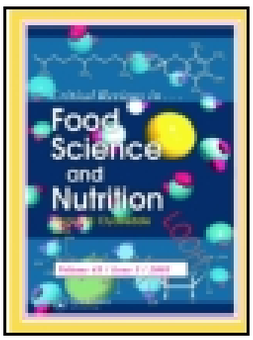

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Effect of vitamin A supplementation on iron status in humans: a systematic review and meta-analysis

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ABSTRACT

Anemia is a worldwide public health problem that can be related to many causes, including vitamin A deficiency. The aim of this study was to assess and estimate the effect of vitamin A supplementation (VAS) on iron status biomarkers and anemia in humans. Six databases, including Cochrane, EMBASE, LILACS, Pubmed, Scopus and Web of Science, were searched for clinical trials and cohort studies that investigated the effect of vitamin A supplementation alone on iron status and anemia, without time-restriction. The search yielded 23 eligible studies, 21 clinical trials and 2 cohort studies, with children, teenagers, pregnant or lactating women. The meta-

analysis of the clinical trials showed that VAS reduces the risk of anemia by 26% and raises hemoglobin levels, compared to non-treated group, independent of the life stage. VAS did not alter the prevalence of iron deficiency among the clinical trials conducted with children and teenagers (RR 0.82, 95% CI 0.60 to 1.12, p = 0.204), whereas a significant increase in serum ferritin levels was observed in trials conducted with pregnant and lactating women (WMD 6.61 μg/L; 95% CI 6.00 to 7.21 μg/L; p < 0.001) . Therefore, vitamin A supplementation alone may reduce the risk of anemia, by improving hemoglobin and ferritin levels in individuals with low serum retinol levels.

KEY WORDS: Review; supplementation; vitamin A supplementation; anemia; iron deficiency; iron status.

INTRODUCTION

Anemia is one of the most important public health problems in developing and developed countries. According to the World Health Organization (WHO), the global prevalence of anemia in 2011 was about 42.6% of the population, affecting mainly children age 6 to 59 months-old and women of reproductive age (WHO 2015). In children, suboptimal iron intake can cause significant damage, leading to disrupted language development, motor and cognitive evolution, and learning problems (Lozoff, et al. 1996). In pregnant women, anemia may limit oxygen supply to placenta, leaving the fetus vulnerable to myelination impairment and neuronal complications (Estrada, et al. 2014, Georgieff 2011), and it also influences post-natal growth (Menon, et al. 2016). Low iron intake during pregnancy increases the risk of chronic disease in offspring's adult life (Gillman 1995).

The etiology of anemia is multifactorial and could be associated with iron deficiency, infectious or chronic diseases, genetic defects, or folate, cobalamin, and vitamin A deficiencies (Dreyfuss, et al. 2000, Righetti, et al. 2012, Sanchaisuriya, et al. 2006, Weinstein, et al. 2002). Vitamin A deficiency impairs iron mobilization, with consequent iron accumulation in tissues (Mendes, et al. 2016, da Cunha, et al. 2014); however, the exact mechanism of interaction between vitamin A and iron metabolism is not yet understood.

Although the literature reports that, the prevalence of vitamin A deficiency has decreased over the years, hypovitaminosis A is still related to deaths from diarrhea and measles, and to the development of xerophthalmia in children and pregnant women (Wirth, et al. 2017; Rahman, et al. 2017; Akhtar, et al., 2013). In order to minimize the mortality and outcomes related to vitamin A deficiency, the World Health Organization has proposed a prophylactic supplementation of vitamin A

for specific populations, including children between 6 to 59 months-old and pregnant women, who are habitants of countries where vitamin A deficiency is a public health problem (WHO 2013a, WHO 2013b).

To our knowledge, the effect of vitamin A supplementation alone on iron status and anemia has not been systematically-reviewed. Michelazzo, et al. (2013) investigated the influence of vitamin A supplementation on iron status through a review, but they included studies with more than one micronutrient supplement, limited their search to only one database (PubMed), and set a time-restriction from 1992 to 2013.

Thus, considering the interaction between the metabolisms of iron and vitamin A and that vitamin A deficiency may cause anemia, the aim of the present study was to assess and estimate the effect of vitamin A supplementation alone on iron status biomarkers, anemia, and iron deficiency through a systematic review and meta-analysis of studies developed with humans.

METHODS

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, et al. 2009) was used to plan and perform this systematic review. The protocol for this systematic review was registered with PROSPERO registration number CRD42016039133.

Search strategy and eligibility criteria

A literature search was conducted in six databases: Cochrane Library, EMBASE, LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde), Pubmed, Scopus, and Web of Science (via ISI Web of Knowledge), from the earliest record to April 2016, without language restrictions. Scholar Google (including the 60 first studies that appeared in relevance order) and ProQuest Dissertations and

Theses were also explored for additional gray literature search. Finally, the reference lists of the selected publications were examined.

The search strategy included the following combination of expressions: “human”, “iron deficiency”, “anemia”, “anaemia”, “iron status”, “hemoglobin”, “haemoglobin”, “vitamin A deficiency”, “hypovitaminosis”, “vitamin A status”, “vitamin A”, “retinoid”, “carotenoids”, “beta carotene”, “supplement*”. A detailed search protocol is provided in supplementary materials (Appendix 1).

Studies considered eligible for this review involved clinical trials or cohort studies with humans, without age restriction, in which, any type of vitamin A supplementation was used and iron status biomarkers were investigated. The outcomes that fit the inclusion criteria were anemia and iron deficiency prevalence, and iron status biomarkers, such as hemoglobin and / or serum ferritin levels or their variations against baseline. Exclusion criteria are listed in Appendix 2.

A two-step screening process was used. In phase 1, two of the reviewers (MSBC and NAC) independently read the titles and abstracts of all material identified electronically in the database search. Any study that did not fulfill the inclusion criteria was discarded. In phase 2, full-texts of the studies selected in phase 1 were read independently by both reviewers (MSBC and NAC) and the same inclusion criteria were applied to confirm their eligibility. Any disagreement was resolved by consensus or by the coordinator (SFA).

Data extraction and risk of bias of individual studies

Data from included studies were extracted independently by two reviewers (MSBC and NAC), using a previously standardized table and checked by the coordinator (SFA). The collected data included reference, year of publication, country, type of the study, sample size and baseline characteristics, type and dose of

vitamin A supplementation, duration of the supplementation, period of follow-up, and main results. For the studies with more than two intervention groups, only vitamin A supplementation and placebo groups were considered.

The risk of bias of the eligible studies was based on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, et al. 2008), for clinical trials, and on the Joanna Briggs Institute Meta-Analysis Statistics Assessment and Review Instrument (MAStARI) Critical Appraisal Tools Comparable Cohort / Case Control Studies (The Joanna Briggs Institute, 2014), for cohort studies.

Data synthesis and statistical analysis

Meta-analysis eligibility

Studies were eligible for meta-analysis if data about cases of anemia and/or iron deficiency (dichotomous outcome) and hemoglobin and/or ferritin levels (continuous outcomes) after intervention were reported for both studies group, vitamin A supplemented (experimental) and placebo (control). For continuous outcomes, mean and standard deviation (SD) were estimated according to Hozo, et al. (2005) and Higgins, et al. (2008).

For studies that did not report the necessary data for meta-analysis, the authors were contacted and the missing data requested in an attempt to include as much literature as possible, but replies were not positive. In those cases, the studies were excluded from meta-analysis.

Meta-analysis

The software Stata version 12.0 software (StataCorp LP, College Station, Texas, USA) was used to analyze data and generating forest plots. The risk ratio (RR) with corresponding 95% confidence interval (CI) was calculated for dichotomous outcomes, and the weighted mean difference (WMD) for continuous

data. Heterogeneity was investigated using the I^2-test statistic with its degree of freedom p-value and the statistic I^2 that estimated the extent of variability across trials. Data were pooled using the fixed-effect model in the case of no heterogeneity ($p > 0.1$ and $I^2 < 50\%$). In the case of significant heterogeneity, results were confirmed using the random-effect model.

RESULTS

Literature search and study selection

The initial search in six electronic databases yielded 1,129 studies. After the exclusion of the duplicated studies, 775 records remained. From these, 41 studies were eligible for full-text reading and 22 were included in this systematic review. Another search conducted one year after the initial search, turning up two new records, but only one fit the inclusion criteria. Therefore, a total of 23 studies were included: 21 clinical trials and two cohort studies. A flow-diagram of the literature search is presented in figure 1, and the exclusion criteria are listed in appendix 2.

Studies characteristics

All the included studies were conducted with children and teenagers (Ahmed, et al. 2001, Al-Mekhlafi, et al. 2014, Awasthi, et al. 2013, Bloem, et al. 1989, Bloem, et al. 1990, Cao, et al. 2013, Chen, et al. 2014, Gebremedhin 2014, Jimenez, et al. 2010, Khan, et al. 1996, Mahawithanage, et al. 2007, Mejía, et al. 1988, Mwanri, et al. 2000, Pangaribuan, et al. 2003, Semba, et al. 1992, Soekarjo, et al. 2004, Talsma, et al. 2016, Zimmermann, et al. 2006, Chen, et al. 2016) or lactating and pregnant women (Haskell, et al. 2005, Suharno, et al. 1993, Tanumihardjo, et al. 1996, Tanumihardjo 2002). The main characteristics are summarized in table 1 and

table 2. Most of the studies were carried out in Asia (*n* = 17), followed by Africa (*n* = 4) and America (*n* = 2), and were published between 1988 and 2016.

Most of the eligible studies evaluated either vitamin A deficiency (VAD) and/or anemia prevalence at the beginning of the studies, except for three studies (Awasthi, et al. 2013, Gebremedhin 2014, Mahawithanage, et al. 2007). The prevalence ranges of anemia and VAD at the baseline were 6.9 to 100% and 1.5% to 100%, respectively (tables 1 and 2).

