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Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women (Review)

Fernández-Gaxiola AC, De-Regil LM

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[Intervention Review]

Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Ana C Fernández-Gaxiola[1], Luz Maria De-Regil[2]

[1]Instituto Nacional de Salud Pública, Cuernavaca, Mexico. [2]Global Technical Services, Nutrition International, Ottawa, Canada

Contact address: Luz Maria De-Regil, Global Technical Services, Nutrition International, 180 Elgin Street, Suite 1000, Ottawa, ON, K2P 2K3, Canada. luzderegil@gmail.com.

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ABSTRACT

Background

Anaemia is a condition in which the number of red blood cells is insufficient to meet physiologic needs; it is caused by many conditions, particularly iron deficiency. Traditionally, daily iron supplementation has been a standard practice for preventing and treating anaemia. However, its long-term use has been limited, as it has been associated with adverse side effects such as nausea, constipation, and teeth staining. Intermittent iron supplementation has been suggested as an effective and safer alternative to daily iron supplementation for preventing and reducing anaemia at the population level, especially in areas where this condition is highly prevalent.

Objectives

To assess the effects of intermittent oral iron supplementation, alone or in combination with other nutrients, on anaemia and its associated impairments among menstruating women, compared with no intervention, a placebo, or daily supplementation.

Search methods

In February 2018, we searched CENTRAL, MEDLINE, Embase, nine other databases, and two trials registers. In March 2018, we also searched LILACS, IBECS and IMBIOMED. In addition, we examined reference lists, and contacted authors and known experts to identify additional studies.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs with either individual or cluster randomisation. Participants were menstruating women; that is, women beyond menarche and prior to menopause who were not pregnant or lactating and did not have a known condition that impeded the presence of menstrual periods. The intervention was the use of iron supplements intermittently (one, two or three times a week on non-consecutive days) compared with placebo, no intervention, or the same supplements provided on a daily basis.

Data collection and analysis

Both review authors independently assessed the eligibility of studies against the inclusion criteria, extracted data from included studies, checked data entry for accuracy, assessed the risk of bias of the included studies, and rated the quality of the evidence using GRADE.

Main results

We included 25 studies involving 10,996 women. Study methods were not well described in many of the included studies and thus assessing risk of bias was difficult. The main limitations of the studies were lack of blinding and high attrition. Studies were mainly funded by international organisations, universities, and ministries of health within the countries. Approximately one third of the included studies did not provide a funding source.

Although quality across studies was variable, the results consistently showed that intermittent iron supplementation (alone or with any other vitamins and minerals) compared with no intervention or a placebo, reduced the risk of having anaemia (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.49 to 0.87; 11 studies, 3135 participants; low-quality evidence), and improved the concentration of haemoglobin (mean difference (MD) 5.19 g/L, 95% CI 3.07 to 7.32; 15 studies, 2886 participants; moderate-quality evidence), and ferritin (MD 7.46 μg/L, 95% CI 5.02 to 9.90; 7 studies, 1067 participants; low-quality evidence). Intermittent regimens may also reduce the risk of having iron deficiency (RR 0.50, 95% CI 0.24 to 1.04; 3 studies, 624 participants; low-quality evidence), but evidence was inconclusive regarding iron deficiency anaemia (RR 0.07, 95% CI 0.00 to 1.16; 1 study, 97 participants; very low-quality evidence) and all-cause morbidity (RR 1.12, 95% CI 0.82 to 1.52; 1 study, 119 participants; very low-quality evidence). Women in the control group were less likely to have any adverse side effects than those receiving intermittent iron supplements (RR 1.98, 95% CI 0.31 to 12.72; 3 studies, 630 participants; moderate-quality evidence).

In comparison with daily supplementation, results showed that intermittent supplementation (alone or with any other vitamins and minerals) produced similar effects to daily supplementation (alone or with any other vitamins and minerals) on anaemia (RR 1.09, 95% CI 0.93 to 1.29; 8 studies, 1749 participants; moderate-quality evidence). Intermittent supplementation may produce similar haemoglobin concentrations (MD 0.43 g/L, 95% CI −1.44 to 2.31; 10 studies, 2127 participants; low-quality evidence) but lower ferritin concentrations on average (MD −6.07 μg/L, 95% CI −10.66 to −1.48; 4 studies, 988 participants; low-quality evidence) compared to daily supplementation. Compared to daily regimens, intermittent regimens may also reduce the risk of having iron deficiency (RR 4.30, 95% CI 0.56 to 33.20; 1 study, 198 participants; very low-quality evidence). Women receiving iron supplements intermittently were less likely to have any adverse side effects than those receiving iron supplements daily (RR 0.41, 95% CI 0.21 to 0.82; 6 studies, 1166 participants; moderate-quality evidence). No studies reported on the effect of intermittent regimens versus daily regimens on iron deficiency anaemia and all-cause morbidity.

Information on disease outcomes, adherence, economic productivity, and work performance was scarce, and evidence about the effects of intermittent supplementation on these outcomes unclear.

Overall, whether the supplements were given once or twice weekly, for less or more than three months, contained less or more than 60 mg of elemental iron per week, or given to populations with different degrees of anaemia at baseline did not seem to affect the findings. Furthermore, the response did not differ in areas where malaria was frequent, although very few trials were conducted in these settings.

Authors' conclusions

Intermittent iron supplementation may reduce anaemia and may improve iron stores among menstruating women in populations with different anaemia and malaria backgrounds. In comparison with daily supplementation, the provision of iron supplements intermittently is probably as effective in preventing or controlling anaemia. More information is needed on morbidity (including malaria outcomes), side effects, work performance, economic productivity, depression, and adherence to the intervention. The quality of this evidence base ranged from very low to moderate quality, suggesting that we are uncertain about these effects.

PLAIN LANGUAGE SUMMARY

Iron supplements taken one, two or three times a week for preventing anaemia, and its consequences in menstruating women

What is the issue?

Across the globe, approximately one out of three non-pregnant women of reproductive age are anaemic; i.e. have fewer red blood cells or less haemoglobin (a red substance that combines with oxygen and carries it around the body) in each red blood cell than normal. Although there are several causes of anaemia, it very often results from sustained iron deficiency. The standard practice to prevent or treat anaemia in women has been daily iron supplementation (sometimes combined with folic acid and other vitamins and minerals) for three months. However, it is frequently associated with side effects such as nausea or constipation. Intermittent supplementation (that is, the consumption of supplements one, two or three times a week on non-consecutive days) has been proposed as an effective and safer alternative to daily supplementation.

Why is this important?

Women with anaemia may have less energy for physical work and become more prone to infections. Most women throughout the world enter pregnancy with anaemia, putting them at greater risk of having low birth-weight babies and other complications during delivery.

Some scientists believe that taking iron a few times a week - instead of every day - can help women with anaemia to feel better and improve their haemoglobin without giving them as many side effects. If women have fewer side effects, they may be more likely to take iron supplements more regularly and for longer periods.

What evidence did we find?

We reviewed the evidence in February 2018. We included 25 randomised controlled trials (a type of experiment in which participants are randomly assigned to one or more treatment groups) involving 10,996 women. We included studies examining the administration of intermittent iron supplements versus no intervention, a placebo (dummy pill) or the same supplements given on a daily basis. Most studies were implemented in school settings and were mainly funded by international organisations, universities, and ministries of health within the countries. Approximately one-third of the included studies did not provide a funding source.

The findings show that women receiving intermittent supplementation with iron alone, or in combination with folic acid or other nutrients, were less likely to be anaemic than those women who received no iron supplements or a placebo. They also had higher concentrations of haemoglobin and ferritin (a protein that carries iron). Intermittent supplementation also reduced the risk of having iron deficiency. The findings indicate that intermittent supplementation was as effective as daily supplementation in reducing the prevalence of anaemia and increasing haemoglobin concentrations, with fewer side effects. It had no effect on raising ferritin concentrations.

We found scarce evidence on the effect of intermittent supplementation compared to placebo or daily supplementation on iron deficiency anaemia, all-cause morbidity, disease outcomes, adherence, economic productivity, and work performance.

What does this mean?

Intermittent iron supplementation in menstruating women may be an effective intervention for reducing anaemia and improving haemoglobin concentrations compared to no treatment, placebo or daily supplementation. Intermittent supplementation may be associated with fewer side effects compared to daily supplementation. The findings were not affected by whether the supplements were given once or twice weekly, for less or more than three months, contained less or more than 60 mg of elemental iron per week, or given to populations with different degrees of anaemia at baseline (starting point for comparisons). The evidence base was of overall low quality.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo in menstruating women

Patient or population: adolescent and adult menstruating women
Setting: community settings
Intervention: intermittent iron supplementation (alone or with any other micronutrients)
Comparison: no supplementation or placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no supplementation or placebo	Risk with intermittent iron supplementation (alone or with any other micronutrients)				
Anaemia (haemoglobin concentration below a cut-off defined by the trialists, adjusted by altitude and smoking as appropriate) Follow-up: range 2 months to 6 months	**Study population**		**RR 0.65** (0.49 to 0.87)	3135 (11 studies)	⊕⊕◯◯ **Low**[a]	Includes seven cluster-randomised trials[b]
	39 per 100	**25 per 100** (19 to 34)				
Haemoglobin (g/L) Follow-up: range 2 months to 6 months	The mean haemoglobin g/L in the control groups ranged from **—0.24 to 133.20**	The mean haemoglobin g/L in the intervention groups was **5.19 higher** (3.07 higher to 7.32 higher)	-	2886 (15 studies)	⊕⊕⊕◯ **Moderate**[c]	Includes five cluster-randomised trials[b]
Iron deficiency (as defined by trialists by using indicators of iron status such as ferritin or transferrin) Follow-up: range 3	**Study population**		**RR 0.50** (0.24 to 1.04)	624 (3 studies)	⊕⊕◯◯ **Low**[d]	Includes one cluster-randomised trial[b]

months to 4 months						
	49 per 100	**25 per 100** (12 to 51)				
Ferritin (µg/L) Follow-up: range 3 months to 6 months	The mean ferritin µg/L in the control groups ranged from **−5.31 to 41**	The mean ferritin μg/L in the intervention groups was**7.46 higher** (5.02 higher to 9.90 higher)	-	1067 (7 studies)	⊕⊕◯◯ **Low**[e]	Includes one cluster-randomised trial[b]
Iron deficiency anaemia (as defined by the presence of anaemia plus iron deficiency diagnosed with an indicator of iron status selected by the trialists) Follow-up: 4 months	**Study population**		**RR 0.07** (0.00 to 1.16)	97 (1 study)	⊕⊕◯◯ **Low**[f]	The included trial is a cluster-randomised trial[b]
	7 per 100	**1 per 100** (0 to 8)				
All-cause morbidity (the most frequent event associated with the intervention, independent of the cause, as defined by the trialists) Follow-up: 4 months	**Study population**		**RR 1.12** (0.82 to 1.52)	119 (1 study)	⊕⊕◯◯ **Low**[g]	-
	55 per 100	**61 per 100** (45 to 83)				
Any adverse side effects	**13 per 100**	**26 per 100** (4 to 100)	**RR 1.98** (0.31 to 12.72)	630 (3 studies)	⊕⊕⊕◯ **Moderate**[h]	

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level due to study limitations (in several trials the method of allocation concealment was not clear and there was a lack of blinding) and one level due to inconsistency (high heterogeneity) (I^2 = 83%).

[b] For cluster-randomised trials (C), the analyses only include the estimated effective sample size, after adjusting the data to account for the clustering effect.

[c] Downgraded one level due to inconsistency (high heterogeneity) (I^2 = 85%).

[d] Downgraded one level due to imprecision (wide CI) and one level due to inconsistency (high heterogeneity) (I^2 = 89%).

[e] Downgraded one level due to study limitations (in several trials the method of allocation concealment was not clear and there was a lack of blinding) and one level due to imprecision (wide CI) (I^2 = 48%).

[f] Downgraded one level due to lack of blinding and one level due to imprecision (wide CI and not enough information to detect a precise estimate of the effect - only one study reported on this outcome) (I^2 = not estimable).

[g] Downgraded one level due to study attrition and one level due to imprecision (not enough information to detect a precise estimate of the effect - only one study reported on this outcome) (I^2 = not estimable).

[h] Downgraded one level due to inconsistency (high heterogeneity) (I^2 = 91%)

BACKGROUND

Description of the condition

Anaemia is a condition in which the oxygen-carrying capacity of the blood is insufficient to meet the physiologic needs of body tissues. The global prevalence of this condition in non-pregnant women of reproductive age is estimated to be 29.0% (WHO 2015), and it is more frequent in low- and middle-income countries or among women who belong to a low socioeconomic stratum (Soekarjo 2001; Bodnar 2002; Bentley 2003). Anaemia has multiple direct causes that very often coexist: it can result from parasitic infections (Kumar 2007; Anah 2008); inflammatory disorders (Yip 1988); inherited disorders of haemoglobin structure; oxidative stress (i.e. imbalance between free radicals and antioxidants) and vitamin and mineral deficiencies such as that of vitamins A and B12, and folate (Herbert 1987; Hercberg 1992; Jimenez 2010), and especially iron, which is responsible for at least half of the cases of anaemia (WHO 2001).

