Systematic Review: Dietary Intervention only Decreases the Risk of Iron Deficiency Anemia among Children

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Research question: Does a dietary source only decrease the risk of Iron Deficiency Anemia (IDA) among children?

Hypothesis: the risk of IDA among children treated with dietary sources only is lower than the risk among those not treated.

Goal: treatment of IDA

Objectives

- Primary objective: determine the effect of dietary intervention only on occurrence of IDA.
- Secondary objective: compare between the different effects of all dietary sources.

Abstract

Iron Deficiency Anemia is the most common type of anemia related to malnutrition worldwide. It represents a major problem in developing countries. Purpose: To determine the effect of dietary intervention only on the occurrence of IDA. Methods: In 6 articles with 8 eligible outcomes, a total of 676 individuals were included within the present systematic review with no of cases 339 and 337 control. Dietary intervention is mainly to eat about 30- 40 g of liver, sheep liver, chicken liver, or 1- 2 eggs, or 30 red dates, etc. before or after the meal once a day. Result: clinical recovery—clinical symptoms disappeared completely, and hemoglobin returned to normal. Clinically effective—clinical symptoms relieved, and the rise of HB >15 g/dl. Invalid— clinical symptoms did not improve or obviously improve, and the rise of HB to 15 g/dl. Dietary intervention was associated with an average change in clinical effectiveness from 94.0% to 100.0%. The clinical effect was increased in dietary intervention in all six trials, among which three trials had a statistical increase of clinical effect. Tests for heterogeneity showed no significant differences across studies, thus the fixed effect model was employed. The overall pooled estimate of or in the dietary intervention on children with IDA was 5.03 (95%) CI: 3.09- 8.18, Z = 6.50, P<0.001. Conclusion: Dietary intervention on children with IDA was established that had a beneficial effect.

***Key Words**: iron deficiency anemia- dietary intervention - children/ infant.*

BACKGROUND

Several studies have been published in the past fifty years on the concentration of blood hemoglobin in children according to age and sex, and have estimated the prevalence of anemia and iron deficiency with overall approximate numbers **(GBD 2017, NFHS, 2000 and Lozoff et al., 2000).** According to WHO, anemia is considered a public health problem **(WHO, 2004; 2015).** It is affecting the majority of the population of the world in both developed and developing countries with major consequences on human health as well as social and economic development with varying prevalence. It is the world's second leading cause of disability of the completely global disease burden **(Sachdev et al, 2005; Glazer and Bilenko, 2010).** Globally, anemia affects around 305 million (25.4%) school-children (SC), (children aged 5.00–14.99 years) **(McLean et al., 2008),8** and it is three to four times more prevalent in non-industrialized regions than in industrialized ones. The prevalence of anemia in SC ranges from 5% in North America to 22% in Europe and 30–63% in Asia **(Yip and Ramakrishnan, 2002; Krivienė and Ragelienė 2006 and Best et al., 2010)**. It also affects millions of SC in resource-limited countries, especially in Africa and Asia. For example, a study conducted in eight countries in Africa and Asia showed that 12–58% of SC were suffering from anemia 12, 41, 54, 57, 58% in Malawi and Kenya, Ghana, Mozambique, Tanzania, and Mali, respectively, and 30% in Vietnam and Indonesia (**Yip and Ramakrishnan, 2002; Krivienė and Ragelienė 2006 and Best et al., 2010)**. In developing countries' SC, factors contributing to the high prevalence of anemia include inadequate consumption of nutrient-rich foods, lack of access to health care services, and inefficient utilization of available micronutrients because of infectious diseases, particularly malaria and helminthic infections **(Krivienė and Ragelienė 2006; Best et al., 2010; Taylor et al., 1988; and Abdel-Rasoul et al., 2015).** Low maternal educational status, poor nutritional practices, and unhealthy food habits are additional factors for the development of anemia in SC

(**Best et al., 2010)**. In addition, the main risk factors in low-income countries are prolonged breast-feeding without iron supplementation beyond the 4th month of life. Limited consumption of meat and fish, which are rich in iron and zinc, is often low because of economic, cultural, and/or religious reasons, diets rich in cereal, legume-based flours, are often rich in phytates, excess of dietary fiber, many common foods, or beverages contain iron-binding phenols. Inadequate vitamin C intake, frequent consumption of coffee and tea, multiparty, hookworm infestation, schistosomiasis, malaria (contributes to IDA by causing intravascular hemolysis with hemoglobinuria), Chronic or repeated infections (functional iron deficiency due to chronic inflammation).