The vitamin A supplementation doses administered to children and teenagers ranged from 500 to 200,000 IU of vitamin A; while in the studies conducted in pregnant and lactating women, the dose was 8,000 IU of vitamin A. The frequency of administration was mostly single oral doses, followed by daily and weekly oral doses, for both subgroups. The outcomes were assessed at two weeks to six months after the supplementation with single oral doses, and right after the supplementation period to three months after the supplementation, for studies with other frequencies of supplementation (tables 1 and 2).

Risk of bias of individual studies

The risk of bias assessment of the clinical trials and cohort studies is summarized in figure 2 and table 3, respectively. Twenty-one clinical trials (Ahmed, et al. 2001, Al-Mekhlafi, et al. 2014, Awasthi, et al. 2013, Bloem, et al. 1989, Bloem, et al. 1990, Cao, et al. 2013, Chen, et al. 2014, Jimenez, et al. 2010, Khan and Baseer 1996, Mahawithanage, et al. 2007, Mejía and Chew 1988, Mwanri, et al. 2000, Semba, et al. 1992, Soekarjo, et al. 2004, Talsma, et al. 2016, Zimmermann, et al. 2006, Chen, et al. 2016, Haskell, et al. 2005, Suharno, et al. 1993, Tanumihardjo, et al. 1996, Tanumihardjo 2002) were evaluated by the Cochrane

Handbook for Systematic Reviews of Interventions domains (Higgins, et al. 2008). In the random sequence generation domain, six studies (28.6%) reported random sample selection. Fourteen (66.6%) did not describe the method used, therefore, are categorized with “unclear risk of bias”. The study developed by Haskell, et al. (2005) was classified as “high risk of bias”, as sample randomization was not properly performed. For the allocation concealment domain, thirteen studies (61.9%) described adequate methods of group randomization, six (28.6%) did not mention the employed procedure, and two (9.5%) were not randomized.

For the performance bias, twelve studies (57.2%) were blinded for participants, four (19.0%) did not mention masking, and five (23.8%) were unblinded. Eight studies (38.1%) showed low risk of detection bias, whereas nine (42.9%) presented unclear risk of detection bias, and four (19.0%) were unblinded for this domain.

All of the included studies presented low risk of attrition bias because the reasons for missing data were explained and the losses were balanced among the groups. Finally, all the studies included in this review were free of selective reporting, because this bias was one of the exclusion criteria (see figure 1 eligibility criteria). Supplementary figure 1 presents a detailed evaluation for each risk-of-bias domain within the studies.

For the two cohort studies (Gebremedhin 2014, Pangaribuan, et al. 2003), the concise risk of bias evaluation is presented in table 3. According to the MAStARI tool (The Joanna Briggs Institute, 2014), both of them were categorized as “low risk of bias”, as both reached 100% of “yes”. The detailed analysis of these studies is presented in Appendix 3.

Effect of vitamin A supplementation on outcomes

Vitamin A deficiency and vitamin A status

All the studies that evaluated VAD prevalence (Awasthi, et al. 2013, Cao, et al. 2013, Chen, et al. 2014, Jimenez, et al. 2010, Zimmermann, et al. 2006, Chen, et al. 2016) showed a decrease in this parameter compared to baseline (BL) and/or placebo (PL), after vitamin A supplementation. Among the 20 studies that evaluated SR levels after vitamin A supplementation, only two studies did not observe any difference in this biomarker (Soekarjo, et al. 2004, Tanumihardjo 2002).

All the studies that evaluated the difference between the final and initial SR levels (∆SR) showed an increase in this biomarker (Ahmed, et al. 2001, Cao, et al. 2013, Khan and Baseer 1996, Mahawithanage, et al. 2007, Mejía and Chew 1988, Semba, et al. 1992, Soekarjo, et al. 2004, Suharno, et al. 1993). However, in the Soekarjo, et al. (2004) study, a significant increase in ∆SR was obtained only in the boy's subgroup, but not in the entire children sample after VA supplementation.

Anemia

Among the eleven studies that estimated the anemia prevalence (Ahmed, et al. 2001, Al-Mekhlafi, et al. 2014, Cao, et al. 2013, Chen, et al. 2014, Gebremedhin 2014, Jimenez, et al. 2010, Mejía and Chew 1988, Mwanri, et al. 2000, Zimmermann, et al. 2006, Chen, et al. 2016, Suharno, et al. 1993), most of them showed a reduction in the number of cases of anemia in the vitamin A supplemented group compared to BL and/or PL, except for one study that did not observe any difference (Al-Mekhlafi, et al. 2014) (tables 1 and 2).

In order to estimate the effect of vitamin A supplementation on the risk of being anemic, a meta-analysis was conducted considering the ten clinical trials that

presented the data about cases of anemia. The studies performed by Zimmermann, et al. (2006) and by Chen, et al. (2016) were twice included, because they provided the data from two periods of time. The results of the forest plot (Figure 3) showed that vitamin A supplementation was significantly associated with a reduced risk of anemia (RR: 0.74; 95% CI 0.66 to 0.82, $p < 0.001$), with a fixed-effect model and a low evidence of heterogeneity across the studies (I^2 = 23.3%). The stratified analysis by life stage also suggested the same effect for both subgroups, a RR of anemia significantly lower in vitamin A supplemented groups (children and teenagers: RR 0.72; 95% CI 0.64 to 0.82, $p < 0.001$; I^2 = 28.7%; lactating or pregnant women: RR 0.78; 95% CI 0.63 to 0.96) (Figure 3).

Hemoglobin levels (Hb)

Fifteen out of the 21 studies that evaluated hemoglobin (Hb) levels showed that vitamin A supplementation increased Hb levels compared to BL, PL, or both (Ahmed, et al. 2001, Bloem, et al. 1989, Bloem, et al. 1990, Cao, et al. 2013, Chen, et al. 2014, Gebremedhin 2014, Jimenez, et al. 2010, Mahawithanage, et al. 2007, Mejía and Chew 1988, Mwanri, et al. 2000, Pangaribuan, et al. 2003, Semba, et al. 1992, Zimmermann, et al. 2006, Chen, et al. 2016, Tanumihardjo 2002), while six studies did not observe any difference in this parameter (Awasthi, et al. 2013, Khan and Baseer 1996, Soekarjo, et al. 2004, Talsma, et al. 2016, Haskell, et al. 2005, Tanumihardjo, et al. 1996) (table 1 and table 2). Considering the difference between the final and initial Hb levels (∆Hb), among the nine studies that evaluated this data, six reported a positive change in this value after vitamin A supplementation (Al-Mekhlafi, et al. 2014, Cao, et al. 2013, Semba, et al. 1992, Suharno, et al. 1993).

According to the random-effects model analysis (Supplementary Figure 2), the combined data of 13 clinical trials indicated a significant increase of Hb levels in vitamin A supplemented group (WMD 3.51 g/L; 95% CI 1.80 to 5.21 g/L; $p < 0.001$; *I2* = 99.3%). These results were also observed in the analysis by life stage: Hb levels increased in children and teenagers (WMD 3.42 g/L, 95% CI 1.62 to 5.22 g/L; $p < 0.001$) and in pregnant and lactating women (WMD 4.04 g/L, 95% CI 2.30 to 5.77 g/L; $p < 0.001$) with vitamin A supplementation. For this analysis, the children and teenagers' subgroup showed a significant heterogeneity (I^2 = 99.4%; Supplementary Figure 2).

In attempt to minimize the data heterogeneity, a sensitivity analysis was performed excluding one study that used β-carotene supplement as a vitamin A source (Talsma, et al. 2016), six studies that presented "unclear" or "high risk" of selection bias (Ahmed, et al. 2001, Chen, et al. 2014, Mejía and Chew 1988, Zimmermann, et al. 2006, Chen, et al. 2016, Suharno, et al. 1993), and one outlier study (Mahawithanage, et al. 2007). In this analysis, a similar result was observed: increased Hb levels by vitamin A supplementation (WMD 4.94 g/L; 95% CI 3.78 to 6.10 g/L; $p < 0.001$; I^2 = 37.9% - Figure 4).

Iron deficiency (ID)

Iron deficiency (ID) was evaluated in only four studies conducted in children or teenagers (Ahmed, et al. 2001, Al-Mekhlafi, et al. 2014, Chen, et al. 2014, Chen, et al. 2016). In three studies (Al-Mekhlafi, et al. 2014, Chen, et al. 2016) a significant decrease in the number of ID cases was observed compared to BL and/or PL, while the other two (Ahmed, et al. 2001, Chen, et al. 2014) showed a significant increase in ID prevalence in groups treated with vitamin A, compared to BL (table 1). No

significant effect of vitamin A supplementation on ID prevalence was observed using data of four clinical trials (Ahmed, et al. 2001, Al-Mekhlafi, et al. 2014, Chen, et al. 2014, Chen, et al. 2016) (RR 0.82, 95% CI 0.60 to 1.12, p = 0.204; I^2 = 65.3% - Figure 5).

Serum ferritin levels (SF)

Eight of the thirteen studies that evaluated SF levels did not observe any difference (Ahmed, et al. 2001, Bloem, et al. 1989, Bloem, et al. 1990, Jimenez, et al. 2010, Khan and Baseer 1996, Mejía and Chew 1988, Zimmermann, et al. 2006, Haskell, et al. 2005); five studies showed an increase (Bloem, et al. 1989, Pangaribuan, et al. 2003, Semba, et al. 1992, Chen, et al. 2016, Tanumihardjo 2002) and two found a decrease (Chen, et al. 2014, Zimmermann, et al. 2006) in SF levels in vitamin A supplemented groups compared to BL group and/or PL. In relation to the difference between final and initial SF levels (ΔSF), three studies did not observe any difference (Ahmed, et al. 2001, Khan and Baseer 1996, Suharno, et al. 1993), one study observed an increase (Semba, et al. 1992), and one study observed a decrease (Al-Mekhlafi, et al. 2014) by vitamin A supplementation (tables 1 and 2).