Iron deficiency results from long-term imbalance caused by inadequate dietary iron intake, poor iron absorption or utilisation, increased iron requirements, or chronic blood loss (Alleyne 2008). Individual iron requirements vary considerably throughout the human life cycle (Lynch 2007), and both physiological (for example, pregnancy or early postpartum) or pathological (for example, HIV infection) conditions affect iron requirements (WHO 2001). Postmenarchal women are at higher risk of developing iron deficiency because of menstrual losses, and if they do not have an adequate iron intake, this condition can progress to anaemia (known as iron deficiency anaemia or IDA).

Iron deficiency is one of the most prevalent forms of malnutrition globally. It is estimated that 50% of anaemia is attributable to iron deficiency worldwide (WHO 2001). Iron deficiency, even in the absence of anaemia, may either cause disability directly or be a risk factor for it (Stoltzfus 2003). For example, it causes impaired muscle function and impaired resistance to infections in all age groups (Beard 2005), and it is associated with reduced physical capacity and work performance in adolescents and adults (Beard 2001; WHO 2001; Clark 2008). Most women throughout the world enter pregnancy with less than desirable iron reserves, which reduce their reproductive performance (Viteri 2005). In addition to iron deficiency, women are frequently deficient in other vitamins and minerals that play important roles in the body (Ramakrishnan 2002; Kontic-Vucinic 2006; Ahmed 2008). An adequate folate intake during the periconceptional period, for example, is crucial to reducing the risk of having a baby with neural tube defects (NTDs) (De-Regil 2015); vitamin B12 and folate deficiencies are major causes of anaemia (Green 2017), while vitamin A regulates many critical functions, including vision, integrity of epithelial tissue (i.e. membranous tissue covering internal organs and other internal surfaces of the body), the expression of several hundred genes, and its deficiency also contributes to nutritional anaemia (WHO 2011a). Although these deficiencies may not translate into a comparable prevalence of anaemia, supplementation of these nutrients in women may improve their health throughout life, as there is some indication that these deficiencies are of public health concern in certain countries (McLean 2008).

Anaemia in women of reproductive age is diagnosed when the haemoglobin concentration in the blood is below 120 g/L, a cut-off that varies with residential elevation above sea level (altitude) and smoking (WHO 2011b). Iron deficiency anaemia is diagnosed by the combined presence of anaemia and iron deficiency, measured by ferritin (< 15 μg/L) or any other indicator of iron status such as serum transferrin receptors or zinc protoporphyrin (WHO 2011c).

Description of the intervention

Daily iron plus folic acid supplementation remains the standard approach for the prevention and treatment of anaemia among menstruating women, since dietary changes alone usually cannot correct this condition, as the iron content in the diet is relatively constant and difficult to increase (DeMaeyer 1989). The recommended daily, supplemental dosage for non-pregnant women of reproductive age living in countries where anaemia is highly prevalent (i.e. above 40%) is 60 mg of elemental iron and 400 µg of folic acid for three months (WHO 2001). The use of folic acid prior to pregnancy aims to improve folate status, and this dose has been shown to be effective for preventing NTDs in women who become pregnant (WHO 2001). Despite its proven efficacy, the main problem with the daily regimen is lack of compliance, due to side effects such as diarrhoea, constipation, dark stools, metallic taste, teeth staining, and nausea (Yip 1994).

Intermittent oral iron supplementation (i.e. one, two or three times a week on non-consecutive days) has been suggested as an effective alternative to daily iron supplementation to prevent anaemia at the population level. The efficacy of intermittent iron supplementation for the prevention of anaemia and iron deficiency has been studied over the last 15 years in children, adolescents and pregnant and non-pregnant women of reproductive age. A review of 22 trials performed in all of these groups concluded that both daily and once-weekly iron supplementation were efficacious under favourable conditions in reducing anaemia (Beaton 1999). Subsequent trials in menstruating women have confirmed these findings (Crape 2005; Khan 2005; Paulino 2005), although some study authors have suggested that the weekly intake of supplemental iron may be insufficient to meet women's needs and have proposed the use of iron supplements twice a week (Kianfar 2000; Olsen 2000). Recent trials have used a variety of intermittent iron supplementation schemes such as: a double dose, once- and twice-a-week scheme, which reduced iron deficiency efficiently (Ahmed 2012); and a once-a-week scheme, with and without other micronutrients, which improved iron status (Bansal 2016) and haemoglobin concentration significantly (Kätelhut 1996).

The international recommendation for weekly supplementation for non-pregnant women of reproductive age is that supplements should contain 60 mg of elemental iron in the form of ferrous sulphate and 2800 µg (2.8 mg) of folic acid (WHO 2011d). Although evidence for the effective dose of folic acid for intermittent supplementation is very limited, the current recommendation is based on the rationale of providing seven times the recommended daily dose to prevent NTDs, and experimental evidence that high weekly doses can improve red blood cell folate concentrations to levels that have been associated with a reduced risk of NTDs (Martinez-de Villareal 2001; Martinez-de Villareal 2002; Norsworthy 2004; Nguyen 2008). However, some countries have chosen to give a higher dose in their programmes. India, for example, provides 100 mg of elemental iron (Vir 2008) under supervised and unsupervised conditions, decreasing the prevalence of anaemia from 73.3% to 25.4%. The provision of vitamins and minerals other than iron and folic acid on an intermittent basis may also help to supplement women's diets and therefore improve health and development throughout the life cycle (Allen 2009a; Allen 2009b; Dalmiya 2009).

How the intervention might work

Intestinal cells turn over every five to six days in humans. Hence, providing iron on an intermittent basis would expose this nutrient to new mucosal cells (made up of epithelial tissue) only, improving absorption efficiency (Viteri 1995), and reducing oxidative stress and side effects (Viteri 2005). It may also reduce absorption blockage due to high iron levels in the gut lumen (i.e. inside space of the gut) and in the enterocyte (i.e. intestinal cell) (Anderson 2005; Oates 2007). Intermittent regimens may be perceived as more tolerable, ergo increasing adherence to supplementation (Casanueva 2006). In order to improve the success of this intervention, the World Health Organization (WHO) encourages the integration of intermittent iron supplementation programmes with other public health measures, including deworming to prevent hookworm infections, improved bioavailable dietary iron intake, and interventions to control other prevalent causes of anaemia, particularly malaria, other infections, and vitamin A deficiency (WHO 2011d).

The endemicity of malaria in a given region is an important consideration when providing iron supplements at the population level. Malaria, which is responsible for more than a million deaths per year (Gajida 2010), causes anaemia through several mechanisms. Provision of iron in malaria-endemic areas, particularly to children, has been a long-standing controversy due to concerns that iron therapy may exacerbate infections, particularly malaria (Oppenheimer 2001; Okabe 2011). Although the mechanisms by which additional iron can benefit the parasite are far from clear (Prentice 2007), intermittent supplementation might be an effective option to prevent anaemia and improve malaria treatment in malaria-endemic areas since less iron is available for the parasite.

Why it is important to do this review

Improving iron and folate nutrition of adolescent and adult menstruating women may contribute to adequate mental and physical performance and reproductive health, which may, in turn, significantly enhance maternal and infant health outcomes. Intermittent supplementation is proposed as a viable approach for improving iron and folate status in populations, especially in areas where anaemia is highly prevalent, and where mass fortification of staple foods with iron and folic acid is not available and not likely to be available in the near future.

After the publication of the first version of this review (Fernández-Gaxiola 2011a), WHO published guidelines on intermittent iron supplementation (WHO 2011d), and WHO Member States committed to the World Health Assembly to halve anaemia in pregnant and non-pregnant women of reproductive age by 2025 (WHO 2014). To date, weekly iron supplementation has been implemented in more than 10 countries in Asia and Africa, but there is still a need for the literature to be systematically reviewed so there is updated evidence on the efficacy, effectiveness, and safety of this intervention, to inform a possible scale-up as part of public health programmes.

This is an update of the previous review (Fernández-Gaxiola 2011a), which was to inform the WHO guideline on intermittent supplementation in menstruating women (WHO 2011d). The evidence will complement the findings of other Cochrane Reviews exploring the effects of intermittent regimens among pregnant women (Peña-Rosas 2015), the effects of intermittent iron supplementation in children under 12 years of age (De-Regil 2011), and the effect of oral iron supplementation on preventing and treating anaemia among children in malaria-endemic areas (Okabe 2011).

OBJECTIVES

To assess the effects of intermittent oral iron supplementation, alone or in combination with other nutrients, on anaemia and its associated impairments among menstruating women, compared with no intervention, a placebo, or daily supplementation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs with randomisation at either the individual or cluster level. Quasi-RCTs are trials that use systematic methods to allocate participants to

treatment groups such as alternation or assignment based on date of birth or case record number (Reeves 2011).

Types of participants

Menstruating women; that is, women beyond menarche and prior to menopause who are not pregnant or lactating or have any condition that impedes the presence of menstrual periods, regardless of their baseline iron status or anaemia status, ethnicity, country of residence, or level of endurance.

We did not include studies targeting women with conditions affecting iron metabolism such as intestinal malabsorption conditions, ongoing excessive blood loss (including ongoing blood donations), inflammatory bowel disease, cancer, chronic congestive cardiac failure, chronic renal failure, chronic liver failure, or chronic infectious disease.

Types of interventions

Interventions involving an intermittent dosage of oral iron, either alone or with other vitamins and minerals, versus no intervention or placebo or the same supplements provided on a daily basis.

Oral iron supplementation refers to the delivery of iron compounds directly to the oral cavity, either as a tablet, capsule, dispersible tablet or liquid. For the purpose of this review, intermittent supplementation is defined as the provision of iron supplements one, two or three times a week on non-consecutive days.

We performed the following comparisons:

1. intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo; and
2. intermittent iron supplementation versus daily iron supplementation.

We included studies that combined iron supplementation with other cointerventions, such as education or deworming, but only if the other cointerventions were the same in both the intervention and comparison groups.

We excluded studies examining tube feeding, parenteral nutrition or supplementary food-based interventions such as mass fortification of staple or complementary foods, home fortification with micronutrient powders, lipid-based supplements or foodlet (i.e. food-like) tablets, or biofortification.

Types of outcome measures

Primary outcomes

1. Anaemia (haemoglobin concentration below a cut-off defined by the trialists, adjusted by altitude and smoking, as appropriate)*
2. Haemoglobin (g/L)*
3. Iron deficiency (as defined by the trialists using indicators of iron status such as ferritin or transferrin)*
4. Ferritin (µg/L)*
5. Iron deficiency anaemia (as defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by the trialists)*
6. All-cause morbidity (the most frequent event associated with the intervention, independent of the cause, as defined by the trialists)*

* Outcomes included in the 'Summary of findings' tables.

Secondary outcomes

1. Diarrhoea (number of women with at least three liquid stools in one day)
2. Respiratory infections (as defined by the trialists)
3. Any adverse side effects (e.g. nausea, vomiting, constipation, gastrointestinal discomfort, as defined by the trialists)
4. Work performance and economic productivity (as defined by the trialists)
5. School performance and cognitive function (for adolescents) (as defined by the trialists)
6. Depression (as defined by trialists)
7. Adherence (percentage of participants who consumed 70% or more of the prescribed dosage throughout the trial)

We considered the following outcomes in malaria settings only.

1. Malaria incidence (as defined by the trialists)
2. Malaria severity (as defined by the trialists)

All outcomes were evaluated at the end of the intervention or at the time point closest to the end.

Search methods for identification of studies

We analysed the indexing terms in the MEDLINE records for the included studies in the first version of this review using Yale MeSH Analyser (Grossetta Nardini 2017), and concluded that a number of indexing terms used in the previous strategy were redundant. We revised the search strategy for this update by removing these terms, which increased the precision of the search (Appendix 1). Search strategies for the previous version of this review are in Appendix 2. We limited our searches to studies published from 1980 onwards since the first trials on this intervention were published after this year. We did not apply any language restrictions. For those articles written in a language other than English, we commissioned their translation into English, to assess them for eligibility according to the prespecified selection criteria (Criteria for considering studies for this review).

