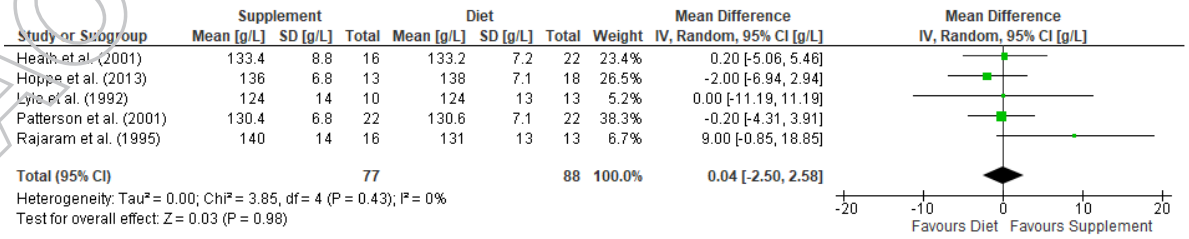

Figure 4. Effect of dietary intervention compared to supplementation on the hemoglobin concentration of adolescents and adults.

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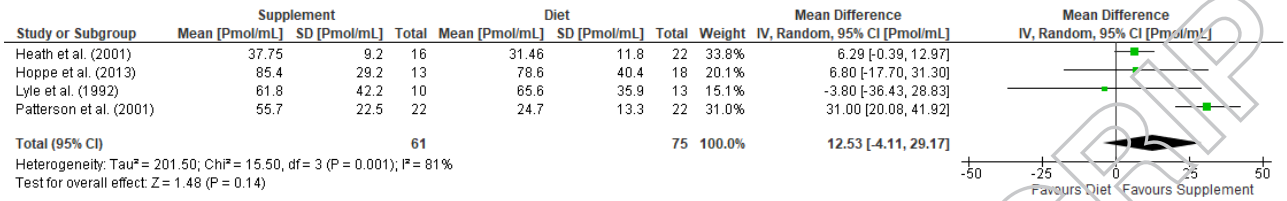

Figure 5. Effect of dietary intervention compared to the supplementation on the ferritin concentration of adolescents and adults.

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