The combined data of seven clinical trials demonstrated no significant effect of vitamin A supplementation in serum ferritin levels (WMD 1.99 μg/L; 95% CI -2.40 μg/L to 6.38 μg/L; p = 0.375, I^2 = 96.4% - Supplementary Figure 3). A stratified data analysis by life stage (children and teenagers or pregnant and lactating women) suggested that in children and teenagers, VA supplementation had no effect in SF levels (WMD 1.32 μg/L; 95% CI -3.56 to 6.22 μg/L; p = 0.598; I^2 = 95.6% - Supplementary Figure 3); while in pregnant and lactating women vitamin A

supplementation increased SF levels (WMD 6.61 μg/L; 95% CI 6.00 to 7.21 μg/L; P < 0.001; I^2 = 0%) (Supplementary Figure 3).

A sensitivity analysis conducted with the exclusion of two outlier studies (Chen, et al. 2014, Khan and Baseer 1996) (Figure 6) showed a significant increase in SF levels with vitamin A supplementation (WMD 5.39 μg/L; 95% CI 2.78 μg/L to 8.00 μg/L; p < 0.001, I^2 = 73.3%). A similar result was also found in the analysis of subgroups: in children (WMD 5.26 μg/L, 95% CI 1.21 to 9.30 μg/L; p = 0.011, I^2 = 78.6%) and lactating women (WMD 6.62 μg/L, 95% CI 6.00 to 7.21 μg/L; p < 0.001, I^2 = 0.0%; Figure 6).

DISCUSSION

In this systematic review and meta-analysis, we investigated the effect of vitamin A supplementation on anemia, iron deficiency, hemoglobin, and serum ferritin levels, in clinical trials and cohort studies. In the present study, the meta-analysis of the clinical trials suggested that vitamin A supplementation alone might reduce the risk of anemia by 26% in children, teenagers, pregnant and lactating women (Figure 3). This beneficial effect of vitamin A supplementation was also evidenced by the higher weighted mean difference (WMD) of hemoglobin levels (Hb) obtained in the pooled sensitivity analysis for vitamin A supplemented groups compared to placebo (Figure 4). Therefore, this data supports the hypothesis that vitamin A supplementation by itself increases Hb levels and reduces the prevalence of anemia. Corroborating our results, Semba, et al. (2002), who analyzed data from observational studies conducted in 12 countries from the Africa, Americas, and Asia, observed that the improvement of vitamin A status promoted a reduction in the number of anemic individuals.

The relationship between vitamin A deficiency and anemia has been widely studied since the beginning of the twentieth-century (Abizari, et al. 2017, Koessler, et al. 1926). Mejia, et al. (1979) observed that vitamin A-deficient rats presented low hemoglobin and serum iron levels, but high iron concentration in liver and spleen. More recently, an *in vivo* study (da Cunha, et al. 2014) showed that vitamin A deficiency promotes an ineffective erythropoiesis by the downregulation of renal erythropoietin expression, which results in erythrocytes malformation and consequently higher erythrophagocytosis of these undifferentiated cells. A pro-inflammatory profile, which promotes tissue iron retention, was also associated with an ineffective erythropoiesis in a condition of vitamin A deficiency (Wieringa, et al. 2004). Therefore, vitamin A supplementation seems to improve hemoglobin levels and decrease anemia prevalence by promoting an anti-inflammatory response, the upregulation of erythropoietin expression and the iron mobilization for erythropoiesis (Citelli, et al. 2012, Schroeder, et al. 2007; Cusick, et al. 2005; Hoag, et al. 2002).

The impact of vitamin A supplementation on reducing the risk of anemia and improving hemoglobin levels might have been even greater, if the iron-deficient individuals had been excluded from the studied sample, because these individuals do not have stored iron to promote hemoglobin synthesis (Camaschella 2015). In the studies performed by Awasthi, et al. (2013) and Khan and Baseer (1996), which did not observe changes in Hb levels by vitamin A supplementation compared to placebo and/or baseline, the Hb levels of the participants were around 95 g/L at the beginning of the study, classified as moderate anemia, according to the World Health Organization criteria (WHO, 2011). Moreover, when moderate or severe anemia is established, the low Hb concentration seems to be associated to multiple

micronutrients deficiencies; therefore, vitamin A supplementation alone is not sufficient to improve Hb levels.

In this systematic review, we also performed a meta-analysis with the results of four studies that evaluated the impact of vitamin supplementation on the prevalence of iron deficiency (ID). However, no improvement was observed in ID prevalence with vitamin A supplementation (Figure 5), despite the significant increase in serum ferritin levels (SF) (Figure 6). The apparent contradictory effect of vitamin A supplementation on iron status (no change in ID prevalence despite the increase of Hb and SF levels) may be explained by the fact that vitamin A changes SF levels by promoting an anti-inflammatory response. In this context, SF level does not seem to be the best biomarker, as it responds both to inflammation and iron status, therefore, other iron-specific markers should be considered in the evaluation (Malope, et al., 2001).

Some limitations of this systematic review and meta-analysis should be considered. First, the meta-analysis included few studies, as many of the authors did not respond to our data requesting and many studies presented unclear or high risk of bias. Second, many studies did not evaluate iron status at the beginning of the intervention, which may have caused underestimation of the impact of vitamin A supplementation in iron status.

In summary, this systematic review and meta-analysis suggests that supplementation with vitamin A alone may reduce the risk of anemia, by improving hemoglobin and ferritin levels in individuals with low serum retinol levels. Finally, the present study brings more scientific evidence and stimulate the development of further studies in order to precisely estimate the prevalence of anemia caused by vitamin A deficiency, and also emphasizes the importance of evaluate vitamin A

status prior the implementation of iron supplementation public health policies to combat anemia, in regions where vitamin A deficiency and anemia coexist.

Supplementary Material

Supplemental data for this article can be accessed on the publisher's website.

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Appendix 1. **Database and search strategy**

Database	Search Strategy
Cochrane Library	(Human):ti,ab,kw AND ("iron deficiency" OR anemia OR anaemia OR "iron status" AND hemoglobin OR haemoglobin):ti,ab,kw AND ("vitamin A" AND "deficiency" OR "hypovitaminosis A" OR "vitamin A status"):ti,ab,kw AND ("vitamin A" OR "retinoid" OR "carotenoids" OR "beta carotene" AND supplement*):ti,ab,kw
EMBASE	(Human) AND ("iron deficiency" OR anemia OR anaemia OR "iron status" AND hemoglobin OR haemoglobin) AND ("vitamin A" AND "deficiency" OR "hypovitaminosis A" OR "vitamin A status") AND ("vitamin A" OR "retinoid" OR "carotenoids" OR "beta carotene" AND supplement*)
LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde)	(Human OR humano) AND (anemia OR anemia OR anaemia OR “deficiência de ferro" OR “deficiencia de hierro” OR “iron deficiency” OR “status de ferro" OR “iron status” OR “nivel de hierro") AND ("deficiência de vitamina A” OR “vitamin A deficiency” or “deficiencia de vitamina A” OR “hipovitaminose A” OR “hypovitaminosis A” OR “hipovitaminosis A” OR “status de vitamina A” OR “vitamin A status” or "nivel de vitamina A”) AND (“vitamina A” OR “vitamin A” OR “retinoides” OR “retinoids” OR “carotenoides” or “carotenoids” OR “beta caroteno” or “beta carotene”) AND (suplementação OR supplementation OR suplementación)
PubMed	(Human) AND ("iron deficiency" OR anemia OR anaemia OR "iron status" AND hemoglobin OR haemoglobin) AND ("vitamin A" AND "deficiency" OR "hypovitaminosis A" OR "vitamin A status") AND ("vitamin A" OR "retinoid" OR "carotenoids" OR "beta carotene" AND supplement*) OR ("Anemia, Iron-Deficiency/prevention & control" OR "Anemia, Iron-Deficiency/blood" OR "Anemia, Iron-Deficiency/drug therapy" [MeSH Terms]) AND ("Vitamin A/administration & dosage" OR "Vitamin A/blood" OR "beta Carotene/pharmacology" OR "Vitamin A Deficiency/blood" OR "Vitamin A Deficiency/drug therapy" OR "Vitamin A Deficiency/therapy" [MeSH Terms])
Scopus	TITLE-ABS-KEY (human) AND TITLE-ABS-KEY ("iron deficiency" OR anemia OR anaemia OR "iron status" AND hemoglobin OR haemoglobin) AND TITLE-ABS-KEY ("vitamin A" AND "deficiency" OR "hypovitaminosis A" OR "vitamin A status") AND TITLE-ABS-KEY ("vitamin A" OR "retinoid" OR "carotenoids" OR "beta carotene" AND supplement*)
Web of Science via ISI Web of Knowledge	TS=(Human) AND TS=("iron deficiency" OR anemia OR anaemia OR "iron status" AND hemoglobin OR haemoglobin) AND TS=("vitamin A" AND "deficiency" OR "hypovitaminosis A" OR "vitamin A status") AND TS=("vitamin A" OR "retinoid" OR "carotenoids" OR "beta carotene" AND supplement*)
ProQuest Dissertations and Theses	Human) AND ("iron deficiency" OR anemia OR anaemia OR "iron status" AND hemoglobin OR haemoglobin) AND ("vitamin A" AND "deficiency" OR "hypovitaminosis A" OR "vitamin A status") AND ("vitamin A" OR "retinoid" OR "carotenoids" OR "beta carotene" AND supplement*)
Google Scholar	(Human) AND ("iron deficiency" OR anemia OR anaemia OR "iron status" AND hemoglobin OR haemoglobin) AND ("vitamin A" AND "deficiency" OR "hypovitaminosis A" OR "vitamin A status") AND ("vitamin A" OR "retinoid" OR