Electronic searches

For this update, we searched the electronic databases and trials registers listed below up to February 2018, apart from Scientific Electronic Library Online (SciELO), IBECS and IMBIOMED, which we searched in March 2018.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1) in the Cochrane Library, which contains the Developmental, Psychosocial and Learning Problems Specialised Register (searched 20 February 2018).
2. MEDLINE Ovid (1946 to February week 2 2018).
3. MEDLINE In-Process & Other Non-Indexed Citations Ovid (searched 20 February 2018).
4. MEDLINE Epub Ahead of Print Ovid (searched 20 February 2018).
5. Embase Ovid (1974 to week 8 2018).
6. CINAHL Plus EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1937 to 21 February 2018).
7. Science Citation Index Web of Science (SCI; 1970 to 20 February 2018).
8. Conference Proceedings Citation Index - Science Web of Science (CPCI-S; 1990 to 20 February 2018).
9. *Cochrane Databse of Systematic Reviews* (CDSR; 2017, Issue 12), in the Cochrane Library (searched 20 February 2018).
10. Database of Abstracts of Reviews of Effectiveness (DARE; 2015, Issue 2), in the Cochrane Library (final issue of DARE searched 13 January 2017).
11. POPLINE (www.popline.org; searched 22 February 2018).
12. SciELO (www.scielo.org/php/index.php?lang=es; searched 8 March 2018).
13. LILACS (Latin American and Caribbean Health Science Information database; lilacs.bvsalud.org/en; searched 20 February 2018).
14. IBECS (ibecs.isciii.es; searched 5 March 2018).
15. IMBIOMED (www.imbiomed.com.mx/1/1/catalogo.html; searched 10 March 2018).
16. ClinicalTrials.gov (clinicaltrials.gov; searched 22 February 2018).
17. WHO International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch; searched 22 February 2018).

See Differences between protocol and review for changes to the search methods used in this update.

Searching other resources

We contacted authors and known experts in the field for additional or unpublished data in order to identify any ongoing or unpublished studies. We also contacted the Departments of Nutrition for Health and Development, regional offices of the WHO, the nutrition section of the US Centers for Disease Control and Prevention (CDC), United Nations Children's Fund (UNICEF), the World Food Programme (WFP), the Micronutrient Initiative (MI), Helen Keller International (HKI), and the Sight and Life Foundation. In addition, we screened the reference lists of previously published reviews in order to identify other possible studies. One review author (LD-R) searched these additional sources.

Data collection and analysis

We summarised the methods that we had planned to use, as per our published protocol (Fernández-Gaxiola 2011b), but did not in Table 1. We may use these methods in future updates of this review.

Selection of studies

Using Covidence systematic review software (Covidence 2017), both reviewers (AF-G; LD-R) independently screened titles and abstracts of all records yielded by the searches against the selection criteria (Criteria for considering studies for this review), discarding those that were clearly irrelevant. Next, they both obtained the full-text reports of all relevant or potentially relevant studies that seemed to meet the inclusion criteria, and assessed them for eligibility. There were a few disagreements, due to oversights of either one of the review authors, which they resolved through discussion. We recorded the decisions of our selection process in a PRISMA diagram (Moher 2009).

Data extraction and management

Both review authors (AF-G; LD-R) independently extracted data from eligible studies using Covidence (Covidence 2017) and a form designed to collect other detailed data for this review. AF-G entered the data into Review Manager 5 (RevMan 5) (Review Manager 2014), and LD-R carried out checks for accuracy. We resolved any discrepancies through discussion. If the information regarding any of the studies was unclear, we attempted to contact the authors of the original reports, to ask them to provide further details.

We completed the data collection form electronically and recorded information (as set out below) on: study design; setting and participants (inclusion and exclusion criteria); study methods and assessment of risk of bias (see Assessment of risk of bias in included studies); intervention (for example, compound, dose, regimen, duration of intervention); outcomes (with details of how and when measured); and results.

1. Trial methods:
   i) method of allocation and unit of randomisation;
   ii) masking of participants and outcomes; and
   iii) exclusion of participants after randomisation and proportion of losses at follow-up.
2. Participants:
   i) country of origin;
   ii) sample size;
   iii) age;
   iv) sex;
   v) socioeconomic status; and
   vi) inclusion and exclusion criteria, as described under Criteria for considering studies for this review.
3. Intervention:
   i) type;

ii) dose;
iii) frequency;
iv) duration and length of time in follow-up; and
v) cointervention.

4. Control:
   i) control, placebo, or daily supplementation.
5. Outcomes:
   i) primary and secondary outcomes, as outlined under Types of outcome measures.

Assessment of risk of bias in included studies

Each reviewer independently assessed the risk of bias in each included study using a simple contingency form that followed the domain-based evaluation (sequence generation; allocation concealment; blinding; incomplete outcome data; selective reporting bias; other sources of bias), described in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) and set out in Appendix 3. If there was insufficient information to assess the risk of bias, we rated the domain at 'unclear risk of bias', until further information was published or made available to us. If there was sufficient information, we categorised the domain as being either at 'low risk of bias' or 'high risk of bias' accordingly. We resolved any disagreements by discussion.

Overall risk of bias

We summarised the risk of bias at two levels: within studies (across domains) and across studies.

For the first, we made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). With reference to the domains listed above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We considered a study to be at low risk of bias overall if it was assessed at low risk of bias for both sequence generation and allocation concealment and either blinding or incomplete outcome data.

For the second, we assessed the quality of the evidence for each individual outcome using the GRADE approach (Balshem 2010; Schünemann 2011); see 'Summary of findings' tables (beneath Data synthesis) below.

We reported the results of our assessment in the 'Risk of bias in included studies' section, in the 'Risk of bias' tables (beneath the Characteristics of included studies tables), in Summary of findings for the main comparison and Summary of findings 2, and graphically.

Measures of treatment effect

Dichotomous data

We presented dichotomous outcome data as average risk ratios (RRs) with 95% confidence intervals (CIs).

Continuous data

We presented continuous outcome data as mean differences (MD) with 95% CIs, measured at the end of the intervention. If studies did not provide this information but reported the mean change, we included these data as suggested in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). See also Table 1 and Fernández-Gaxiola 2011b.

Unit of analysis issues

Cluster-randomised studies

We included cluster-randomised studies in the analyses with individually-randomised studies; cluster-randomised studies are labelled with a (C). We estimated effective sample sizes for each one of them in order to perform correct analyses according to Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

We obtained the intra-cluster correlation coefficients (ICC) from Hall 2002 (C) (ICC = 0.0698; average cluster size (ACS) = 18.55; design effect (DE) = 2.22) and Roschnik 2003 (C) (ICC = 0.1123; ACS = 29.0, DE = 4.35), which we imputed to all cluster studies except Roschnik 2003 (C). We then calculated the ACS from the reports and estimated each study's effective sample size. Based on other reports (Okabe 2011), we assumed an average cluster size of 32 for classes, when the average cluster size or number of clusters and individuals were not clear (Agarwal 2003 (C); Soekarjo 2004 (C)). In summary, we used the following information to account for the effect clustering in the data: Jayatissa 1999 (C) (ACS = 25.6; DE = 2.71); Muro 1999 (C) (ACS = 43.1; DE = 3.94); Agarwal 2003 (C) (ACS = 32; DE = 3.16); Soekarjo 2004 (C) (ACS = 32; DE = 3.16); Mozaffari 2010 (C) (ACS = 25; DE = 2.68).

Additionally, we conducted sensitivity analyses to examine the potential effect of clustering on the CI of the summary estimates, by removing cluster-RCTs from the analyses and comparing the effects (Sensitivity analysis).

Studies with more than two treatment groups

For studies with more than two intervention groups (multi-arm studies), we included the directly relevant arms only. When we identified studies with various relevant arms, we combined the groups into a single pair-wise comparison (Higgins 2011a), and included the disaggregated data in the corresponding subgroup category. When the control group was shared by two or more study arms, we divided the control group (events and total population) over the number of relevant subgroup categories to avoid

double counting the participants. The details are described in the Characteristics of included studies tables.

Cross-over trials

As specified in our protocol (Fernández-Gaxiola 2011b), we did not include cross-over trials.

Dealing with missing data

For included studies, we noted the levels of attrition and reported it in the 'Risk of bias' tables (beneath the Characteristics of included studies tables).

We carried out analyses, as far as possible, on an intention-to-treat (ITT) basis; that is, by attempting to include all participants randomised to each group in the analyses. If this was not possible, we performed an available case analysis, in which we analysed the data for each and every participant for whom the outcome was obtained.

Assessment of heterogeneity

We assessed methodological heterogeneity by examining the risk of bias of the studies, and clinical heterogeneity by examining the similarity between the types of participants, interventions and outcomes. For statistical heterogeneity, we examined the forest plots from meta-analyses to look for heterogeneity among studies, and used the I^2 statistic, Tau^2 and Chi^2 tests as heterogeneity statistics to quantify the level of heterogeneity among the studies included in each analysis. When we identified moderate or substantial heterogeneity (I^2 greater than approximately 30%), we explored it by conducting prespecified subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

When we suspected reporting bias (see 'Selective reporting bias' under Assessment of risk of bias in included studies), we attempted to contact the study authors to ask them to provide missing outcome data. We investigated reporting biases (such as possible publication bias) using funnel plots, assessing asymmetry visually.

Data synthesis

We carried out statistical analyses using RevMan 5 (Review Manager 2014). We used random-effects meta-analyses due to possible heterogeneity in the interventions, populations and methods used in different trials. We used Mantel-Haenszel weighting for dichotomous outcomes and inverse variance for continuous outcomes, to adjust the effect measure according to the extent of its variation both between and within studies.

'Summary of findings' table

We presented the main findings of the review in 'Summary of findings' tables, which we prepared using GRADE profiler software (GRADEpro 2015). We created two 'Summary of findings' tables for both main comparisons: 1. Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo (Summary of findings for the main comparison); and 2. intermittent iron supplementation versus daily iron supplementation (Summary of findings 2). We included the following primary outcomes at the end of the intervention or at the time point closest to the end in these tables: anaemia (haemoglobin concentration below a cut-off defined by trialists); haemoglobin (g/L); iron deficiency (as defined by trialists by using indicators of iron status such as ferritin or transferrin); ferritin (µg/L); iron deficiency anaemia (defined by the presence of anaemia plus iron deficiency diagnosed with an indicator of iron status selected by trialists); all-cause morbidity (the most frequent event associated with the intervention independent of the cause, as defined by the trialists) (see Primary outcomes). We also listed estimates of relative effects along with the number of participants and studies contributing data for each outcome.

Both review authors independently assessed the quality of the evidence for each individual outcome using the GRADE approach (Balshem 2010; Schünemann 2011), which involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias. The results were expressed as one of four levels of quality (high, moderate, low, or very low).

Subgroup analysis and investigation of heterogeneity

When data were available and it was appropriate, we carried out the following subgroup analyses on three primary outcomes (anaemia, haemoglobin, and ferritin concentrations), to look for possible differences between studies (note, we pragmatically decided not to conduct subgroup analyses on those outcomes with three trials or fewer).

1. Composition: iron alone; iron + folic acid; iron + multiple micronutrients
2. Anaemia status at baseline (haemoglobin < 120 g/L, adjusted by altitude and smoking, as appropriate): anaemic; non-anaemic; mixed/unknown
3. Iron status at baseline (as defined by the trialists): iron deficient; not iron deficient; mixed/unknown
4. Dose of elemental iron per week in the intermittent group: 60 mg of iron or less; more than 60 mg of iron
5. Duration of supplementation: three months or less; more than three months
6. Malaria status of the area at the time of the trial (as reported by trialists): yes; no/unknown

We examined differences between subgroups by visual inspection of the subgroups' CI, with non-overlapping CI suggesting a sta-

tistically significant difference in treatment effect between subgroups. We also used the Borenstein 2008 approach to formally investigate differences between two or more subgroup categories.