While risk factors in developed countries mainly are gastrointestinal bleeding of any etiology, genitourinary bleeding of any etiology, and Iron malabsorption of any etiology **(Elpis, et al., 2020).** Many challenges in the absorption of dietary iron as it is also affected by the iron source and duodenal conditions, such as PH. The proportion of iron absorbed from hem iron and non-food sources such as iron salts or saccharides is approximately 10–15% of elemental iron, while less than 2% of elemental iron from vegetable sources is absorbed. Iron Deficiency (ID) may double the percent iron absorption from any given source and that has of the challenges in plant vegetarian diets increasing adaption prevalence (**Taylor et al., 1988)**. There was a significant negative correlation between increased consumption of tea, chips, and soft drinks and hematological values **(Bethesda, 2010)16,** which could be because they contain polyphenols, which inhibit non-hem iron absorption **(Sun et al., 2018)**. It has been highlighted that IDA has a significant impact on motor, cognitive and socioe-motional development, and is not reversible in children (**Glazer and Bilenko, 2010; McLean et al., 2008 and Yip and Ramakrishnan, 2002)**.

Emerging evidence on the role of IDA in worsening clinical outcomes of various diseases continues to accumulate, which prompted careful consideration of

IDA diagnosis and management in international practice guidelines. The multiple etiologies of IDA and non-specificity of symptoms, however, can challenge the diagnosis. Moreover, the availability of different formulations of iron supplementation can complicate treatment decisions **(Sun et al., 2018 and WHO 2016)**.

Not to mention anemia is a major contributor to maternal and fetal morbidity and mortality, particularly in less developed countries **(Hare et al., 2019; Haghdoost et al., 2007 and Stroup et al., 2000)**. In Egypt, previous studies have shown IDA affects ~30-40% of children **(Youssef and Khedr, 2015)** also, to be the most common cause of anemia among Egyptian infants 6 to 24 months of low socioeconomic standard affecting 43% of them **(Abdel-Rahman et al., 2008)**. The Emerging, evidence on the role of IDA in worsening clinical outcomes of various diseases continues to accumulate, which prompted careful consideration of IDA diagnosis and management in international practice guidelines. The multiple etiologies of IDA and non-specificity of symptoms, however, can challenge the diagnosis. Moreover, the availability of different formulations of iron supplementation can complicate treatment decisions **(Sun et al., 2018 and WHO 2016)**.

Though several strategies and approaches have been established and suggested still IDA remains among the five leading causes of years lived with disability in humans. That is why the need for adding different approaches especially nutritional intervention and nutritional education together with the already existing medical updated practice is a mandatory need. Alternative and complementary treatment for IDA had been suggested, such as lifestyle modifications, especially dietary intervention. Increasing evidence indicates that dietary intervention, assisting the treatments of IDA in children, can also improve the clinical effect (**Haghdoost et al., 2007)**. The WHO has identified that the collection of 'additional data on the safety of iron supplementation in non-anemic or non- iron- deficient children' should be a research priority, and

that 'additional long-term studies on functional outcomes (e.g. cognitive and motor development)' should be conducted (**Stroup et al., 2000)**. With growing concern about the delayed effects of unnecessary iron intake during critical windows of development, we believe this study is timely and will provide an evidence-based case for revisiting nutritional guidelines in these countries, some of which are based on public health policies that were initially devised over half a century ago **(Youssef and Khedr, 2015)**. Employing meta-analyses for the identification and analysis of findings from observational studies, one will synthesize research results that are needed by health care professionals and policymakers and provide them with important information on epidemiological indicators **(Abdel-Rahman et al., 2008 and Mansour et al., 2004)**.

Qena governorate, the prevalence of IDA was 12% among children in the age group of 6-11 years **(Mansour et al., 2004)**.

The present systematic review aims to know that the risk of IDA among children treated with dietary sources only is lower than the risk among those not treated.