	"carotenoids" OR "beta carotene" AND supplement*)

Appendix 2 - Excluded studies and reasons

Reference	Reason for exclusion
Alvarez, et al. (1995)	1
Arguello, et al. (2012)	1
Arguello, et al. (2015)	8
Broek, et al. (2006)	3
Chen, et al. (2008)	4
Chen, et al. (2011)	1
Chen, et al. (2014)	1
Davidsson, et al. (2003)	3
Leenstra, et al. (2009)	7
Miller, et al. (2006)	7
Mariath, et al. (1988)	1
Mohanram, et al. (1977)	1
Paiva, et al. (2012)	8
Panth, et al. (1990)	3
Robles Sardin, et al. (1998)	3
Semba, et al. (2001)	3
Villamor, et al. (2002)	7
Villamor, et al. (2000)	7
Zhang, et al. (2010)	4
Wang, et al. (2016)	7

Legend - Exclusion criteria: [1] reviews, cross-sectional studies, letters, personal opinions, book chapters, conference abstracts, patents, full-text not available, or duplicated references (*n = 6*); [2] cell- or animal-based studies (*n = 0*); [3] studies with more than one type of nutrient supplement *(n = 4)*; [4] food fortification-based studies (n = 2); [5] studies in which the dose of vitamin A supplement dose was not informed (*n = 0*); [6] studies in which the effect of vitamin A supplementation during pregnancy was observed only in the offspring (*n = 0*); [7] studies in which subjects presented any type of disease that could alter any iron status biomarkers *(n = 5)*; and [8] studies that did not report the outcome *(n = 3)*.

References

Alvarez, M.C., Rocha, A.P. and Zambrana, L.M. (1995). Efecto de la suplementación combinada con hierro y vitamina A sobre el status del hierro en mujeres lactantes. Quito.

Arguello, M.A., Schulze, K.J., Wu, L.S.F., Dreyfuss, M.L., Christian, P. and West, K.P. (2012). Circulating insulin-like growth Factor-1 (IGF-1) is associated with vitamin A (VA) status and increased circulating hemoglobin (Hb) during pregnancy in Nepalese Women. *FASEB journal* 26.

Arguello, M.A., Schulze, K.J., Wu, L.S., Dreyfuss, M.L., Khatry, S.K., Christian, P. and West, K.P. (2015). Circulating IGF-1 may mediate improvements in haemoglobin associated with vitamin A status during pregnancy in rural Nepalese women. *Asia Pac J Clin Nutr* 24, 128-137.

Broek, N.R., White, S.A., Flowers, C., Cook, J.D., Letsky, E.A., Tanumihardjo, S.A., Mhango, C., Molyneux, M. and Neilson, J.P. (2006). Randomised trial of vitamin A supplementation in pregnant women in rural Malawi found to be anaemic on screening by HemoCue *Bjog*, 569-576).

Chen, K., Li, T.Y., Chen, L., Qu, P. and Liu, Y.X. (2008). Effects of vitamin A, vitamin A plus iron and multiple micronutrient-fortified seasoning powder on preschool children in a suburb of Chongqing, China. *J Nutr Sci Vitaminol (Tokyo)* 54, 440-447.

Chen, K., Liu, Y.F., Chen, L., Zhang, X., Liu, Y.X., Chen, J. and Li, T.Y. (2011). [Effects of vitamin A, vitamin A plus iron and multiple micronutrient-fortified seasoning powder on iron metabolic homeostasis]. *Zhonghua er ke za zhi. Chinese journal of pediatrics* 49, 926-932.

Chen, K., Zhang, L., Luo, H., Wang, J., Li, Q. and Mao, M. (2014). Effect of vitamin A supplements on iron metabolic homeostasis for preschoolers. *Zhonghua Yu Fang Yi Xue Za Zhi* 48, 18-22.
Davidsson, L., Adou, P., Zeder, C., Walczyk, T. and Hurrell, R. (2003). The effect of retinyl palmitate added to iron-fortified maize porridge on erythrocyte incorporation of iron in African children with vitamin A deficiency. *British Journal of Nutrition* 90, 337-343.
Leenstra, T., Kariuki, S.K., Kurtis, J.D., Oloo, A.J., Kager, P.A. and ter Kuile, F.O. (2009). The effect of weekly iron and vitamin A supplementation on hemoglobin levels and iron status in adolescent schoolgirls in western Kenya. *Eur J Clin Nutr* 63, 173-182.
Miller, M.F., Stoltzfus, R.J., Iliff, P.J., Malaba, L.C., Mbuya, N.V., Humphrey, J.H., Chidawanyika, H., Mahomva, A., Majo, F., Marinda, E., Mbizvo, M., Moulton, L., Mutasa, K., Ndhlovu, M., Ntozini, R., Piwoz, E., Propper, L., Rambanepasi, P., Ruff, A., Tavengwa, N., Ward, B., Zijenah, L., Zunguza, C., Zvandasara, P. and Nathoo, K. (2006). Effect of maternal and neonatal vitamin A supplementation and other postnatal factors on anemia in Zimbabwean infants: A prospective, randomized study. *American Journal of Clinical Nutrition* 84, 212-222.
Mariath, J.G.R., Dricot, J.M. and D'Ans, C.H.D. (1988). Estratégia alternativa de doses periódicas de vitamina A no Estado da Paraíba. *CCS* 10, 231-236.
Mohanram, M., Kulkarni, K.A. and Reddy, V. (1977). Hematological studies in vitamin A deficient children. *Int J Vitam Nutr Res* 47, 389-393.
Paiva, A.A., Rondo, P.H., Reinaldo, L.G., Pedraza, D.F. and Ruz, M. (2012). The effect of vitamin A supplementation on retinol concentrations of children with anaemia. *Nutr Hosp* 27, 2151-2152.
Panth, M., Shatrugna, V., Yasodhara, P. and Sivakumar, B. (1990). Effect of vitamin A supplementation on haemoglobin and vitamin A levels during pregnancy. *British Journal of Nutrition* 64, 351-358.
Robles Sardin, A.E., Astiazarán García, H., Dávalos Navarro, R., Quihui Cota, L., Cabrera Pacheco, R.M. and Valencia, M.E. (1998). Efecto de la suplementación con una dosis masiva de vitamina A en niños de 6 a 36 meses de edad. *Salud Publica Mex* 40, 309-315.
Semba, R.D., Kumwenda, N., Taha, T.E., Mtimavalye, L., Broadhead, R., Garrett, E., Miotti, P.G. and Chiphangwi, J.D. (2001). Impact of vitamin A supplementation on anaemia and plasma erythropoietin concentrations in pregnant women: a controlled clinical trial. *European Journal of Haematology* 66, 389-395.
Villamor, E., Mbise, R., Spiegelman, D., Hertzmark, E., Fataki, M., Peterson, K.E., Ndossi, G. and Fawzi, W.W. (2002). Vitamin A supplements ameliorate the adverse effect of HIV-1, malaria, and diarrheal infections on child growth. *Pediatrics* 109.
Villamor, E., Mbise, R., Spiegelman, D., Ndossi, G. and Fawzi, W.W. (2000). Vitamin A supplementation and other predictors of anemia among children from Dar es Salaam, Tanzania. *American Journal of Tropical Medicine and Hygiene* 62, 590-597.
Zhang, X., Chen, K., Qu, P., Liu, Y.X. and Li, T.Y. (2010). Effect of biscuits fortified with different doses of vitamin A on indices of vitamin A status, haemoglobin and physical growth levels of pre-school children in Chongqing. *Public Health Nutrition* 13, 1462-1471.
Wang, Y., Gao, Y., Liu, Q., Zhan, X., Li, Z., Hu, H., Li, T. and Chen, J. (2016). Effect of vitamin A and Zn supplementation on indices of vitamin A status, haemoglobin level and defecation of children with persistent diarrhea. *J Clin Biochem Nutr* 59, 58-64.

References

WHO (2015). The Global Prevalence of Anaemia in 2011. Geneva.

Lozoff, B., Wolf, A.W. and Jimenez, E. (1996). Iron-deficiency anemia and infant development: effects of extended oral iron therapy. *J Pediatr* 129, 382-389.

Estrada, J.A., Contreras, I., Pliego-Rivero, F.B. and Otero, G.A. (2014). Molecular mechanisms of cognitive impairment in iron deficiency: alterations in brain-derived neurotrophic factor and insulin-like growth factor expression and function in the central nervous system. *Nutr Neurosci* 17, 193-206.

Georgieff, M.K. (2011). Long-term brain and behavioral consequences of early iron deficiency. *Nutr Rev* 69 Suppl 1, S43-48.

Menon, K.C., Ferguson, E.L., Thomson, C.D., Gray, A.R., Zodpey, S., Saraf, A., Das, P.K. and Skeaff, S.A. (2016). Effects of anemia at different stages of gestation on infant outcomes. *Nutrition* 32, 61-65.

Gillman, M.W. (1995). Mothers, Babies, and Disease in Later Life. *BMJ* 310, 68.

Dreyfuss, M.L., Stoltzfus, R.J., Shrestha, J.B., Pradhan, E.K., LeClerq, S.C., Khatry, S.K., Shrestha, S.R., Katz, J., Albonico, M. and West, K.P., Jr. (2000). Hookworms, malaria and vitamin A deficiency contribute to anemia and iron deficiency among pregnant women in the plains of Nepal. *J Nutr* 130, 2527-2536.

Righetti, A.A., Koua, A.Y., Adiossan, L.G., Glinz, D., Hurrell, R.F., N'Goran E, K., Niamke, S., Wegmuller, R. and Utzinger, J. (2012). Etiology of anemia among infants, school-aged children, and young non-pregnant women in different settings of South-Central Cote d'Ivoire. *Am J Trop Med Hyg* 87, 425-434.