Sensitivity analysis

We conducted sensitivity analyses ad hoc to examine the potential effect of clustering on the CI of the summary estimates, by removing cluster-RCTs from the analyses and comparing the effects (see Appendix 4). We conducted an additional sensitivity analysis ad hoc with two studies (Hall 2002 (C); Roschnik 2003 (C)), in which approximately half of the participants were young females (< 12 years of age) to see their effect on the analyses (see Effects of interventions).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

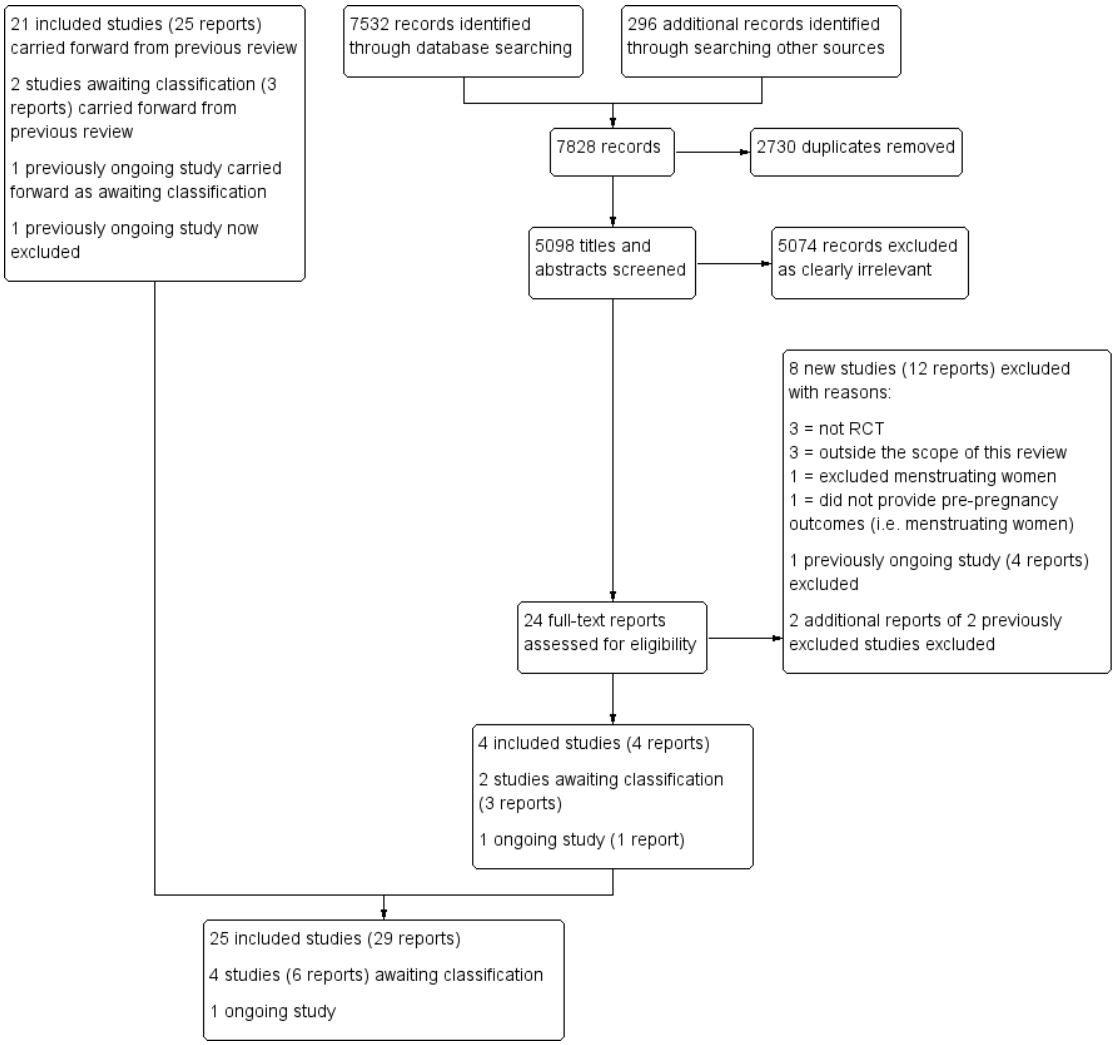
The search strategy for the first publication of this review identified 9484 records for possible inclusion, 2706 of which were duplicates. We assessed 52 full-text reports and: included 21 studies (from 25 reports); excluded 20 studies (from 24 reports); identified two studies (from three reports) as awaiting classification; and identified two ongoing studies (see Fernández-Gaxiola 2011a).

The updated search identified 7532 records through database searches and 296 additional records through searching other sources. Having removed duplicates, we screened 5098 records on the basis of title and abstract, and removed 5074 clearly ineligible records. We retrieved 24 full-text reports, which we assessed against the inclusion criteria (Criteria for considering studies for this review). We excluded 18 reports (related to: eight newly excluded studies (12 reports), two previously excluded studies (two reports), and one previously ongoing study (four reports)) from the review, and included four new studies (from four reports). We also identified two studies (from three reports) as awaiting classification (of which, one study (two reports) was previously ongoing), and one new ongoing study (from one report).

Altogether this review excluded 28 studies (from 38 reports), included 25 studies (from 29 reports), has four studies (from six reports) awaiting classification, and one ongoing study (from one report).

Figure 1 depicts the process for assessing and selecting the studies.

Figure 1. Study flow diagram.



Included studies

We included 25 studies, involving 10,996 participants, all of which met the pre-established inclusion criteria (Criteria for considering studies for this review). All studies were published between 1997 and 2018. Most studies focused on the prevention of anaemia and iron deficiency by improving iron status indicators (Primary outcomes); few studies reported data on the prespecified secondary outcomes (Secondary outcomes). See the Characteristics of included studies tables for more detail.

Settings

Studies were conducted in 15 different countries, most of them low- and middle-income countries: Bangladesh, Brazil, France, Guatemala, India, Indonesia, Iran, Kenya, Malawi, Mali, Mexico, Nepal, Pakistan, Peru, Sri Lanka and Tanzania. One study was conducted in Europe (Riuvard 2006), four in Latin America (Dos Santos 1999; Zavaleta 2000; Gonzalez-Rosendo 2002; Nguyen 2008), five in Africa (Muro 1999 (C); Beasley 2000; Hall 2002 (C); Roschnik 2003 (C); Leenstra 2009), and 15 in Asia (Angeles-Agdeppa 1997; Jayatissa 1999 (C); Kianfar 2000; Ahmed 2001; Gilgen 2001; Februhartanty 2002; Shah 2002; Agarwal 2003 (C); Shobha 2003; Soekarjo 2004 (C); Mozaffari 2010 (C); Joshi 2013; Gupta 2014; Rezaeian 2014; Jalambo 2018).

Most studies were conducted in school settings; however, five stud-

ies implemented the intervention in rural and urban communities, health centres, and villages (Dos Santos 1999; Beasley 2000; Gilgen 2001; Nguyen 2008; Joshi 2013), and one study was conducted among garment factory workers (Ahmed 2001). Five studies explicitly mentioned that they were conducted in areas with some degree of malaria endemicity (Muro 1999 (C); Beasley 2000; Februhartanty 2002; Hall 2002 (C); Leenstra 2009).

Participants

Participants' ages ranged from six (Hall 2002 (C) to 49 (Nguyen 2008) years of age. While we did not include studies specifically recruiting premenarchal girls - as these are the subject of a separate review (De-Regil 2011) - two studies recruited young females and separate data were not available for postmenarchal girls only (Hall 2002 (C); Roschnik 2003 (C)). Based on the age range reported in these studies, we assumed that at least half of the participants fulfilled our inclusion criteria and thus we decided to retain them in the review. If the disaggregated data are made available to us, we will include them in future updates of the review.

Most studies involved a mix of anaemic and non-anaemic women, with the exception of six studies that included women with mild-to-moderate anaemia (Dos Santos 1999; Ahmed 2001; Shobha 2003; Leenstra 2009; Joshi 2013; Gupta 2014), one of which, Shobha 2003, included only severely anaemic women (i.e. women with haemoglobin concentrations $\leq$ 8 g/dL). The remaining studies excluded these severely anaemic women and gave them treatment or referred them to health care (or both). Only two studies specifically included iron-deficient women (i.e. women with serum ferritin concentrations $\leq$ 15 mcg/L) (Riuvard 2006; Jalambo 2018).

Samples size varied among included studies, ranging from 24 in Riuvard 2006 to 2461 in Soekarjo 2004 (C); however, for cluster-randomised studies, the analyses only include the estimated effective sample size, after adjusting the data to account for the clustering effect.

Interventions (intermittent regimens, supplement composition and iron dose)

Intermittent regimens

Most studies provided intermittent iron supplementation once a week and compared it to control (i.e. no intervention), placebo, daily iron supplementation or other nutrients or dosages also given intermittently once a week. Five studies provided supplements twice a week compared with: once weekly supplementation (Kianfar 2000; Gupta 2014); daily supplementation (Shobha 2003; Riuvard 2006); or control (Rezaeian 2014). One study provided iron supplements three days a week and compared this with daily supplementation and placebo (Zavaleta 2000).

Duration of the intervention

Duration of the intervention varied greatly among studies. In 13 studies, women were supplemented for three months or less (Angeles-Agdeppa 1997; Dos Santos 1999; Jayatissa 1999 (C); Muro 1999 (C); Kianfar 2000; Ahmed 2001; Hall 2002 (C); Shobha 2003; Soekarjo 2004 (C); Riuvard 2006; Nguyen 2008; Joshi 2013; Jalambo 2018). The duration of the intervention was: three and a half months in three studies (Shah 2002; Agarwal 2003 (C); Roschnik 2003 (C)); four months in six studies (Beasley 2000; Zavaleta 2000; Februhartanty 2002; Gonzalez-Rosendo 2002; Mozaffari 2010 (C); Rezaeian 2014); five months in one study (Leenstra 2009); and six months in one study (Gilgen 2001). The maximum duration of supplementation was one year (Gupta 2014).

Supplements composition

In 11 studies, women were supplemented with iron only (Dos Santos 1999; Beasley 2000; Kianfar 2000; Zavaleta 2000; Gonzalez-Rosendo 2002; Shobha 2003; Riuvard 2006; Leenstra 2009; Mozaffari 2010 (C); Rezaeian 2014; Jalambo 2018). In the remaining studies, women received iron plus folic acid supplements in 10 studies (Jayatissa 1999 (C); Muro 1999 (C); Gilgen 2001; Februhartanty 2002; Hall 2002 (C); Shah 2002; Agarwal 2003 (C); Roschnik 2003 (C); Gupta 2014; Joshi 2013), iron plus multiple micronutrients supplements in two studies (Angeles-Agdeppa 1997; Nguyen 2008), and iron plus folic acid and iron plus multiple nutrients in one (Ahmed 2001) and iron plus folic acid or vitamin A or iron plus folic acid plus vitamin A in another (Soekarjo 2004 (C)).

Most studies supplemented iron with ferrous sulphate, with the exception of three studies that used ferrous fumarate (Gilgen 2001; Joshi 2013; Jalambo 2018) and one study that used ferrous chloride (Riuvard 2006). Six studies did not specify the form of iron used for supplementing women (Angeles-Agdeppa 1997; Muro 1999 (C); Agarwal 2003 (C); Shobha 2003; Nguyen 2008; Mozaffari 2010 (C)). All studies used supplements as tablets or caplets.

Iron dose

The 25 studies tested several supplemental doses of iron in the intermittent group but none of the studies exceeded 120 mg of elemental iron per week. See below.

1. 10 mg of elemental iron (one study: Rezaeian 2014)
2. 30 mg of elemental iron (one study: Mozaffari 2010 (C))
3. 50 mg of elemental iron (two studies: Kianfar 2000; Riuvard 2006)
4. 60 mg of elemental iron (seven studies: Dos Santos 1999; Jayatissa 1999 (C); Zavaleta 2000; Februhartanty 2002; Gonzalez-Rosendo 2002; Shobha 2003; Soekarjo 2004 (C))
5. 65 mg of elemental iron (five studies: Muro 1999 (C); Hall 2002 (C); Roschnik 2003 (C); Jalambo 2018)

6. 66 mg of elemental iron (one study: Gilgen 2001)
7. 70 mg of elemental iron (one study: Shah 2002)
8. 100 mg of elemental iron (three studies: Agarwal 2003 (C); Joshi 2013; Gupta 2014)
9. 120 mg of elemental iron (three studies: Beasley 2000; Ahmed 2001; Leenstra 2009)

Angeles-Agdeppa 1997 and Nguyen 2008 examined the effects of two different doses of elemental iron: 60 mg and 120 mg of elemental iron per week.

Funding sources

Five studies were partially funded (Soekarjo 2004 (C)) or fully funded by international organisations (Jayatissa 1999 (C); Gilgen 2001; Hall 2002 (C); Agarwal 2003 (C)). Four studies were partially funded by government organisations; two by the Department for International Development in the UK (Beasley 2000; Ahmed 2001) and two by the Ministry of Health within the country (Kianfar 2000; Soekarjo 2004 (C)). Four studies were funded by universities and institutes (Kianfar 2000; Shah 2002; Mozaffari 2010 (C); Rezaeian 2014), and four were partially funded by a pharmaceutical company, as they provided the supplements used (Angeles-Agdeppa 1997; Ahmed 2001; Riuvard 2006; Leenstra 2009). Two studies were partially funded by a technical collaboration (an agreement whereby a developed country agrees to provide technical assistance to a developing country) (Angeles-Agdeppa 1997; Februhartanty 2002) and two were partially funded by a foundation (Beasley 2000; Leenstra 2009). Only two studies declared no funding source was used to implement their study (Shobha 2003; Jalambo 2018). Seven studies did not provide a funding source (Dos Santos 1999; Muro 1999 (C); Zavaleta 2000; Gonzalez-Rosendo 2002; Roschnik 2003 (C); Nguyen 2008; Joshi 2013).