Primary objective: To determine the effect of dietary intervention only on the occurrence of IDA, secondary objective: To describe the effect of all dietary sources only

Furthermore, in meta-analysis sample size is raised as the studies are collected, out coming the best statistical power. Meta-analysis can also explore the observed heterogeneity among the results of primary studies **(Moher et al., 2007; Wang et al., 2008; Liu 2010; Tian and Li 2010; Zhu 2011; Qi 2011 and Lan 2012)**.

METHODS

- ***Strategy of literature search***

The available articles published (up to March 2021) were identified by extended computer based searches from the following online databases searched from Google scholar, Embase, psyc

INFO, science Direct, Pub med, Scopus, Web of Knowledge, Biological abstracts, CINAHL. In order to maximize the sensitivity of the search, general keywords such as (iron deficiency anemia) and (dietary intervention) and (children or infant). This Study also reviewed the references cited in the studies and review articles to identify additional studies not captured by our database searches.

- **Inclusion criteria and quality assessment:** Studies were independently selected for inclusion and were included in the study if they were diagnosed with iron deficiency anemia in children according to the standard, in English, in the last 10 years, trials for which the intervention was applied directly towards the child.
- **Studies were excluded** if they were not primary studies, duplicated publication, non-English, non-children age group, unreliable reference, trials for which the intervention was not applied directly towards the child and so on. A third reviewer by assessed any disagreement between two reviewers published.
- Critical appraisal was done on the reviewed paper regarding study type, sample size and confidence interval, related desired outcome, related exposure with review for reference strength.
- Seven independent reviewers together reviewed all the resultant titles and abstracts for IDA in children after removing author's name, journal name. All reviewers (Flowchart figure 1) then assessed the full-texts of all relevant articles.

STUDY DESIGN:

Prospective randomized controlled where each patient had the same probability to enter in any group, follow-up studies of previous trials.

Intervention measures the investigators give the research subjects a particular medicine or other intervention. Usually, their compare the treated subjects (Intervention Group) to subjects

who receive no treatment or standard treatment (control group). Then the researchers measure how the subjects' health changes.

Children of IDA were randomly divided into treatment group and control group, children in control group treating with routine dose iron agent; and treatment group taken because of drug therapy dietary intervention. Dietary intervention is mainly to eat about 30~ 40 g of liver, sheep liver, chicken liver, or 1~ 2 egg, or 30 red dates etc. before or after the meal once a day.

Overall assessment of result; Clinical recovery—clinical symptoms disappeared compl-etely, and hemoglobin returned to normal. Clinically effective—clinical symptoms relieved, and the rise of Hb>15 g/dl. Invalid—clinical symptoms did not improve or obviously improve, and the rise of Hb < 15 g/dl (Figure 1).

The selection of all studies and data extraction of eligible studies was both performed independently by 2 authors. A consultation was performed with third party when a dispute occurred. Extracting information Excel spreadsheet and fetching information:

1. The general information: title, the first author, publish time and region
2. The characteristics of research: research type, the number of the case and the control group, the crowd source and distribution proportion of boy and girl.
3. Data characteristics: capacity for IDA, unit, relative risk (RR) and 95% confidence interval or odds ratio (OR) and 95% confidence interval. If data did not give within the literature, by statistical software got.

Statistical analysis

The data were collected, analyzed and checked in accordance with the requirements of Meta-analysis. Statistical analysis was performed by STATA software, which was provided by the Cochran Collaboration. If there was no statistically significant heterogeneity in this meta-analysis, the fixed effect model was employed. In addition, the random effects model was used for meta-analysis when the results of trials had heterogeneity. The

odds ratio (OR) or relative risk (RR) was calculated for dichotomous data with 95% confidence intervals (CIs) for all analyses. *P* values that were $p \leq 0.05$ considered statistically significant. If necessary, the present systematic review could use sensitivity analysis to test the stability of the results. Funnel-plot analysis was used to identify the publication bias.

RESULTS

Characteristics of studies

To identified 6 articles with 8 eligible outcomes for this meta-analysis (**Wang et al., 2008; Liu 2010; Tian and Li 2010; Zhu 2011; Qi 2011 and Lan 2012)** [26-31] .All articles were randomized control trials. Having assessed the quality of the full-texts of potentially relevant studies, 6 studies with a total of 676 individuals were included in the present systematic review with no of cases 339 and 337 control.