Sanchaisuriya, K., Fucharoen, S., Ratanasiri, T., Sanchaisuriya, P., Fucharoen, G., Dietz, E. and Schelp, F.P. (2006). Thalassemia and hemoglobinopathies rather than iron deficiency are major causes of pregnancy-related anemia in northeast Thailand. *Blood Cells Mol Dis* 37, 8-11.

Weinstein, D.A., Roy, C.N., Fleming, M.D., Loda, M.F., Wolfsdorf, J.I. and Andrews, N.C. (2002). Inappropriate expression of hepcidin is associated with iron refractory anemia: implications for the anemia of chronic disease. *Blood* 100, 3776-3781.

Mendes, J.F., Siqueira, E.M., de Brito, E.S.J.G. and Arruda, S.F. (2016). Vitamin A deficiency modulates iron metabolism independent of hemojuvelin (Hfe2) and bone morphogenetic protein 6 (Bmp6) transcript levels. *Genes Nutr* 11, 1.

da Cunha, M.S., Siqueira, E.M., Trindade, L.S. and Arruda, S.F. (2014). Vitamin A deficiency modulates iron metabolism via ineffective erythropoiesis. *J Nutr Biochem* 25, 1035-1044.

Wirth, J.P., Petry, N., Tanumihardjo, S.A., Rogers, L.M., McLean, E., Greig, A., Garrett, G.S., Klemm, R.D. and Rohner, F. (2017). Vitamin A Supplementation Programs and Country-Level Evidence of Vitamin A Deficiency. *Nutrients* 9.

Rahman, S., Rahman, A.S., Alam, N., Ahmed, A.S., Ireen, S., Chowdhury, I.A., Chowdhury, F.P., Rahman, S.M. and Ahmed, T. (2017). Vitamin A deficiency and determinants of vitamin A status in Bangladeshi children and women: findings of a national survey. *Public Health Nutr* 20, 1114-1125.Akhtar, S., Ahmed, A., Randhawa, M.A., Atukorala, S., Arlappa, N., Ismail, T. and Ali, Z. (2013). Prevalence of vitamin A deficiency in South Asia: causes, outcomes, and possible remedies. *J Health Popul Nutr* 31, 413-423.

WHO (2013a). Guideline: Vitamin A supplementation in pregnant women. Geneva.

WHO (2013b). Guideline: Vitamin A supplementation in infants and children 6–59 months of age. Geneva.

Michelazzo, F.B., Oliveira, J.M., Stefanello, J., Luzia, L.A. and Rondo, P.H. (2013). The influence of vitamin A supplementation on iron status. *Nutrients* 5, 4399-4413.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. and Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6, e1000097.

Higgins, J., Green, S. and Cochrane Collaboration. (2008). *Cochrane handbook for systematic reviews of interventions*. Chichester, England ; Hoboken, NJ: Wiley-Blackwell.

Institute, T.J.B. (2014). *Joanna Briggs Institute Reviewers' Manual: 2014 edition*. Australia: The Joanna Briggs Institute.

Hozo, S.P., Djulbegovic, B. and Hozo, I. (2005). Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 5, 13.

Ahmed, F., Khan, M.R. and Jackson, A.A. (2001). Concomitant supplemental vitamin A enhances the response to weekly supplemental iron and folic acid in anemic teenagers in urban Bangladesh. *Am J Clin Nutr* 74, 108-115.

Al-Mekhlafi, H.M., Al-Zabedi, E.M., Al-Maktari, M.T., Atroosh, W.M., Al-Delaimy, A.K., Moktar, N., Sallam, A.A., Abdullah, W.A., Jani, R. and Surin, J. (2014). Effects of vitamin A supplementation on iron status indices and iron deficiency anaemia: a randomized controlled trial. *Nutrients* 6, 190-206.

Awasthi, S., Peto, R., Read, S., Clark, S., Pande, V. and Bundy, D. (2013). Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial. *The Lancet* 381, 1469-1477.
Bloem, M.W., Wedel, M., Egger, R.J., Speek, A.J., Schrijver, J., Saowakontha, S. and Schreurs, W.H. (1989). Iron metabolism and vitamin A deficiency in children in northeast Thailand. *Am J Clin Nutr* 50, 332-338.
Bloem, M.W., Wedel, M., van Agtmaal, E.J., Speek, A.J., Saowakontha, S. and Schreurs, W.H. (1990). Vitamin A intervention: short-term effects of a single, oral, massive dose on iron metabolism. *Am J Clin Nutr* 51, 76-79.
Cao, J., Wei, X., Tang, X., Jiang, H., Fan, Z., Yu, Q., Chen, J., Liu, Y. and Li, T. (2013). Effects of egg and vitamin A supplementation on hemoglobin, retinol status and physical growth levels of primary and middle school students in Chongqing, China. *Asia Pac J Clin Nutr* 22, 214-221.
Chen, K., Zhang, L., Luo, H.-y., Wang, J., Li, Q. and Mao, M. (2014). No Enhancing Effect of Vitamin A Administration on Iron Absorption or Body Total Iron Content in Preschool Children from Chengdu, China. *Journal of Nutritional Science and Vitaminology* 60, 223-230.
Gebremedhin, S. (2014). Effect of a single high dose vitamin A supplementation on the hemoglobin status of children aged 6-59 months: propensity score matched retrospective cohort study based on the data of Ethiopian Demographic and Health Survey 2011. *BMC Pediatr* 14, 79.
Jimenez, C., Leets, I., Puche, R., Anzola, E., Montilla, R., Parra, C., Aguilera, A. and Garcia-Casal, M.N. (2010). A single dose of vitamin A improves haemoglobin concentration, retinol status and phagocytic function of neutrophils in preschool children. *Br J Nutr* 103, 798-802.
Khan, I. and Baseer, A. (1996). Hematologic effect of vitamin A supplementation in anemic Pakistani children. *J Pak Med Assoc* 46, 34-38.
Mahawithanage, S.T., Kannangara, K.K., Wickremasinghe, R., Chandrika, U.G., Jansz, E.R., Karunaweera, N.D. and Wickremasinghe, A.R. (2007). Impact of vitamin A supplementation on health status and absenteeism of school children in Sri Lanka. *Asia Pac J Clin Nutr* 16, 94-102.
Mejía, L.A. and Chew, F. (1988). Hematological effect of supplementing anemic children with vitamin A alone and in combination with iron. *The American journal of clinical nutrition* 48, 595-600.
Mwanri, L., Worsley, A., Ryan, P. and Masika, J. (2000). Supplemental vitamin A improves anemia and growth in anemic school children in Tanzania. *J Nutr* 130, 2691-2696.
Pangaribuan, R., Erhardt, J.G., Scherbaum, V. and Biesalski, H.K. (2003). Vitamin A capsule distribution to control vitamin A deficiency in Indonesia: effect of supplementation in pre-school children and compliance with the programme. *Public Health Nutr* 6, 209-216.
Semba, R.D., Muhilal, M.P.H., West Jr, K.P., Winget, M., Natadisastra, G., Scott, A. and Sommer, A. (1992). Impact of vitamin A supplementation on hematological indicators of iron metabolism and protein status in children. *Nutrition Research* 12, 469-478.
Soekarjo, D.D., Pee Sd, S., Kusin, J.A., Schreurs, W.H., Schultink, W., Muhilal and Bloem, M.W. (2004). Effectiveness of weekly vitamin A (10,000 IU) and iron (60 mg) supplementation for adolescent boys and girls through schools in rural and urban East Java, Indonesia. *Eur J Clin Nutr* 58, 927-937.
Talsma, E.F., Brouwer, I.D., Verhoef, H., Mbera, G.N., Mwangi, A.M., Demir, A.Y., Maziya-Dixon, B., Boy, E., Zimmermann, M.B. and Melse-Boonstra, A. (2016). Biofortified yellow cassava and vitamin A status of Kenyan children: a randomized controlled trial. *Am J Clin Nutr* 103, 258-267.
Zimmermann, M.B., Biebinger, R., Rohner, F., Dib, A., Zeder, C., Hurrell, R.F. and Chaouki, N. (2006). Vitamin A supplementation in children with poor vitamin A and iron status increases erythropoietin and hemoglobin concentrations without changing total body iron. *Am J Clin Nutr* 84, 580-586.
Chen, K., Xie, H.M., Tian, W., Zheng, X. and Jiang, A.C. (2016). Effect of single-dose albendazole and vitamin A supplementation on the iron status of pre-school children in Sichuan, China. *Br J Nutr* 115, 1415-1423.
Haskell, M.J., Pandey, P., Graham, J.M., Peerson, J.M., Shrestha, R.K. and Brown, K.H. (2005). Recovery from impaired dark adaptation in nightblind pregnant Nepali women who receive small daily doses of vitamin A as amaranth leaves, carrots, goat liver, vitamin A-fortified rice, or retinyl palmitate. *American Journal of Clinical Nutrition* 81, 461-471.
Suharno, D., Muhilal, Karyadi, D., West, C.E., Hautvast, J.G.A.J. and West, C.E. (1993). Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. *The Lancet* 342, 1325-1328.
Tanumihardjo, S.A., Muherdiyantiningsih, Permaesih, D., Komala, Muhilal, Karyadi, D. and Olson, J.A. (1996). Daily supplements of vitamin A (8.4 mumol, 8000 IU) improve the vitamin A status of lactating Indonesian women. *Am J Clin Nutr* 63, 32-35.
Tanumihardjo, S.A. (2002). Vitamin A and iron status are improved by vitamin A and iron supplementation in pregnant Indonesian women. *J Nutr* 132, 1909-1912.