Excluded studies

We excluded 28 studies: 13 studies were not RCTs (Cook 1995; Jackson 2003; Siddiqui 2003; Berger 2005; Crape 2005; Horjus 2005; López de Romaña 2006; Deshmukh 2008; Vir 2008; Casey 2009; Pasricha 2009; Joseph 2013; Shah 2016); two were reviews (Beaton 1999; Dwividi 2006); one was a commentary on another study (Perrin 2002); nine compared interventions outside the scope of this review (Bruner 1996; Kätelhut 1996; Tee 1999; Viteri 1999; Ahmed 2005; Ahmed 2010; Ahmed 2012; Moretti 2015; Bansal 2016); two used a different population (Ramakrishnan 2012; Sen 2012); and one excluded postmenarchal girls because the anthelmintic drug given along with the iron supplementation was not safe in cases of pregnancy (Taylor 2001).

See the Characteristics of excluded studies tables for a detailed description of the studies and the reasons for their exclusion.

Studies awaiting classification

Four studies are awaiting classification (Olsen 2000; Sharma 2000; Brabin 2014; Malhotra 2013); two of these four RCTs are from Africa (Olsen 2000; Brabin 2014) and the other two are from India (Sharma 2000; Malhotra 2013). Olsen 2000 compared the efficacy of twice-weekly iron supplementation versus placebo. Brabin 2014 compared the efficacy of once-weekly iron-folate supplementation versus folate (control). Sharma 2000 compared the efficacy of once-weekly versus daily iron and folic acid supplementation plus the effect of added ascorbic acid on the efficacy of iron-folate supplementation. Malhotra 2013 compared the efficacy of twice-weekly iron-folate supplementation versus control versus twice-weekly iron-folate supplementation plus the effect of nutrition education versus nutrition education only on haematological status. The dosages of elemental iron used in the studies were: 60 mg in Olsen 2000 and Malhotra 2013, 100 mg in Sharma 2000, and unclear for Brabin 2014.

We were unable to extract data for our outcomes from Olsen 2000 as the data were not disaggregated by sex, or from Sharma 2000 as the data were categorised by percentages. Malhotra 2013 was only available as an abstract and did not provide data for our comparisons. The Brabin 2014 report included only the qualitative part of the RCT and was missing the quantitative part for our meta-analysis. In addition, the participants in Brabin 2014 were young women enrolled prior to their first pregnancy, and more information is needed to clarify the study's eligibility for inclusion in the review.

Ongoing studies

We found one ongoing study from India (CTRI/2017/11/010453). This study is comparing the efficacy of once-a-week versus daily iron supplementation at controlling anaemia in adolescent school girls aged 12 to 16 years with anaemia. The trial will provide 60 mg of elemental iron for three months. Recruitment has been completed and some results have been already published. See Characteristics of ongoing studies table.

Risk of bias in included studies

Overall, many included studies did not describe study methods completely, which made it difficult to assess risk of bias. We contacted some study authors for support and are still awaiting a reply at the time of publication of this review. With the exception of two studies (Hall 2002 (C); Nguyen 2008), we considered all of the studies included in this update to be at high risk of bias (or of low quality).

See the 'Risk of bias' tables (under the Characteristics of included studies tables) for an assessment of the risk of bias of each included trial, and Figure 2 and Figure 3 for an overall graphical summary of the risk of bias of all included trials. In the 'Summary of findings' tables, we presented the overall quality of the evidence for each

primary outcome, by comparison (Summary of findings for the main comparison; Summary of findings 2).

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

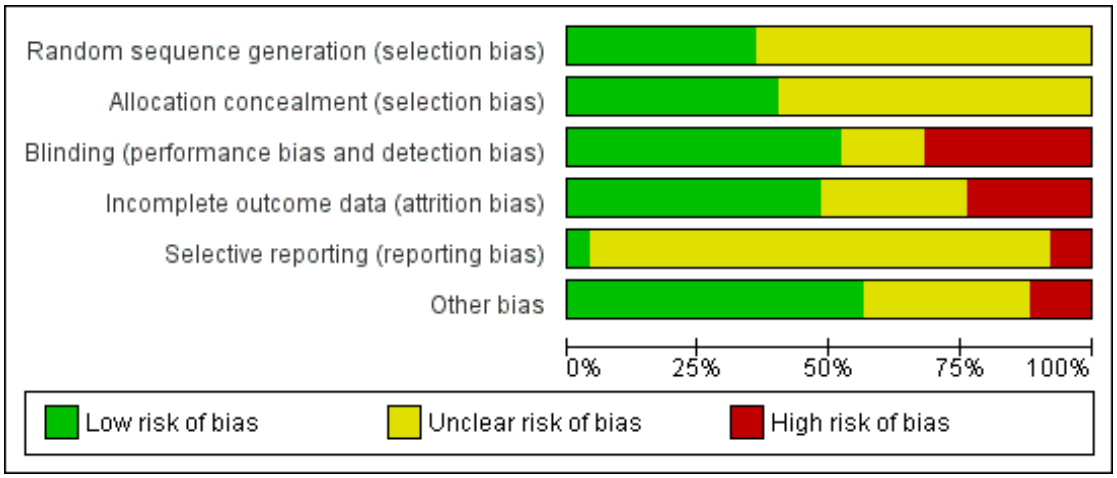
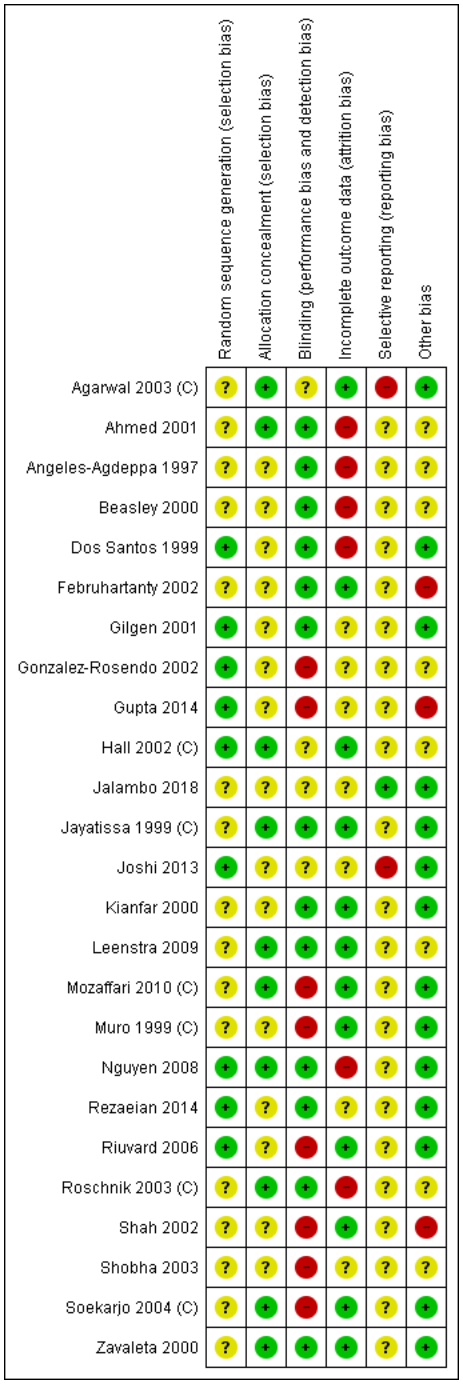


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

Nine studies adequately randomised the participants to the intervention group (Dos Santos 1999; Gilgen 2001; Gonzalez-Rosendo 2002; Hall 2002 (C); Riuvard 2006; Nguyen 2008; Joshi 2013; Gupta 2014; Rezaeian 2014). Of these nine studies, four used a random number generator (Gilgen 2001; Gonzalez-Rosendo 2002; Hall 2002 (C); Nguyen 2008), one used drawing of lots (Dos Santos 1999), one used a randomisation table (Riuvard 2006), one used a generated block (Joshi 2013), one used a lottery method (Gupta 2014), and another used a simple draw (Rezaeian 2014).

Sixteen studies did not state the method used to generate the random sequence clearly, so we rated these at unclear risk of bias (Angeles-Agdeppa 1997; Jayatissa 1999 (C); Muro 1999 (C); Beasley 2000; Kianfar 2000; Zavaleta 2000; Ahmed 2001; Februhartanty 2002; Shah 2002; Agarwal 2003 (C); Roschnik 2003 (C); Shobha 2003; Soekarjo 2004 (C); Leenstra 2009; Mozaffari 2010 (C); Jalambo 2018).

Allocation concealment

Ten studies reported adequate allocation concealment (Jayatissa 1999 (C); Zavaleta 2000; Ahmed 2001; Hall 2002 (C); Agarwal 2003 (C); Roschnik 2003 (C); Soekarjo 2004 (C); Nguyen 2008; Leenstra 2009; Mozaffari 2010 (C)). Of these 10 studies, three kept the code secure until all data were entered into the computer (Ahmed 2001) or until after study completion (Nguyen 2008; Leenstra 2009), and seven were randomised at cluster level and we considered that the risk of selection bias at the individual level was unlikely (Jayatissa 1999 (C); Zavaleta 2000; Hall 2002 (C); Agarwal 2003 (C); Roschnik 2003 (C); Soekarjo 2004 (C); Mozaffari 2010 (C)).

In 15 studies, the method used to conceal the allocation was unclear or not mentioned (Angeles-Agdeppa 1997; Dos Santos 1999; Muro 1999 (C); Beasley 2000; Kianfar 2000; Gilgen 2001; Februhartanty 2002; Gonzalez-Rosendo 2002; Shah 2002; Shobha 2003; Riuvard 2006; Joshi 2013; Gupta 2014; Rezaeian 2014; Jalambo 2018).

Blinding

We rated 13 studies at low risk of performance and detection bias (Angeles-Agdeppa 1997; Dos Santos 1999; Jayatissa 1999 (C); Beasley 2000; Kianfar 2000; Zavaleta 2000; Ahmed 2001; Gilgen 2001; Februhartanty 2002; Roschnik 2003 (C); Leenstra 2009; Nguyen 2008; Rezaeian 2014). Of these 13 studies, nine were described as being single or double blinded (Angeles-Agdeppa 1997; Dos Santos 1999; Jayatissa 1999 (C); Beasley 2000; Zavaleta 2000; Ahmed 2001; Gilgen 2001; Februhartanty 2002; Nguyen 2008), and of these nine, five specified that the placebos were of identical appearance (Angeles-Agdeppa 1997; Jayatissa 1999 (C); Zavaleta 2000; Nguyen 2008; Gilgen 2001). Four studies did not mention or describe blinding in the study, so we rated them at unclear risk of performance and detection bias (Hall 2002 (C); Agarwal 2003 (C); Joshi 2013; Jalambo 2018). We rated eight studies at high risk of performance and detection bias because participants, personnel and outcome assessors seemed to be aware of the treatments (Muro 1999 (C); Gonzalez-Rosendo 2002; Shah 2002; Shobha 2003; Soekarjo 2004 (C); Riuvard 2006; Mozaffari 2010 (C); Gupta 2014).

Incomplete outcome data

Loss to follow-up varied greatly among studies, from 1% in Agarwal 2003 (C) to 41% in Roschnik 2003 (C). We rated six studies, which lost more than 20% of randomised participants or had imbalanced losses between study groups (or both), at high risk of attrition bias (Angeles-Agdeppa 1997; Dos Santos 1999; Beasley 2000; Ahmed 2001; Roschnik 2003 (C); Nguyen 2008). We judged a further seven studies, which did not mention attrition making it difficult to judge whether the lack of data were due to no losses to follow-up or to incomplete reporting, at unclear risk of attrition bias (Gilgen 2001; Gonzalez-Rosendo 2002; Shobha 2003; Joshi 2013; Gupta 2014; Rezaeian 2014; Jalambo 2018). We considered the remaining 12 studies to be at low risk of attrition bias (Jayatissa 1999 (C); Muro 1999 (C); Kianfar 2000; Zavaleta 2000; Februhartanty 2002; Hall 2002 (C); Shah 2002; Agarwal 2003 (C); Soekarjo 2004 (C); Riuvard 2006; Leenstra 2009; Mozaffari 2010 (C)).

Selective reporting

Although it was difficult to assess reporting bias, because we did not have access to study protocols, we did not find a clear indication of reporting or publication bias by assessing funnel plot asymmetry visually.

Of the 25 included studies, we rated 22 at unclear risk of reporting bias. We rated one study at low risk of reporting bias because there was apparently no selective reporting (Jalambo 2018). We considered two studies to be at high risk of reporting bias (Agarwal 2003 (C); Joshi 2013). In Agarwal 2003 (C), data for plasma ferritin concentrations were estimated only in some girls and it was unclear how the selection was made. In Joshi 2013, there was missing information on compliance at the individual level that was recorded through home visits and postintervention interviews.