The change and the corresponding 95% CIs for children is IDA in each trial and overall are presented in Fig. 2.

In comparison to control (no intervention) group, cases (dietary intervention) was associated with change in clinical effectiveness from 94.0% to 100.0% where clinical effect was increased in all the six trials. Tests for heterogeneity showed no significant differences across studies, thus the fixed effect model was employ. The overall pooled estimate of OR in the dietary intervention on children with IDA was 5.03 (95% CI: 3.09-8.18, Z = 6.50).

Tests for heterogeneity showed no significant differences across studies (4 weeks: $\chi 2 = 0.00$, P = 0.95; 2 months. In addition, it was found that the OR of 4 weeks in the dietary intervention on children with IDA was significant 6.04 (95% CI: 3.26-11.21, Z = 5.71, $p<0.0001$), and OR of 2 months was 3.71(95% CI: 1.68-8.20, Z = 3.25, p = 0.001) so duration of dietary intervention had no significant effect on OR.

Begg's test shows that p value is higher than 0.05, by using STATA software to analyze the publication bias for the 6 articles, indicating that there are no significant publication (Begg's funnel plot was symmetric Fig. 4).

DISCUSSION

Basic approach to control IDA should comprise education and linked way to increase the dietary intake of iron, dietary modification to enhance the iron absorption, fortification of food articles, in addition to control the infection and worm infestations **(Youssef and Khedr, 2015)**.

In terms of socioeconomic standard, children from low and middle socioeconomic standard had a two-fold increased risk of developing IDA. This may be attributed to the lack of knowledge of basic food requirements and awareness of food rich in iron **(Hare et al., 2019)**.

The present meta-analysis is about the effect of dietary intervention on children with iron deficiency anemia established that dietary intervention had a beneficial effect on children with IDA, as supported by significantly increase effect of dietary intervention (OR = 5.03, 95% CI: 3.09- 8.18). In this research, a meta-analysis with the literature retrieved over the past 10 years about dietary intervention role in IDA recovery and discuss the beneficial effect of dietary intervention on IDA recovery. Our result demonstrated that dietary intervention had a beneficial effect on children with IDA.

The study shows a certain evidences that dietary intervention might play a certain role in children with IDA. Several limitations in our current study should be addressed. First, only a small number of trials (n = 6), with a relatively small sample size, have been included in the current study (n=676). Second, due to the small sample size, we failed to determine the role of clinical effect of dietary intervention in terms of intervention time (**Haghdoost et al., 2007)**.

WHO guidelines suggest in infants and toddlers 6–23 months of age fortification of complementary foods with iron-containing micronutrient powders (MNPs), which should include 12.5 mg of elemental iron per sachet, preferably as coated ferrous fumarate, corresponding to 37.5 mg of ferrous fumarate or 62.5 mg of ferrous sulfate heptahydrate or other equivalent amounts in the various iron compounds. In children 6–12

months old, sodium iron EDTA (Na Fe EDTA) is not recommended. The same guidelines suggest fortification of complementary foods with iron-containing MNPs in children 2–12 years, including 12.5 mg of elemental iron for children aged 2–4 years and 12.5 to 30 mg elemental iron for children 5–12 years of age) **(WHO, 2016).** If Na Fe EDTA is selected as a source of iron, the dose of elemental iron should be reduced by 3–6 mg due to its higher bioavailability. The UNICEF's MNP product contains 10 mg of iron per sachet, as coated ferrous fumarate, .Na Fe EDTA or ferrous bis-glycinate **(WHO, 2009)**.

In-home iron fortification of complementary foods with MNPs has been shown to effectively reduce the risk of iron deficiency in children less than two years of age in low-income countries without changing their customary diet **(Suchdev et al.,2020)**. Unfortunately, MNPs are associated with unfavorable changes in gut flora and induction of intestinal inflammation that may lead to diarrhea and increased risk of hospitalization **(Weiss, 2015 and Jaeggi 2015).** Moreover, the benefits of this intervention on survival or the developmental outcomes of infants and toddlers are unclear.