Abizari, A.R., Azupogo, F. and Brouwer, I.D. (2017). Subclinical inflammation influences the association between vitamin A- and iron status among schoolchildren in Ghana. *Plos One* 12, e0170747.
Koessler, K.K., Maurer, S. and Loughlin, R. (1926). The relation of anemia, primary and secondary, to vitamin A deficiency. *Journal of the American Medical Association* 87, 476-482.
Citelli, M., Bittencourt, L.L., da Silva, S.V., Pierucci, A.P. and Pedrosa, C. (2012). Vitamin A modulates the expression of genes involved in iron bioavailability. *Biol Trace Elem Res* 149, 64-70.
Ameny, M.A., Raila, J., Walzel, E. and Schweigert, F.J. (2002). Effect of iron and/or vitamin A re-supplementation on vitamin A and iron status of rats after a dietary deficiency of both components. *J Trace Elem Med Biol* 16, 175-178.
Roodenburg, A.J., West, C.E., Hovenier, R. and Beynen, A.C. (1996). Supplemental vitamin A enhances the recovery from iron deficiency in rats with chronic vitamin A deficiency. *Br J Nutr* 75, 623-636.
Camaschella, C. (2015). Iron deficiency: new insights into diagnosis and treatment. *Hematology Am Soc Hematol Educ Program* 2015, 8-13.
Semba, R.D. and Bloem, M.W. (2002). The anemia of vitamin A deficiency: Epidemiology and pathogenesis. *European Journal of Clinical Nutrition* 56, 271-281.
Mejia, L.A., Hodges, R.E. and Rucker, R.B. (1979). Clinical signs of anemia in vitamin A-deficient rats. *Am J Clin Nutr* 32, 1439-1444.
Wieringa, F.T., Dijkhuizen, M.A., West, C.E., van der Ven-Jongekrijg, J., van der Meer, J.W. and Muhilal (2004). Reduced production of immunoregulatory cytokines in vitamin A- and zinc-deficient Indonesian infants. *Eur J Clin Nutr* 58, 1498-1504.
Schroeder, S.E., Reddy, M.B. and Schalinske, K.L. (2007). Retinoic acid modulates hepatic iron homeostasis in rats by attenuating the RNA-binding activity of iron regulatory proteins. *J Nutr* 137, 2686-2690.
Cusick, S.E., Tielsch, J.M., Ramsan, M., Jape, J.K., Sazawal, S., Black, R.E. and Stoltzfus, R.J. (2005). Short-term effects of vitamin A and antimalarial treatment on erythropoiesis in severely anemic Zanzibari preschool children. *Am J Clin Nutr* 82, 406-412.
WHO (2011). Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: World Health Organization.
Hoag, K.A., Nashold, F.E., Goverman, J. and Hayes, C.E. (2002). Retinoic acid enhances the T helper 2 cell development that is essential for robust antibody responses through its action on antigen-presenting cells. *J Nutr* 132, 3736-3739.
Malope, B.I., MacPhail, A.P., Alberts, M. and Hiss, D.C. (2001) The ratio of serum transferrin receptor and serum ferritin in the diagnosis of iron status. *Br J Haematol* 115(1):84-89.

Table 1. Characteristics of the included studies of vitamin A supplementation with children and teenagers.

Reference / Country	Sample (*n*)/ (age)	Study design	Baseline			Intervention			Summary of findings	
			VAD (%)	AN (%)	ID (%)	Dose (UI)	Frequency	Measurement	Vitamin A status	Iron status
Ahmed, et al. 2001 Bangladesh	480 teenagers (14-19y)	DB-RCT	70.5	88.0	79.5	8,066	Weekly, for 3 mo	After last dose	↑ ΔSR, SR vs PL	⇔ ΔHb, ΔSF, SF vs PL ↑ Hb vs PL ↓ AN vs PL ↑ ID vs BL (not PL)
Al-Mekhlafi, et al. 2014 Malaysia	250 children (7-12y)	DB-RCT	NE	48.5	34.0 (IDA)	200,000	Single	3 mo after	NE	↑ΔHb vs PL ↓ ΔSF vs PL ↓ IDA vs BL and PL ⇔ AN vs BL and PL
Awasthi, et al. 2013 India	5,165 children (1-6y)	Cluster- RT	NE	NE	NE	200,000	Single, every 6 mo, for 5 y	1 to 5 mo after last dose	↑ SR vs PL ↓ VAD vs PL	⇔ Hb vs PL
Bloem, et al. 1989 Thailand	166 children (1-6y)	Non-RCT	NE	100	NE	366,666	Single	2 and 4 mo after	After 2 mo: ↑ SR vs PL and BL After 4 mo: ↑ SR vs BL (not PL)	After 2 mo: ↑ Hb vs BL (not PL) ⇔ SF vs BL and PL After 4 mo: ↑ SF, Hb vs BL (not PL)
Bloem, et al. 1990 Thailand	134 children (3-9y)	Non-RCT	100	NE	NE	366,666	Single	2 wks after	↑ SR vs PL and BL	↑ Hb vs PL and BL ⇔ SF vs BL and PL

Cao, et al. 2013 China	288 students (10-18y)	Non-RCT	12.9	11.9	NE	200,000	Single	6 mo after	↑ SR vs BL ↑ΔSR vs PL ↓ VAD vs BL	↑ Hb levels vs BL ↑ΔHb vs PL ↓ AN vs BL
Chen, et al. 2014 China	445 children (3-6y)	SB-RCT	9.0	25.5	30.0	200,000	Single	6 mo after	↑ SR vs PL and BL ↓ VAD vs PL and BL	↑ Hb, ID vs BL and PL ↓ SF, AN vs BL and PL
Chen, et al. 2016 China	186 children (3-6y)	SB-RCT	13.1	100	NE	200,000	Single	3 and 6 mo after	After 3 mo: ↑ SR vs BL and PL ↓ VAD vs BL and PL After 6 mo: ↑ SR vs BL and PL ↓ VAD vs BL and PL	After 3 mo: ↑ Hb, SF vs BL and PL ↓ AN, ID vs BL and PL After 6 mo: ↑ Hb vs BL (not PL) ↑ SF vs BL and PL ↓ AN vs BL (not PL) ↓ ID vs BL and PL
Gebremedhin, 2014 Ethiopia	4,794 children (6-59mo)	R-CH	NE	NE	NE	100,000 or 200,000	Single	6 mo after	NE	↑ Hb vs PL ↓ AN vs PL
Jimenez, et al. 2010 Venezuela	80 children (2-6y)	Non-RCT	25.0	16.9	NE	200,000	Single	1 mo after	↑ SR vs BL and PL ↓ VAD vs BL and PL	↑ Hb vs BL and PL ⇔ SF vs BL and PL ↓ AN vs BL (not

										PL)
Khan and Baseer 1996 Pakistan	101 children (4-8y)	Non-RCT	2.0	100	NE	200,000	Single	1.5 mo after	↑ SR vs BL ↑ ΔSR vs PL	⇔ Hb, SF vs BL ⇔ ΔHb, ΔSF vs PL
Mahawithanage, et al. 2007 Sri Lanka	659 children (5-13y)	DB-RCT	NE	NE	NE	200,000	Single, every 4 mo, 3 times	4, 8 and 12 mo after first dose	4 and 8 mo after first dose: ↑ SR vs BL e PL ↑ ΔSR vs PL	12 mo after first dose: ↑ Hb vs BL ⇔ ΔHb vs PL
Mejía and Chew, 1988 Guatemala	115 children (1-8y)	Non-RCT	NE	100	NE	10,000	Daily, for 2mo	After last dose	↑ SR vs BL (not PL) ↑ ΔSR vs PL	↑ Hb vs BL (not PL) ↑ ΔHb vs PL ⇔ SF vs BL and PL ↓ AN vs BL
Mwanri, et al. 2000 Tanzania	136 children (9-12y)	DB-RCT	NE	100	NE	5,000	3d/wk, for 3 mo	3 mo after	NE	↑ Hb vs BL ↑ ΔHb vs PL ↓ AN vs BL and PL
Pangaribuan, et al. 2003 Indonesia	400 children (12-60mo)	P-CH	18.2	25.7	NE	200,000	Single	2 mo after	↑ SR vs PL and BL	↑ Hb, SF vs BL (not PL)
Semba, et al. 1992 Indonesia	236 children (3-6y)	DB-RCT	NE	8.9	NE	200,000	Single	5 wks after	↑ SR vs BL ↑ ΔSR vs PL	↑ SF vs BL ↑ ΔSF vs PL For anemic childrn at the admission: ↑ Hb vs BL

										↑ ΔHb vs PL
Soekarjo, et al. 2004 Indonesia	5,166 children (12-15y)	RCT	1.5	19.5	NE	10,000	Weekly, for 3.5 mo	After last dose	Boys and girls: ⇔ SR vs PL Boys: ↑ ΔSR vs PL Girls:⇔ ΔSR vs PL	Boys and girls: ⇔ Hb vs PL
Talsma, et al. 2016 Kenya	342 children (5-13y)	SB-RCT	27.0	6.9	37.3	501.42 (β-carotene 1053 μg)	6d/wk, for 4.5 mo	After last dose	↑ SR vs PL	⇔ Hb vs PL
Zimmerman, et al. 2006 Morocco	81 children (5-13y)	RCT	17.0	54.0	NE	200,000	Single, every 5 mo, twice	5 mo after both doses	5 mo after the first dose: ↑ SR vs BL (not PL) ↓ VAD vs BL and PL 5 mo after the second dose: ↑ SR vs BL and PL ↓ VAD vs BL and PL	5 mo after the first dose: ↑ Hb vs BL (not PL) ⇔ SF vs BL and PL ↓ AN vs PL (vs BL not reported) 5 mo after the second dose: ↑ Hb vs BL and PL ↓ SF vs BL and PL ↓ AN vs PL (vs BL not reported)

DB-RCT: double-blinded randomized controlled clinical trial; SB-RCT: single-blinded randomized controlled clinical trial; Cluster-RT: cluster randomized clinical trial; Non-RCT: non-randomized controlled clinical trial; RCT: randomized controlled clinical trial; NRUT: non-randomized uncontrolled clinical trial; R-CH: retrospective cohort; P-CH: prospective cohort; VAD:

vitamin A deficiency; AN: anemia; ID: iron deficiency; IDA: iron deficiency anemia; SR: serum retinol; ΔSR: variation of serum retinol; Hb: hemoglobin; ΔHb: variation of hemoglobin; SF: serum ferritin; ΔSF: variation of serum ferritin; BL: baseline; PL: placebo group; d: days; wks: weeks; mo: months; y: years; ↑: significant increase observed on outcome; ↓: significant decrease observed on outcome; ⇔: no change observed on outcome; vs.: versus; NE: not estimated.