Other potential sources of bias

We rated 14 studies, which appeared to be free of other sources of bias, at low risk of other bias (Dos Santos 1999; Jayatissa 1999 (C); Muro 1999 (C); Kianfar 2000; Zavaleta 2000; Gilgen 2001; Agarwal 2003 (C); Soekarjo 2004 (C); Riuvard 2006; Nguyen 2008; Mozaffari 2010 (C); Joshi 2013; Rezaeian 2014; Jalambo 2018).

We rated eight studies at unclear risk of other sources of bias (Angeles-Agdeppa 1997; Beasley 2000; Ahmed 2001; Gonzalez-Rosendo 2002; Hall 2002 (C); Roschnik 2003 (C); Shobha 2003; Leenstra 2009). In Angeles-Agdeppa 1997, the intervention was unsupervised during the four-week period, as the supplements were provided on a take-home basis. In Beasley 2000, the control group was given vitamin B12, which could have potentially impacted anaemia status. Ahmed 2001 had some variability in the administration of the supplements depending on the factory (i.e. supplements were given before versus after lunch, with an empty stomach versus having eaten little). In Roschnik 2003 (C), the results were affected by a famine in Malawi at the time of the trial. In Angeles-Agdeppa 1997, Gonzalez-Rosendo 2002, Hall 2002 (C) and Shobha 2003, the distribution of anaemia was not shown. In Leenstra 2009, most of the results for the four randomised groups were presented in graphs that were difficult to interpret (and consequently have not been included in our Data and analyses tables), and data on several outcomes were described as non-significant but were not shown (side effects, including vomiting and diarrhoea).

We rated three studies at high risk of other sources of bias (Februhartanty 2002; Shah 2002; Gupta 2014). In Februhartanty 2002, there was a higher prevalence of anaemia in the group that received supplements weekly. In Shah 2002, the daily group were not explicitly supervised while those in the weekly group were supervised. Finally, Gupta 2014 had missing information on side effects that were recorded by the intervention group.

Effects of interventions

See: **Summary of findings for the main comparison** Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo in menstruating women; **Summary of findings 2** Intermittent iron supplementation versus daily iron supplementation in menstruating women

The summary of results is organised by comparisons. In the analyses, we have provided overall totals along with subtotals for subgroups and the statistics for subgroup differences. See the Data and analyses section for detailed results on primary and secondary outcomes.

Intermittent supplementation of iron (alone or plus any other micronutrients) versus no supplementation or placebo

Eighteen studies involving 8988 women examined intermittent iron supplementation versus no supplementation or placebo (Angeles-Agdeppa 1997; Muro 1999 (C); Jayatissa 1999 (C); Beasley 2000; Kianfar 2000; Zavaleta 2000; Ahmed 2001; Gilgen 2001; Februhartanty 2002; Hall 2002 (C); Shah 2002; Agarwal 2003 (C); Roschnik 2003 (C); Soekarjo 2004 (C); Leenstra 2009; Mozaffari 2010 (C); Rezaeian 2014; Jalambo 2018). Nine of these studies met the prespecified criteria mentioned above (see Assessment of risk of bias in included studies) for being at lower risk of bias.

Primary outcomes

Anaemia

Eleven studies reported data on this outcome (Angeles-Agdeppa 1997; Jayatissa 1999 (C); Muro 1999 (C); Zavaleta 2000; Ahmed 2001; Hall 2002 (C); Shah 2002; Agarwal 2003 (C); Roschnik 2003 (C); Soekarjo 2004 (C); Mozaffari 2010 (C)). We pooled these studies in a meta-analysis and found evidence that women receiving intermittent supplementation were less likely to have anaemia at the end of the intervention than those women who received no intervention or placebo (RR 0.65, 95% CI 0.49 to 0.87; 3135 participants; Analysis 1.1). However, treatment effect sizes varied between studies (T^2 = 0.16; Chi^2 = 58.75 (P < 0.001); I^2 = 83%).

We conducted a subgroup analysis and found no evidence to suggest that the composition of the supplement (iron only, iron plus folic acid, or iron plus any other micronutrients) affected anaemia (Analysis 1.2). However, we did find evidence that mixed/unknown anaemic women in the intervention group were less likely to have anaemia than anaemic women in the intervention group (RR 0.71, 95% CI 0.55 to 0.93; 2913 participants; Analysis 1.3; Test for subgroup differences: Chi^2 = 9.38 (P = 0.002); I^2 = 89.3%). All studies reported iron status as mixed/unknown at baseline so we were not able to conduct subgroup analysis (Analysis 1.4). In further subgroup analyses, we found no evidence to suggest that dose of elemental iron per week in the intervention group (Analysis 1.5), duration of supplementation (Analysis 1.6), or malaria endemicity at the time when the study was conducted (Analysis 1.7) affected anaemia. There was a high level of heterogeneity between the studies in these analyses (between 79% and 84%). We rated the quality of this evidence as low.

Haemoglobin

Fifteen studies examined haemoglobin concentrations (Angeles-Agdeppa 1997; Jayatissa 1999 (C); Beasley 2000; Kianfar 2000; Ahmed 2001; Gilgen 2001; Februhartanty 2002; Hall 2002 (C); Roschnik 2003 (C); Agarwal 2003 (C); Soekarjo 2004 (C); Leenstra 2009; Mozaffari 2010 (C); Rezaeian 2014; Jalambo 2018). We pooled these studies in a meta-analysis and found evidence that women receiving iron supplements intermittently had 5.19 more grams of haemoglobin per litre (95% CI 3.07 to 7.32;

2886 participants; Analysis 1.8), than those who received no intervention or a placebo. Again, treatment effect sizes varied between studies (T^2 = 14.01; Chi^2 = 87.02 (P < 0.001); I^2 = 84%).

We conducted subgroup analyses and found no evidence to suggest that the composition of the supplement (iron only, iron plus folic acid, or iron plus any other micronutrients) (Analysis 1.9), or anaemia status at baseline (anaemic status before the supplementation) (Analysis 1.10) affected haemoglobin. Not enough studies contributed data for the analysis on women's iron status at baseline (iron deficiency before the supplementation) so that most women had a mixed/unknown iron status (Analysis 1.11). In further subgroup analyses, we found no evidence to suggest that dose of elemental iron per week in the intervention group (Analysis 1.12), duration of supplementation (Analysis 1.13), or malaria endemicity at the time when the study was conducted (Analysis 1.14) affected haemoglobin. There was a high level of heterogeneity between the studies in these analyses (around 85%). We rated the quality of this evidence as moderate.

Iron deficiency

Three studies reported data on iron deficiency (Angeles-Agdeppa 1997; Ahmed 2001; Mozaffari 2010 (C)). We pooled these studies in a meta-analysis and found no evidence that iron deficiency differed between the groups (RR 0.50, 95% CI 0.24 to 1.04; 624 participants; Analysis 1.15). The heterogeneity was high but the directions of the results were consistent (T^2 = 0.36, Chi^2 = 17.52 (P < 0.001); I^2 = 89%) . We rated the quality of this evidence as low.

Ferritin

Seven studies examined ferritin concentrations (Angeles-Agdeppa 1997; Beasley 2000; Ahmed 2001; Gilgen 2001; Februhartanty 2002; Mozaffari 2010 (C); Jalambo 2018). We pooled these studies in a meta-analysis and found evidence in favour of the intervention group (MD 7.46 μg/L, 95% CI 5.02 to 9.90; 1067 participants, Analysis 1.16). The heterogeneity was moderate (T^2 = 4.10; Chi^2 = 10.94 (P = 0.09); I^2 = 45%). We rated the quality of this evidence as low.

We conducted subgroup analyses and found no evidence to suggest that the composition of the supplement (iron only, iron plus folic acid, or iron plus any other micronutrients) (Analysis 1.17) or anaemic status at baseline (Analysis 1.18) affected ferritin. Not enough studies contributed data for the analysis on women's iron status at baseline (iron deficiency before the supplementation) so that most women had a mixed/unknown iron status (Analysis 1.19). In further subgroup analyses, we found no evidence to suggest that dose of elemental iron per week in the intervention group (Analysis 1.20), duration of supplementation (Analysis 1.21), or malaria endemicity at the time when the study was conducted (Analysis 1.22) affected ferritin.

Iron deficiency anaemia

A single study reported data on this outcome (Mozaffari 2010 (C)). It found no difference in iron deficiency anaemia between those women who received iron supplements intermittently and those women who did not receive iron (RR 0.07, 95% CI 0.00 to 1.16; 97 participants; see the illustrative forest plot in Analysis 1.23). We rated the quality of this evidence as low.

All-cause morbidity

A single study reported data on this outcome (Beasley 2000). It found no difference in all-cause morbidity between those women who received iron supplements intermittently and those who women did not receive iron (RR 1.12, 95% 0.82 to 1.52; 119 participants; see the illustrative forest plot in Analysis 1.24). We rated the quality of this evidence as low.

Secondary outcomes

Diarrhoea

A single study reported data on diarrhoea (Angeles-Agdeppa 1997). It found no evidence that diarrhoea differed between the groups (RR 0.28, 95% CI 0.05 to 1.49; 209 participants; see the illustrative forest plot in Analysis 1.25).

Any adverse side effects

Three studies examined any adverse side effects (Angeles-Agdeppa 1997; Gilgen 2001; Leenstra 2009). We pooled these studies in a meta-analysis and found no evidence that adverse side effects differed between the groups (RR 1.98, 95% CI 0.31 to 12.72; 630 participants; Analysis 1.26).

Adherence

Two studies examined adherence (Zavaleta 2000; Ahmed 2001). We pooled these studies in a meta-analysis and found no evidence that women receiving iron supplements intermittently adhered to the intervention better than those women who did not receive iron (RR 0.99, 95% CI 0.96 to 1.02; 417 participants; Analysis 1.27).

Malaria outcomes

Two studies reported data on malaria outcomes (Beasley 2000; Leenstra 2009). We pooled these studies in a meta-analysis and found no evidence that the prevalence (Analysis 1.28) and incidence Analysis 1.29) of parasitaemia, prevalence of high-density parasitaemia (Analysis 1.30), and clinical malaria (Analysis 1.31) differed between those women who received iron supplements intermittently and those women who did not receive iron.

No studies reported on our other prespecified secondary outcomes: respiratory infections; school performance and cognitive function; or depression.

Sensitivity analyses

We conducted sensitivity analyses by reanalysing the data for anaemia, haemoglobin, iron deficiency and ferritin with cluster-RCTs excluded (Jayatissa 1999 (C); Muro 1999 (C); Hall 2002 (C); Agarwal 2003 (C); Roschnik 2003 (C); Soekarjo 2004 (C); Mozaffari 2010 (C), and found no significant differences in the results. See Appendix 4.

In two studies (Hall 2002 (C); Roschnik 2003 (C)), approximately half of the participants (276 participants and 376 participants, respectively) were young females (< 12 years of age). We conducted a sensitivity analysis ad hoc and found that excluding these studies changed the estimate for anaemia from RR 0.65 (95% CI 0.49 to 0.87) to RR 0.58 (95% CI 0.40 to 0.86; results not shown), and haemoglobin from MD 5.19 g/L (95% CI 3.07 to 7.32) to MD 5.67 g/L (95% CI 3.37 to 7.97; results not shown). As the interpretation of our results did not change, we decided to retain these trials in our analyses and thus minimise the risk of publication bias.

Intermittent iron supplementation versus daily iron supplementation

We included 13 studies involving 6213 women in this comparison (Angeles-Agdeppa 1997; Dos Santos 1999; Jayatissa 1999 (C); Kianfar 2000; Zavaleta 2000; Gonzalez-Rosendo 2002; Shah 2002; Agarwal 2003 (C); Shobha 2003; Riuvard 2006; Nguyen 2008; Joshi 2013; Gupta 2014). We considered only two of these studies to be at higher risk of bias overall (Shah 2002 and Gupta 2014) and six of these to be at lower risk of bias overall (Jayatissa 1999 (C); Kianfar 2000; Zavaleta 2000; Gonzalez-Rosendo 2002; Soekarjo 2004 (C); Nguyen 2008.

Primary outcomes

Anaemia

Eight studies reported data on this outcome (Angeles-Agdeppa 1997; Dos Santos 1999; Jayatissa 1999 (C); Zavaleta 2000; Gonzalez-Rosendo 2002; Shah 2002; Agarwal 2003 (C); Joshi 2013). We pooled these studies in a meta-analysis and found evidence that women receiving iron supplements daily were as likely to have reduced anaemia at the end of the intervention as those women receiving iron supplements intermittently (RR 1.09, 95% CI 0.93 to 1.29; 1749 participants; Analysis 2.1). The heterogeneity was low (T^2 = 0.01; Chi^2 = 7.93 (P = 0.34); I^2= 12%). We rated the quality of this evidence as moderate.