On other hand, studies were done regarding diet modification by adding iron rich diet like date consumption-based nutritional program on IDA in primary school girls in Iran and the results showed Hb, Hct, and ferritin levels increased after the date consumption in the female primary school students. All the participants who had IDA at the beginning of the study demonstrated an increase in the blood indices, which can be said that this is due to the presence of iron in the dates and its role in the production of RBCs **(Mousavi et al., 2014).** Other study found that the use of dates for 2 months by children aged 9 to 11 years in the orphanage has increased the levels of Hg and Ferritin **(Youssef and Khedr, 2015).** Also, anther one reported that Hb levels improved in pregnant Egyptian women after consuming 100 g of dates daily for 7 weeks **(Abdel-Rahman et al., 2008)** this data supported by many studies up to 2010 **(Hernández et al., 2006; Sazawal et al., 2010)**.

The study in 2019 was conducted a research titled "Comparative study on Hb levels on amla with honey and dates. The findings demonstrated that both dates and amla with honey have a drastic increase in the level of Hb **(Akilarooran et al., 2019)**.

The studies found that foods rich in corn, chickpea, and cow's lungs are effective in controlling IDA. It has increased the Hb levels significantly in primary school children **(Moreira-Araújo et al., 2008).** Also, Anita found that the date extract increases the level of Hb. Which indicates that the dates are rich in iron, and the presence of proteins, carbohydrates, lipids, and elements such as Zn, Ca, and the presence of abundant amounts of vitamin A is helping in the synthesis of Hb **(Kusumawardani and Machfudlo, 2020)**.

Thus, study recommend to emphasize on the importance of nutritional education cooking techniques, useful food additives, behavior change orientation aiming to preserve positive traditional practices. Food quality and safety issues, right diet to complement therapy as it will help patients avoid food that interfere with the absorption of dietary iron, and even of prescribed supplements. It will prevent interactions between food and iron supplements that can aggravate adverse effects; so that after their therapy they will continue to eat iron rich foods and avoid a recurrence of anemia **(Santoyo-Sánchez et al., 2015 and Engle-Stone et al., 2017)**, and stressing on more high quality trials are needed to confirm with current findings.

CONCLUSION:

To increase overall healthy food intake, and micronutrient iron rich foods, management and control of inhibitors and enhancers, as mentioned for the risk factors. In low-income countries, iron deficiency should not be addressed alone, but deficiencies of other micronutrients and hematinic factors, infections, and lead poisoning should be resolved, too and that will require measures to improve social and economic policies that fight poverty.