Table 2. Characteristics of the included studies of vitamin A supplementation with pregnant and lactating women.

Reference / Country	Sample (*n*)/ (age)	Study design	Baseline			Intervention			Summary of findings	
			VAD (%)	AN (%)	ID (%)	Dose (UI)	Frequency	Measurement	Vitamin A status	Iron status
Haskell, et al. 2005 Nepal	8,764 pregnant women (18-45y)	NRUT	22.3	50.9	NE	High: 6,666 Low: 2,833	6 d / wk, for 1.5 mo	After last dose	NE	For both doses: ⇔ Hb, SF vs BL
Suharno, et al. 1993 Indonesia	305 pregnant women (17-35y)	DB-RCT	10.0	100	NE	8,000	Daily, for 2 mo	In the first wk after last dose	↑ ΔSR vs PL	↓ AN vs BL ↑ ΔHb vs PL ⇔ ΔSF vs PL
Tanumihardjo, et al. 1996 Indonesia	25 lactating women (15-40y)	NRUT	26.0	9.0	NE	8,000	Daily, for 1 mo	After last dose	↑ SR vs BL	⇔ Hb vs BL
Tanumihardjo, et al. 2002 Indonesia	27 pregnant women (18-37y)	RCT	7.4	NE	NE	8,000	Daily, for 2 mo	After last dose	⇔ SR vs BL and PL	↑ Hb vs BL and PL ↑ SF vs PL (not BL)

DB-RCT: double-blinded randomized controlled clinical trial; RCT: randomized controlled clinical trial; NRUT: non-randomized uncontrolled clinical trial; VAD: vitamin A deficiency; AN: anemia; ID: iron deficiency; IDA: iron deficiency anemia; SR: serum retinol; ΔSR: variation of serum retinol; Hb: hemoglobin; ΔHb: variation of hemoglobin; SF: serum ferritin; ΔSF: variation of serum ferritin; BL: baseline; PL: placebo group; d: days; wks: weeks; mo: months; y: years; ↑: significant increase observed on outcome; ↓: significant decrease observed on outcome; ⇔: no change observed on outcome; vs.: versus; NE: not estimated.

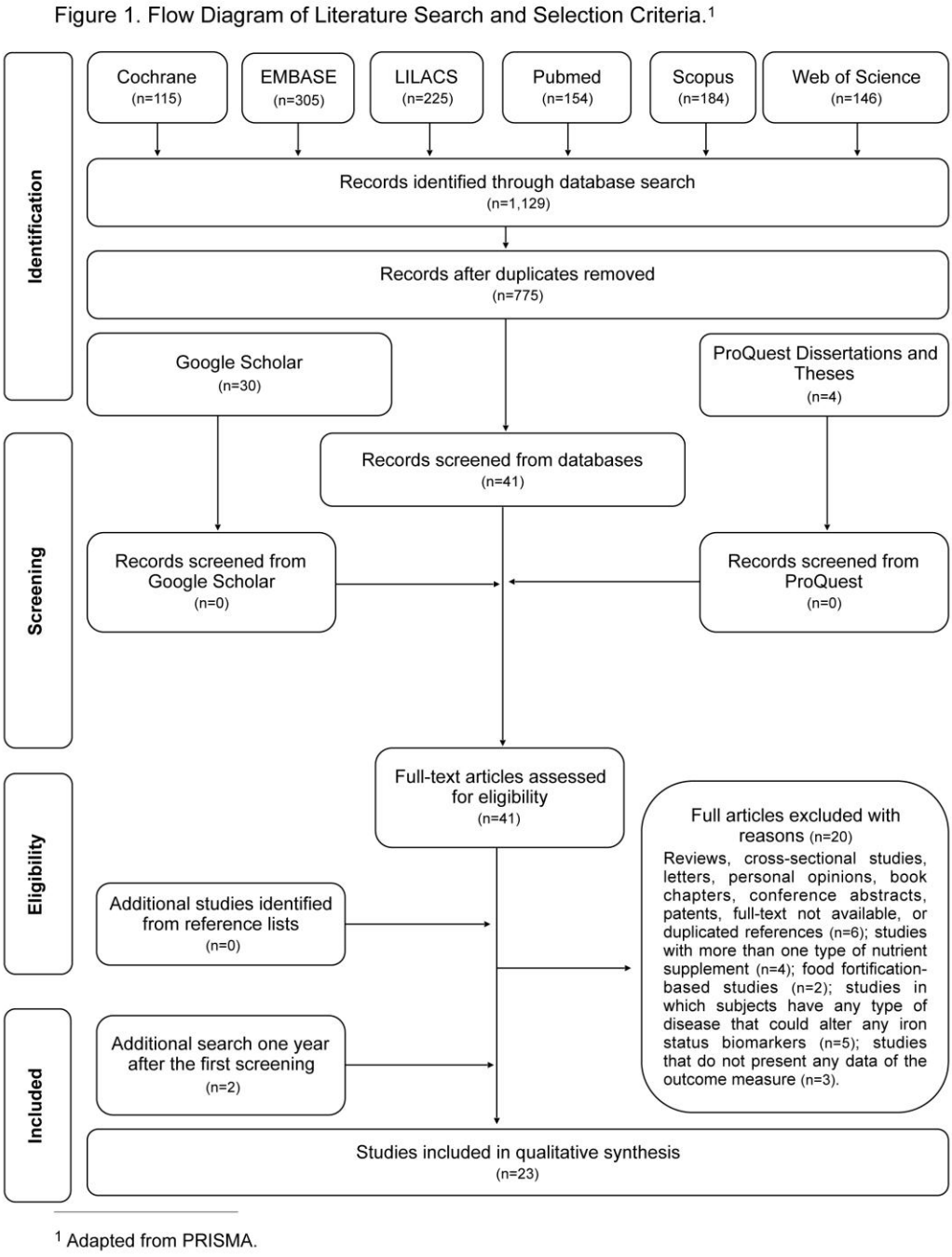

Figure 1. Flow Diagram of Literature Search and Selection Criteria. (Adapted from PRISMA)

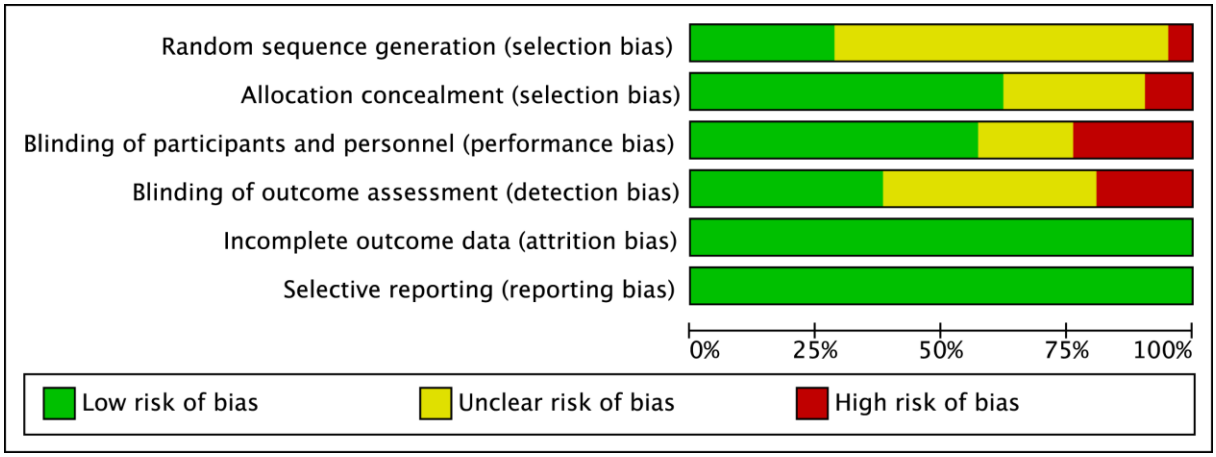

Figure 2. Risk of bias summary graph across the included trials. Each risk of bias item is presented as percentages across all included studies.