We conducted subgroup analyses and found no evidence to suggest that the composition of the supplement affected anaemia (Analysis 2.2). We found inconclusive results that anaemia status at baseline (anaemia status before the supplementation) affected anaemia (Analysis 2.3), and no studies reported data for the analysis exploring the effects of iron status at baseline (Analysis 2.4). Almost an even number of studies provided 60 mg of elemental iron or less per week (four studies) or more than 60 mg of elemental iron per week (five studies), and we found no evidence to suggest that the dose in the intervention group affected anaemia (Analysis 2.5). In further subgroup analyses, we found no evidence to suggest that the duration of the intervention (Analysis 2.6) or the malaria endemicity at the time when the study was conducted (Analysis 2.7) affected anaemia.

Haemoglobin

Ten studies reported data on this outcome (Angeles-Agdeppa 1997; Dos Santos 1999; Jayatissa 1999 (C); Kianfar 2000; Gonzalez-Rosendo 2002; Agarwal 2003 (C); Shobha 2003; Riuvard 2006; Joshi 2013; Gupta 2014). We pooled these studies in a meta-analysis and found no evidence that mean haemoglobin concentrations differed between women receiving intermittent iron supplementation and women receiving daily iron supplementation (MD 0.43, 95% CI −1.44 to 2.31; 2127 participants; Analysis 2.8). The level of heterogeneity was high (T^2 = 6.45; Chi^2 = 40.60 (P < 0.001); I^2 = 78%). We rated the quality of the evidence as low.

We conducted subgroup analyses and found no evidence that the composition of the supplement (iron only, iron plus folic acid, or iron plus other micronutrients) affected haemoglobin (Analysis 2.9). However, we did find evidence that anaemic women had a stronger response to intermittent supplementation than women with mixed/unknown anaemia status (MD 0.43, 95% CI -1.44 to 2.31; 804 participants; Analysis 2.10), but only four studies contributed to this analysis so the results should be interpreted with caution. Not enough studies contributed data for the analysis on women's iron status at baseline (iron deficiency before the supplementation) so that most women had a mixed/unknown iron status (Analysis 2.11). Almost an even number of studies provided 60 mg of elemental iron or less per week (six studies) and more than 60 mg of iron per week (five studies); there was no statistical difference between the groups. In Angeles-Agdeppa 1997, women who received 60 mg or less intermittently showed higher haemoglobin concentrations than women who received higher doses (Analysis 2.12). We found no evidence of any subgroup differences by duration of the intervention (Analysis 2.13) or malaria endemicity at the time when the study was conducted (Analysis 2.14). There was substantial heterogeneity between the studies in these analyses (between 76% and 80%).

Iron deficiency

Only a single study reported data on this outcome (Angeles-Agdeppa 1997). It found no evidence that iron deficiency differed between the groups (RR 4.30, 95% CI 0.56 to 33.20; 198 participants; see the illustrative forest plot in Analysis 2.15). We rated the quality of this evidence as very low.

Ferritin

Four studies reported data on this outcome (Angeles-Agdeppa 1997; Agarwal 2003 (C); Riuvard 2006; Gupta 2014). We pooled these studies in a meta-analysis and found evidence that women receiving iron supplements daily had higher concentrations of ferritin at the end of the intervention than those women receiving iron supplements intermittently (MD −6.07 μg/L, 95% CI −10.66 to −1.48; 988 participants; Analysis 2.16). The heterogeneity was high (T^2 = 15.55; Chi^2 = 33.80 (P < 0.001); I^2= 91%). We rated the quality of this evidence as very low.

We found statistical differences in all subgroup analyses: daily supplementation was more effective than intermittent supplementation at increasing ferritin concentrations in women regardless of the composition of the supplement (Analysis 2.21), anaemia (Analysis 2.18) or iron status at baseline (Analysis 2.19), dose of elemental iron (Analysis 2.20), duration of supplementation (Analysis 2.17), or malaria endemicity at the time when the study was conducted (Analysis 2.22). However, it should be noted that most subgroups had only one study or included all four studies in the same subgroup, or had no studies, and that there was substantial heterogeneity between studies in these analyses (between 74.4% and 91%). Therefore, results were inconclusive and should be interpreted with caution.

None of the included studies reported data on the other prespecified primary outcomes: iron-deficiency anaemia and all-cause morbidity.

Secondary outcomes

Diarrhoea

Only a single study reported data on this outcome (Angeles-Agdeppa 1997). It found no evidence that diarrhoea differed between the groups (RR 2.41, 95% CI 0.12 to 49.43; 198 participants; see the illustrative forest plot in Analysis 2.23).

Any adverse side effects

Six studies reported data on this outcome (Angeles-Agdeppa 1997; Jayatissa 1999 (C); Shobha 2003; Nguyen 2008; Joshi 2013; Gupta 2014). We pooled these studies in a meta-analysis and found evidence that women receiving iron supplements intermittently were less likely to have any adverse side effects than those women receiving iron supplements daily (RR 0.41, 95% CI 0.21 to 0.82; 1166 participants; Analysis 2.24).

Depression

Only a single study reported data on this outcome (Nguyen 2008). It found no evidence that depression differed between the groups (RR 0.82, 95% CI 0.63 to 1.07; 369 participants; see the illustrative forest plot in Analysis 2.25).

Adherence

Four studies reported data on this outcome (Dos Santos 1999; Gonzalez-Rosendo 2002; Shah 2002; Riuvard 2006). We pooled these studies in a meta-analysis and found no evidence that adherence to intermittent supplementation differed from that for daily supplementation (RR 1.04, 95% CI 0.99 to 1.09; 507 participants; Analysis 2.26).

None of the included studies reported data on the other prespecified secondary outcomes: respiratory infections; work performance and economic productivity; school performance and cognitive function; and malaria incidence and severity.

Sensitivity analyses

We conducted sensitivity analyses to examine the potential effect of clustering on the CI of the summary estimates, by removing cluster-RCTs from the analysis and comparing the effect for anaemia, haemoglobin, and ferritin. We found no significant differences in the results. See Appendix 4.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Intermittent iron supplementation versus daily iron supplementation in menstruating women

Patient or population: adolescent and adult menstruating women
Setting: community settings
Intervention: intermittent iron supplementation alone or with any other micronutrients
Comparison: daily iron supplementation alone or with any other micronutrients

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with daily iron supplementation	Risk with intermittent iron supplementation				
Anaemia (haemoglobin concentration below a cut-off defined by the trialists, adjusted by altitude and smoking as appropriate) Follow-up: range 2 months to 4 months	**Study population**		**RR 1.09** (0.93 to 1.29)	1749 (8 studies)	⊕⊕⊕◯ **Moderate**[a]	Includes two cluster-randomised trials*[b]
	23 per 100	**25 per 100** (22 to 30)				
Haemoglobin (g/L) Follow-up: range 2 months to 1 year	The mean haemoglobin g/L in the control groups ranged from **7.40 g/L to 132.00 g/L**	The mean haemoglobin g/L in the intervention groups was **0.43 g/L higher** (1.44 lower to 2.31 higher)	-	2127 (10 studies)	⊕⊕◯◯ **Low**[c]	Includes two cluster-randomised trials*[b]
Iron deficiency (as defined by the trialists using indicators of iron status such as ferritin or transferrin) Follow-up: mean 3 months	**Study population**		**RR 4.30** (0.56 to 33.20)	198 (1 study)	⊕◯◯◯ **Very low**[d]	-

	2 per 100	**7 per 100** (1 to 52)				
Ferritin (µg/L) Follow-up: range 2 months to 1 year	The mean ferritin µg/L in the control groups ranged from **16.70 µg/L to 62.00 µg/L**	The mean ferritin µg/L in the intervention groups was **6.07 µg/L lower** (10.66 lower to 1.48 lower)	-	988 (4 studies)	⊕⊕◯◯ **Low**[e]	Includes one cluster-randomised trial[b]
Iron deficiency anaemia (as defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by the trialists)	Not estimable		-	(0 studies)	-	-
All-cause morbidity (the most frequent event associated with the intervention, independent of the cause, as defined by the trialists)	Not estimable		-	(0 studies)	-	-
Any adverse side effects	**29 per 100**	**2 per 100** (6 to 24)	**RR 0.41** (0.21 to 0.82)	1166 (6 studies)	⊕⊕⊕◯ **Low**[f]	Includes one cluster-randomised trial[b]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level due to study limitations (in several trials the method of allocation concealment was not clear and there was a lack of blinding) (I^2 = 12%).

[b] For cluster-randomised studies (C), the analyses only include the estimated effective sample size, after adjusting the data to account for the clustering effect.

[c] Downgraded two levels due to inconsistency (in the direction of the effect and the CI of some of the included studies cross the line of no effect, and high heterogeneity) (I^2 = 78%).

[d] Downgraded two levels due to imprecision (only one study with 25 losses to follow-up reported data on this outcome; wide CI) and one level for study limitations (concerns about attrition) (I^2 = not estimable).

[e] Downgraded two levels due to inconsistency (in the direction of the effect and the CI of some of the included studies cross the line of no effect, and high heterogeneity) (I^2 = 91%).

[f] Downgraded two levels due to inconsistency (in the direction of the effect and the CI of some of the included studies cross the line of no effect, and high heterogeneity) (I^2 = 82%).

DISCUSSION

Summary of main results

Available data indicate that, among menstruating women, intermittent oral supplementation with iron (alone or plus any other nutrients) increases haemoglobin and ferritin concentrations and reduces the prevalence of anaemia compared to no supplementation or placebo. Overall, this positive response does not differ when providing iron supplementation weekly or twice weekly; nor does it differ with the duration of the intervention, dose used, or malaria endemicity. As the quality of the evidence was, on average, low, the confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect.

Compared with daily supplementation, findings suggest that intermittent supplementation has a similar effect in reducing the prevalence of anaemia and increasing haemoglobin concentrations at the end of the intervention. However, information from a fewer number of trials shows that women receiving intermittent supplementation are more likely to have lower ferritin concentrations and fewer side effects at the end of the intervention. As the quality of the evidence was also, on average, low, the confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect.

Information on morbidity (including malaria outcomes), work performance and economic productivity, depression, and adherence to the intervention was scarce, but, thus far, there is no evidence that intermittent supplementation has any effect on these outcomes, either when compared with a placebo, no intervention, or with daily iron supplementation. There were no data for the subgroup analysis of the effect of iron status at baseline on anaemia for intermittent iron supplementation compared to placebo or no intervention; and, for the other outcomes, there was only one trial.

Overall completeness and applicability of evidence

This review included a total of 25 RCTs involving 10,996 women; most of them were conducted in low- and middle-income countries in Latin America, Africa, and Asia where anaemia is a public health problem. The overall quality of the evidence was, on average, low, and the main limitation of the studies was the lack of blinding and high attrition.

Intermittent iron supplementation regimens have been proposed as an efficacious and efficient approach to the prevention and control of anaemia and at least 100 studies on intermittent iron supplementation regimens in different age groups have been published during the last 15 years. Although the real effect of an intervention is context-specific, the results of this review showed that weekly or twice weekly iron supplementation regimens are effective in reducing the prevalence of anaemia and improving haemoglobin and ferritin concentrations in menstruating women in comparison with no supplementation or placebo. There was insufficient information to assess with certainty the effect of this intervention on other health and nutrition outcomes.

The results suggest that the provision of supplements once a week with 60 mg to 120 mg of iron is enough to produce a positive haematological response in populations with different degrees of anaemia. The efficacy of this intervention to treat anaemia was similar to the efficacy of daily supplementation. Furthermore, in all of the studies in which anaemia was an inclusion criterion, there was a higher increase in haemoglobin concentrations among women who received supplements intermittently. This finding was true even in different settings and with different levels of supervision. Folic acid merits a special mention, as its consumption did not have a differential effect on anaemia and haemoglobin concentrations; however, its use during the periconceptional period has been proven to reduce the risk of having babies with NTDs, an outcome that was outside the scope of this review (De-Regil 2015).

According to our review, daily supplementation was more effective at increasing ferritin concentrations, compared with the provision of supplements once or twice a week. This may have implications for the use of intermittent iron supplementation regimens in populations with a high prevalence of iron deficiency where increasing ferritin concentrations are needed.

Although improved adherence and fewer side effects have been proposed as an advantage of intermittent supplementation over daily supplementation, there is no evidence that in relatively well-controlled environments and for short periods of supplementation, women adhere better to intermittent regimens. However, there was no difference when women were compared with those receiving a placebo either. Clearly, there are gaps on how the duration, frequency and intensity of side effects affect short- and long-term adherence to supplementation.