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Flowchart Figure 1

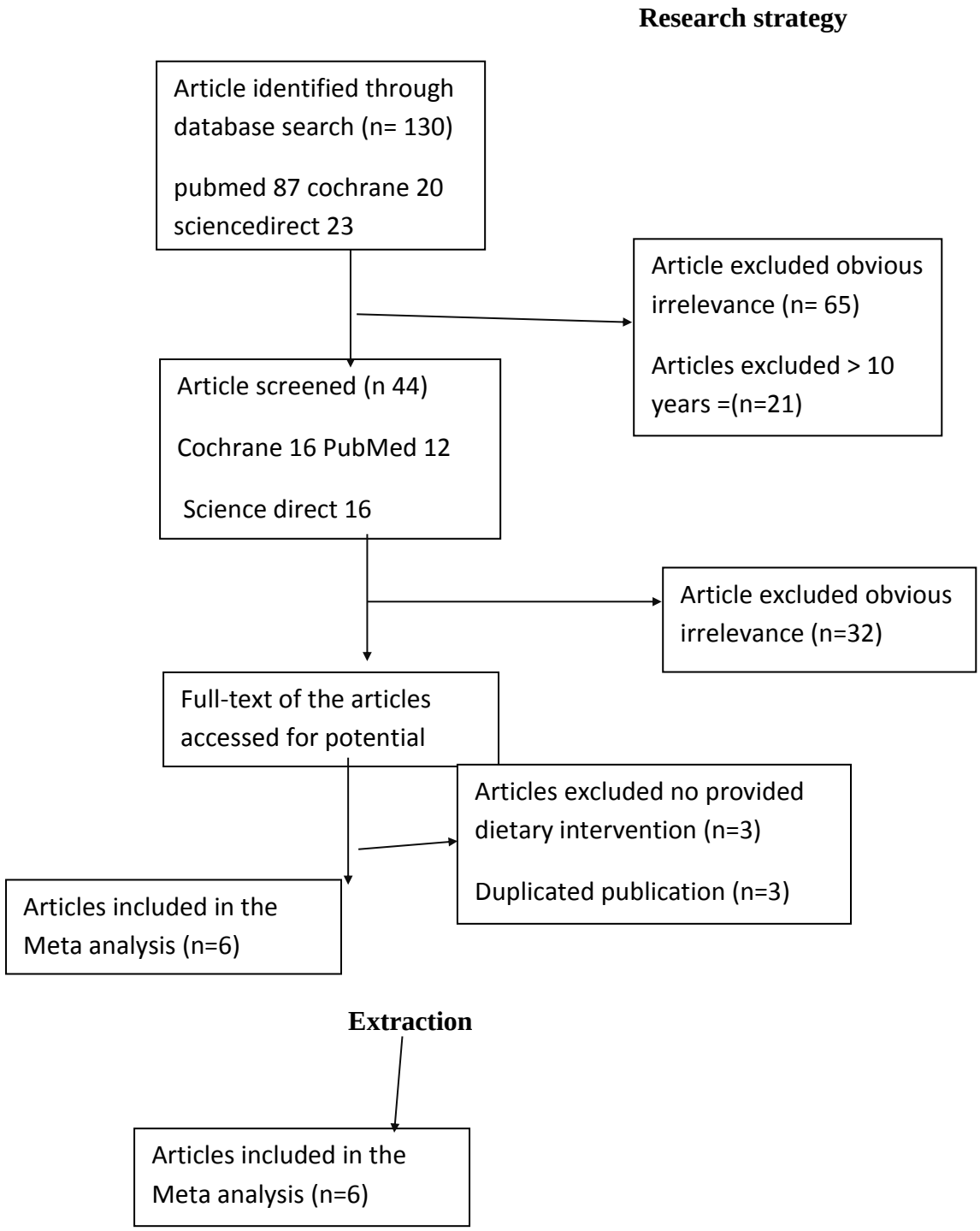

Table 1: descriptive summary of included studies in the present systematic review

Author	Year	Randomization	Blinding	Age	Case number		Intervention time	Intervention type and dosing	
					treatment	Control		Treatment	Control
Wang SH	2008	Semi randomized	Unclear	1-13 years	50	49	4weeks	Shengxuening tablet (0.5g/tid po) + dietary intervention	Shengxuening tablet (0.5g/tid po)
Liu M	2010	Unclear	Unclear	2-65 years	75	75	28 days	Shengxuening tablet (0.5g/tid po) + dietary intervention	Shengxuening tablet (0.5g/tid po)
Tlan J	2010	Randomization	Unclear	9 months-11 years	60	60	8 weeks	Elemental iron (1mg/kg bid po)+Vc (0.1g/tid po)+dietary intervention	Elemental iron (1mg/kg bid po)+Vc (0.1g/tid po)+
Zhu M	2011	Randomization	Unclear	11 months - 10 years	32	32	8 weeks	Elemental iron (1mg/kg bid po)+Vc (0.1g/tid po)+dietary intervention	Elemental iron (2mg/kg bid po)+Vc (0.1g/tid po)+
Qi Gi	2011	Randomization	Unclear	8 months -12 years	70	70	8 weeks	Elemental iron (1mg/kg bid po)+Vc (0.1g/tid po) +dietary intervention	Elemental iron (2mg/kg bid po)+Vc (0.1g/tid po)+
Lan H	2012	Randomization	Unclear	6monthes-9 years	52	51	8 weeks	Elemental iron (1mg/kg bid po)*Vc (0.1g/tid po)* dietary intervention	Elemental iron (2mg/kg bid po)+Vc (0.1g/tid po)+