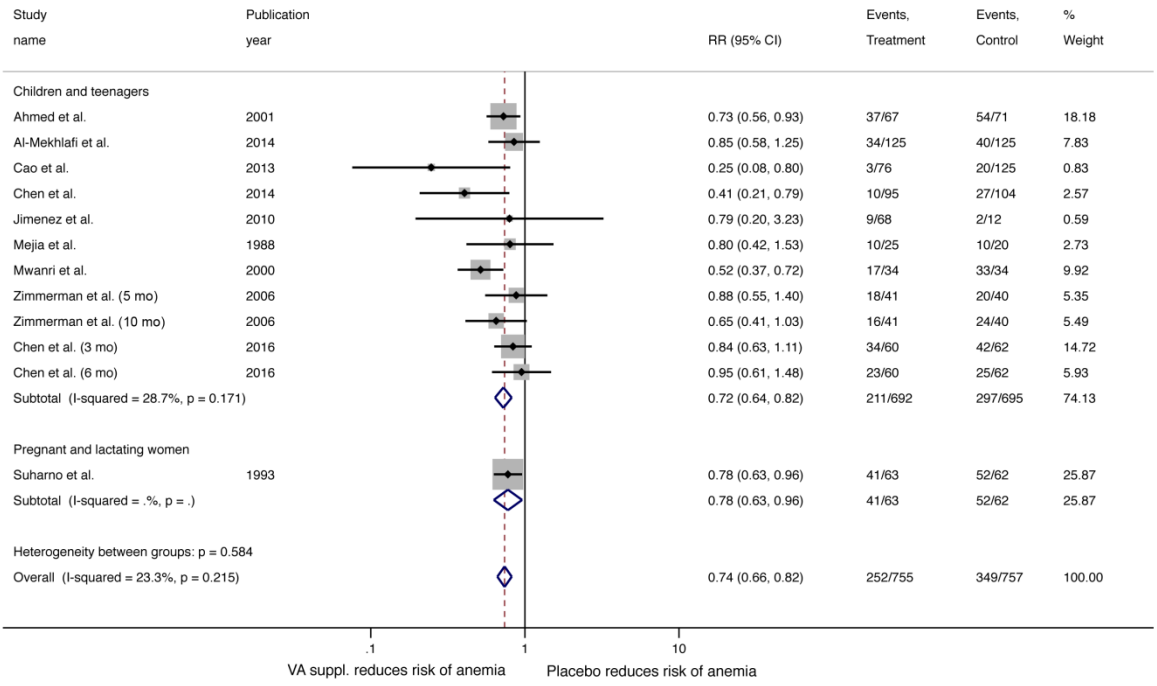

Figure 3. Effect of vitamin A supplementation on risk of anemia. The forest plot indicates the risk ratio (RR) with 95% confidence interval (CI) for ten studies.

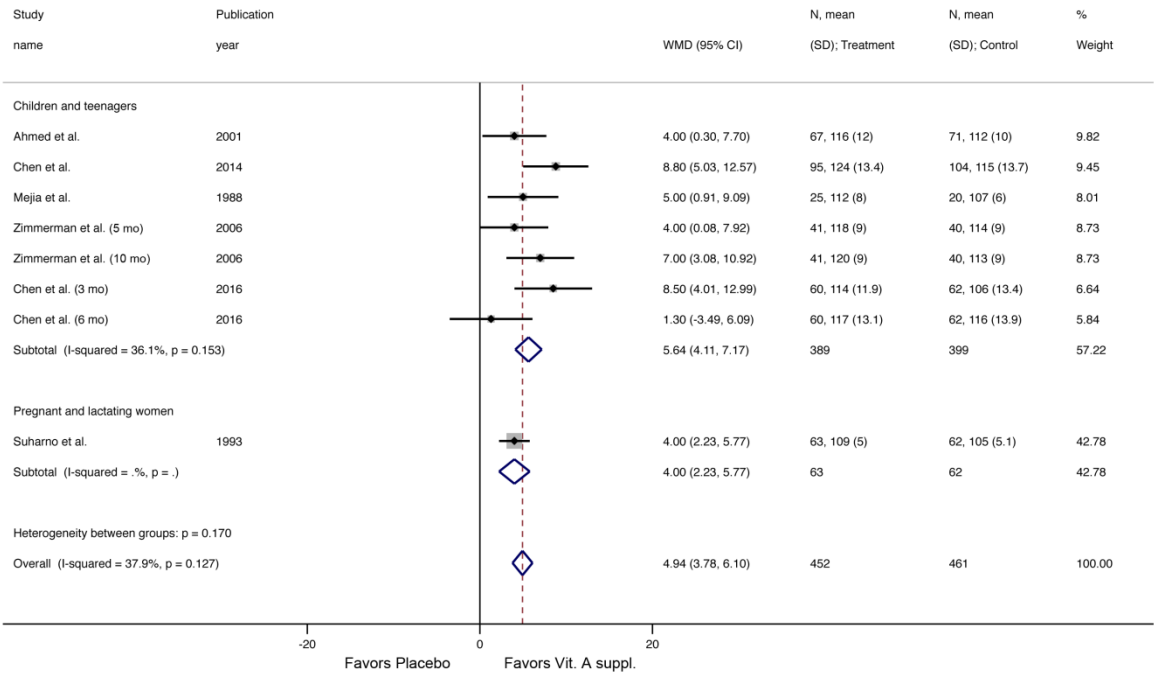

Figure 4. Sensitivity analysis of the effect of vitamin A supplementation on hemoglobin levels. The forest plot indicates the weighted mean difference (WMD) with 95% confidence interval (CI) for six studies. The studies of Chen, et al. (2016) and Zimmerman, et al. (2006) were twice included because the data from two periods of time were provided.

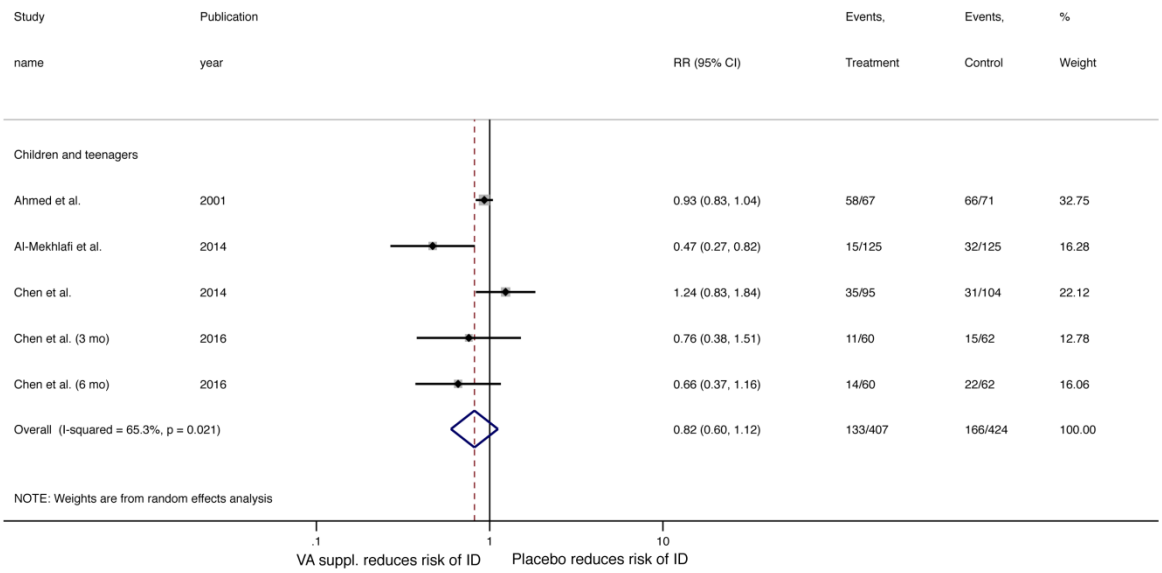

Figure 5. Effect of vitamin A supplementation on risk of iron deficiency. The forest plot indicates the risk ratio (RR) with 95% confidence interval (CI) for four studies. The study of Chen, et al. (2016) was twice included because the data from two periods of time were provided.

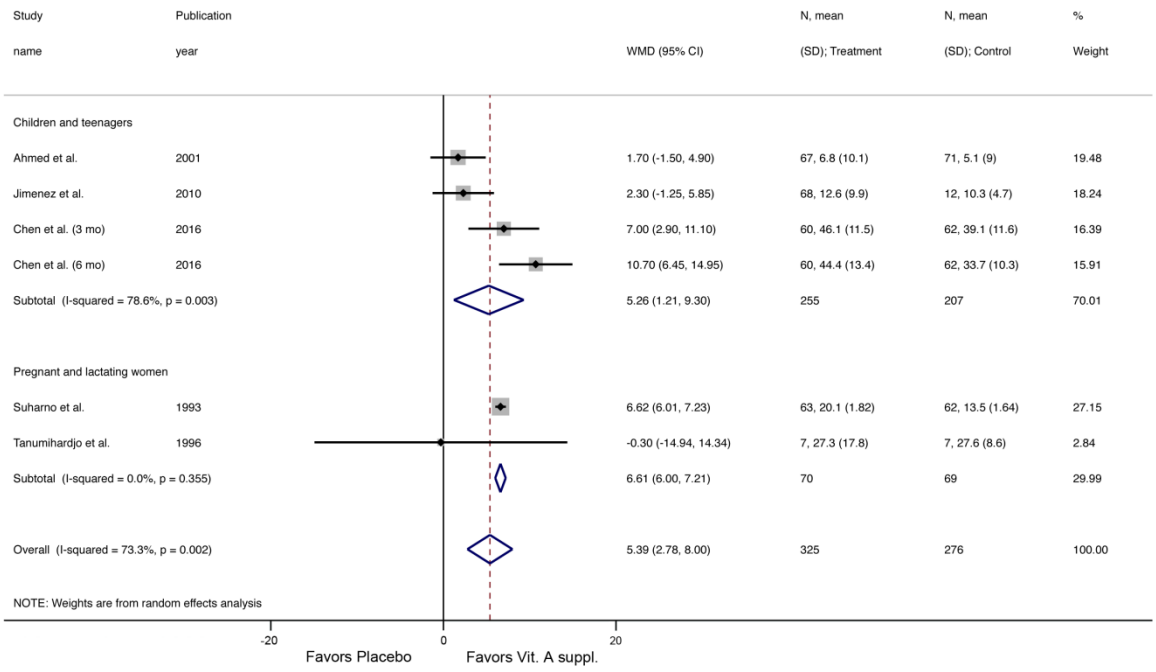

Figure 6. Sensitivity analysis of the effect of vitamin A supplementation on serum ferritin levels. The forest plot indicates the weighted mean difference (WMD) with 95% confidence interval (CI) for five studies. The study of Chen, et al. (2016) was twice included because the data from two periods of time were provided.