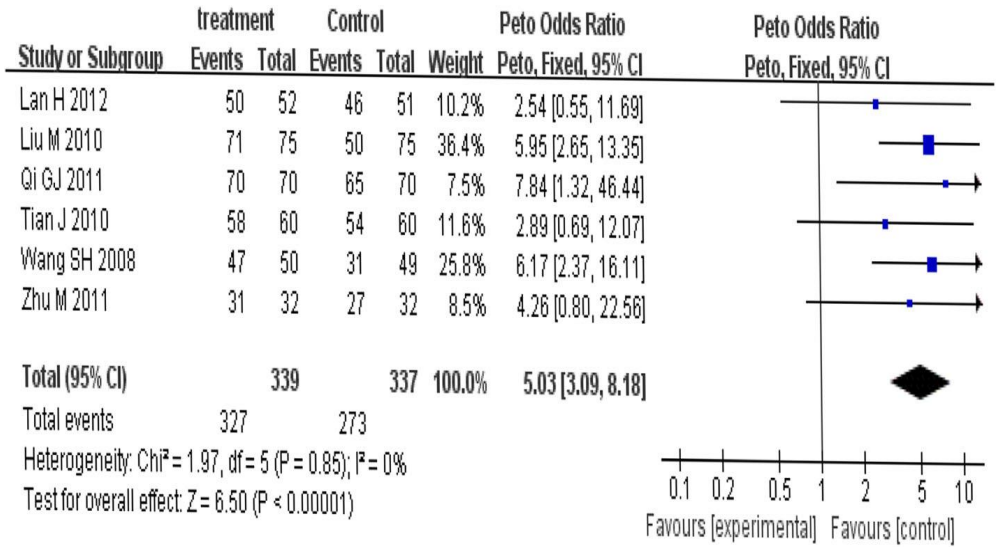

Fig. 2 Meta-analysis of the effect of dietary intervention on children with IDA in fixed effect model.

Table 2 Results of stratified analysis for the duration of dietary intervention

Group (duration of intervention)	Total data included	OR (95%CI)	*P*	P for heterogeneity	I^2,%
4 weeks	2	6.04 (3.26, 11.21)	*<0.00001*	0.95	0
2 months	4	3.71 (1.68, 8.20)	*0.001*	0.79	0
All	6	5.03 (3.09,8.18)	*<0.00001*	0.85	0

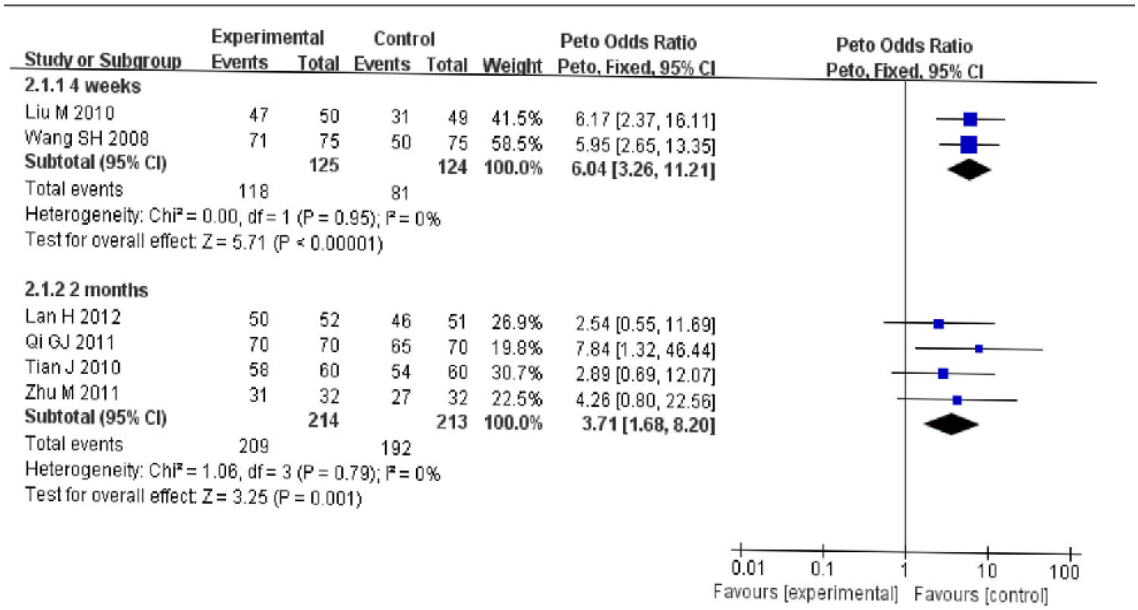

Fig. 3 Stratified analysis of the effect of dietary intervention on children with IDA in random effects model

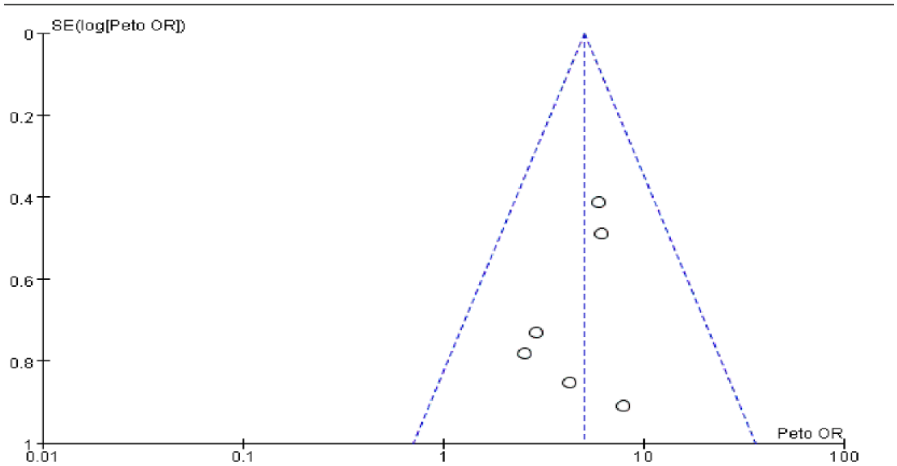

Fig. 4 Funnel-plot of random control trials

عرض منهجي: تأثير التدخل الغذائي فقط للتقليل من خطر الإصابة بفقر الدم الناجم عن نقص الحديد بين الأطفال

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الملخص العربي

فقر الدم الناجم عن نقص الحديد هو النوع الأكثر شيوعًا المرتبط بسوء التغذية في جميع أنحاء العالم. إنه يمثل مشكلة رئيسية في البلدان النامية. الغرض: تأثير التدخل الغذائي فقط على فقر الدم الناجم عن نقص الحديد. الطرق: في ٦ مقالات مع ٨ نتائج مؤهلة ، تم تضمين ما مجموعه ٦٧٦ فردًا في المراجعة المنهجية الحالية مع عدم وجود حالات ٣٣٩ و ٣٣٧ مجموعة ضابطة. التدخل الغذائي هو بشكل أساسي تناول حوالي ٣٠-٤٠ جم من الكبد ، كبد الأغنام ، كبد الدجاج ، أو بيضتين ، أو ٣٠ واحدة من التمرة اللاحمر ، إلخ قبل أو بعد الوجبة مرة واحدة في اليوم. النتيجة: الشفاء السريري - اختفت الأعراض السريرية تمامًا وعاد الهيموغلوبين إلى طبيعته. فعال سريريًا - تخفيف الأعراض السريرية وزيادة نسبة الهيموجلوبين <١٥جم / ديسيلتر. غير صالح - الأعراض السريرية لم تتحسن أو تتحسن بشكل واضح ، وارتفاع الهيموجلوبين إلى ١٥ جم / ديسيلتر. ارتبط التدخل الغذائي بمتوسط تغيير في الفعالية السريرية من ٩٤,٠٪ إلى ١٠٠,٠٪. تم زيادة التأثير السريري في التدخل الغذائي في جميع التجارب الست ، من بينها ثلاث تجارب كان لها زيادة إحصائية في التأثير السريري. أظهرت اختبارات عدم التجانس عدم وجود فروق ذات دلالة إحصائية عبر الدراسات ، وبالتالي تم استخدام نموذج الأثر الثابت. كان التقدير الإجمالي المجمع أو في التدخل الغذائي للأطفال المصابين بفقر الدم الناجم عن نقص الحديد ٣و٥ (٩٥%) CI: 3.09-8.18، Z = 6.50، P <0.001 . الاستنتاج: أثبت البحث أن التدخل الغذائي على الأطفال المصابين بفقر الدم الناجم عن نقص الحديد كان له تأثير مفيد.

الكلمات المفتاحية: *فقر الدم الناجم عن نقص الحديد - التدخل الغذائي - الأطفال / الرضع.*