One study (459 participants) reported on the incidence of hospitalisation (Nguyen 2008) and one study (24 participants) reported on oxidative stress post-supplementation (expressed as the Ferric Reducing Ability of the Plasma or FRAP) (Riuvard 2006). These studies found no evidence that the effects of intermittent supplementation on these indicators were different from that produced by daily supplementation. None of the other included studies reported data on these outcomes.

Quality of the evidence

We found the overall quality of the available evidence ranged between moderate to low in comparison 1 and comparison 2, both primarily due to substantial heterogeneity, risk of bias, and methodological inconsistency. Most outcomes with very low quality evidence have only one included study.

Study limitations/risk of bias in included studies

With the exception of two studies (Hall 2002 (C); Nguyen 2008), we considered all of the studies included in this update to be at high risk of bias (see Risk of bias in included studies; Figure 2; Figure 3). Most studies did not describe the methods used to randomly assign participants and conceal allocation. Generally, blinding of participants, care providers and outcome assessors was not attempted, although some studies reported that technical staff carrying out laboratory investigations were unaware of group allocation. This lack of blinding could represent a potentially serious source of bias. Inconsistency was also a problem in many of these studies.

Inconsistency

We considered that clinical inconsistency was unlikely for our outcomes. Variability in participants characteristics, interventions, and outcomes across the included studies was likely to be low (Ryan 2016). However, methodological inconsistency was a potentially important factor in the overall assessment of evidence for our outcomes. We found differences between studies in terms of methodological factors, specifically blinding and allocation concealment, that may have led to differences in the observed intervention effects (Higgins 2011a). We found substantial heterogeneity in some outcomes, especially anaemia and haemoglobin, that could be partly explained by subgroup analyses. Although this does not necessarily mean that the true intervention effect varies, results should be interpreted with some caution.

Imprecision

Imprecision due to small sample sizes or few events in the included studies was unlikely. However, we considered imprecision in continuous outcomes (i.e. haemoglobin and ferritin measurements) an important factor in the overall assessment of the evidence. There was a lot of variation in the effects of the intervention among participants for continuous outcomes, as results showed wide CIs around the effect estimate (Ryan 2016).

Indirectness

We considered that indirectness was unlikely. We found no indirectness regarding population, interventions, or outcomes assessed across studies. The study populations paralleled those of clinical and public health interest under real conditions. The evidence summarised in the review comes from studies addressing the main review questions, especially for our primary outcomes; and our secondary outcomes were almost not addressed.

Publication bias

We considered that publication bias was unlikely. Data used in the analyses came from representative samples from the studies that have been conducted. Overall, included studies had large sample sizes and numbers of events (i.e. more than 300) (Ryan 2016). However, some subgroup analyses had small sample sizes.

Potential biases in the review process

We attempted to minimise bias in several ways. We tried to be as inclusive as possible to avoid potential bias in the search strategy and found publications in different languages in journals from all continents, although the literature identified was predominantly written in English. We were also able to obtain some unpublished information. Both review authors independently assessed the eligibility of studies for inclusion, participated in data extraction, and conducted the 'Risk of bias' assessments. One review author entered the data into a form design for the review and the other checked the data for accuracy. However, carrying out reviews is not an exact science and may require a number of subjective judgements; it is possible that a different review team may have reached different decisions regarding assessments of eligibility and risk of bias. We would encourage readers to examine the Characteristics of included studies tables to assist in the interpretation of results. Several studies had selection bias, with both unclear random sequence generation and unclear concealment of the allocation sequence, which could have introduced bias at the group level in terms of differences between the baseline characteristics of the groups that were compared. When the intervention was allocated at class level or studies were cluster (C) RCTs, such as Jayatissa 1999 (C) and Agarwal 2003 (C), we assumed that bias at the individual level was unlikely. We also assumed a low risk of bias when tablets had the same colour and shape, or were manufactured by the same laboratory, although some studies did not describe the method to conceal the allocation, such as Zavaleta 2000 and Leenstra 2009.

Agreements and disagreements with other studies or reviews

To our knowledge, only one meta-analysis of RCTs has been conducted previously on the efficacy of intermittent iron supplementation in the control of iron deficiency anaemia (Beaton 1999). That review included the results of 22 studies completed before 1999 in different age groups. Of the included studies, nine were carried out among adolescents and compared once or twice a week versus daily supplementation; most of them also assessed a control group that did not receive iron. All studies reported results for haemoglobin and three also measured ferritin. The Beaton 1999 review did not include adult non-pregnant women, and the review authors pooled the results from school-aged children and adolescents.

Like us, the authors of Beaton 1999 concluded that intermittent supplementation increased haemoglobin and ferritin levels and re-

duced anaemia when compared with no intervention or a placebo. However, findings from Beaton 1999 and Fernández-Gaxiola 2011a suggested that intermittent supplementation was less efficacious than daily supplementation in reducing anaemia (RR 1.44, 95% CI 1.33 to 1.56; and RR 1.26: 95% CI 1.04 to 1.52, respectively), but there were no statistical differences in haemoglobin concentrations between regimens. The authors of Beaton 1999 concluded that weekly supplementation should be considered for school-aged children and adolescents only in situations where there is strong assurance of supervision and high adherence. A more recent unpublished review included 12 studies evaluating the effects of weekly iron and folic acid supplementation among non-pregnant women of reproductive age (Margetts 2007). The results suggested that the consumption of supplements containing 60 mg of elemental iron with folic acid for at least 12 weeks, with or without deworming treatment, increased iron status, as judged by increased haemoglobin and, in some studies, serum ferritin levels. The effect of weekly supplementation on haemoglobin concentration was similar to that reported for daily supplementation, except in subsets of women who were severely anaemic at baseline where daily supplementation was more effective.

Overall, the findings of these reviews agree with the findings of this Cochrane Review. The 25 studies included in our review, conducted in different age groups, contexts and with different levels of supervision, show that intermittent supplementation may be an effective public health intervention. In contexts where daily supplementation has failed, has not been implemented or there is a strong need to increase coverage in at-risk populations and economic resources are limited, the feasibility of delivering intermittent supplementation could make this intervention a viable alternative to consider.

The results of the present review are only applicable to menstruating women. However, another systematic review assessing the benefits and safety of this intervention in preschool-aged and school-aged children concurs with our findings (De-Regil 2011). From the programme implementation perspective, a recent narrative review reports that weekly iron and folic acid supplementation has been successfully implemented in Cambodia, Egypt, India, Laos, the Philippines, and Vietnam, reaching over half a million menstruating women (WHO-WPRO 2011).

AUTHORS' CONCLUSIONS

Implications for practice

Intermittent supplementation with iron alone or in combination with other micronutrients may reduce anaemia and may improve iron stores among menstruating women in populations with different anaemia and malaria backgrounds. Women receiving supplements intermittently can probably reduce their anaemia and may achieve similar haemoglobin concentrations at the end of the intervention than women receiving supplements daily. With the current evidence, there is no indication that this intervention has detrimental effects on women's health and other indicators of nutritional status. Good supervision and adherence is fundamental for the intervention to succeed. Intermittent iron supplementation is a feasible intervention for reaching other populations in a variety of settings, outside antenatal-care (ANC) visits, immunisation programmes, and health programmes for adolescents and women of reproductive age.

Most studies provided 60 mg of elemental iron or more on a weekly basis, and the effect on the haematological status may not be affected by the duration of the intervention. The provision of micronutrients other than iron may not alter the haematological response. Iron and folic acid supplementation, therefore, have the possibility of impacting not only menstruating women, but also of benefiting those women who become pregnant and their babies, and improving their nutritional status and impacting other indicators of micronutrients status and health.

The evidence on the efficacy and effectiveness of this intervention is uncertain due to the low quality of the evidence base. The true effect may be substantially different from the estimate of the effect.

Implications for research

This review has highlighted the need for further research in this area, particularly on:

1. side effects and adherence to the intervention;
2. patient-important outcomes and adverse effects;
3. the effects of the provision of multiple micronutrients on an intermittent basis and their effect on iron status and other indicators of micronutrients status and health;
4. the periodicity of intermittent iron supplementation to maintain an adequate iron status throughout the reproductive years;
5. the effective and safe dose of folic acid that should be used along with iron to supplement women intermittently;
6. the effects of intermittent iron supplementation regimens on work performance and productivity outcomes;
7. economic analyses; and
8. the effects of intermittent iron supplementation regimens on malaria outcomes.

Lack of methodological rigor in some RCTs included in this review has resulted in low-quality evidence in the review. Improving the quality of primary studies is needed.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agarwal 2003 (C)

Methods	**Design:** 3-arm, cluster-randomised trial **Unit of randomisation:** class; "As school teachers did not agree to randomization at the individual girl level, the randomization was done at the class section level for the 60 class sections (all class sections taken)" (quote)
Participants	**Setting/location:** 4 government senior secondary schools (all of these schools cater to the middle socioeconomic group population) in North-East Delhi, India **Sample size:** 2088 girls **Age range:** 10-17 years **Baseline prevalence of anaemia:** ~ 48% **Inclusion criteria:** secondary school girls aged 10-17 years old **Exclusion criteria:** girls with haemoglobin < 7.0 g/dL
Interventions	**Intervention:** 60 class sections were allocated to 1 of 3 groups. 1. Group 1 (n = 691): participants did not receive any tablets for the first 100 days and haemoglobin was estimated at 115 (± 5) days. They were thereafter given tablets containing 100 mg of elemental iron and 500 μg (0.5 mg) of folic acid with advice to take 1 tablet daily for 100 days; blister packs were distributed once a week (as in group 2). 2. Group 2 (n = 702): participants received same tablet, containing 100 mg of elemental iron and 500 μg (0.5 mg) of folic acid, one every day for 100 days; blister packs were provided once a week. 3. Group 3 (n = 695): participants received same tablet weekly until group 1 completed the study (230 days). **Length of the intervention:** 100 days (we did not consider the second period in which group 1 and 3 received supplementation)
Outcomes	1. Anaemia (haemoglobin < 120 g/L) 2. Haemoglobin 3. Ferritin
Notes	**Comments:** 1. The intervention was supervised. Compliance was monitored verbally on weekly visits when 7 tablets in a blister pack were distributed. The used blisters were collected each week; results were not reported. 2. Sexual maturity rating was done using Tanner's criteria. 3. The time of menarche and regularity of menstrual periods were noted. 4. We adjusted the results of this study to account for the effect of clustering in the data; we used the estimated effective sample size in the analyses. 5. Malaria endemicity was not reported. **Study start date:** August 1996 **Study end date:** February 1999 **Funding source:** UNICEF, Delhi

Agarwal 2003 (C) (*Continued*)

	Conflicts of interest: Not available	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment:** randomisation was done at the class section level for 60 class sections. Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	**Comment:** not mentioned; however, since randomisation was performed at class section level, selection bias at individual level was unlikely
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Comment:** not described for participants, personnel nor outcome assessors; however, seems unlikely to have been blinded, and no placebo was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** 7 girls in the daily administered group during the second week of intervention complained of gastric side effects and requested not to continue in the study and were excluded
Selective reporting (reporting bias)	High risk	**Comment:** girls with haemoglobin < 70 g/L (0.3%) were eliminated from the analysis. Plasma ferritin and C-reactive proteins (CRP) were estimated in every tenth girl of the study groups; it is unclear how each girl was selected for these analyses. Data not available for the second measurement
Other bias	Low risk	**Comment:** appears to be free of other bias

Ahmed 2001

Methods	**Design:** 2 × 2, randomised, double-blind, placebo-controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** garment factories in Dhaka City, Bangladesh **Sample size:** 480 postmenarchal, non-pregnant teenagers **Age range:** 14-19 years **Baseline prevalence of anaemia:** ~ 90% **Inclusion criterion:** haemoglobin concentration between 80 and 120 g/L (anaemic) **Exclusion criteria:** 1. haemoglobin below 80 g/L

Ahmed 2001 (*Continued*)

	2. clinical manifestations of chronic or infectious disease
Interventions	Participants were allocated to 1 of 4 groups. 1. Group 1 (n = 120): participants received a placebo. 2. Group 2 (n = 120): participants received vitamin A only (2.42 mg retinol as retinyl palmitate). 3. Group 3 (n = 120): participants received 120 mg elemental of iron (as ferrous sulphate), 3500 μg (3.5 mg) of folic acid, and a placebo for vitamin A. 4. Group 4 (n = 120): participants received 120 mg of elemental iron (as ferrous sulphate), 3500 μg (3.5 mg) of folic acid, and 2.42 mg retinol as retinyl palmitate. All groups received weekly supplementation. **Length of the intervention:** 12 weeks For the purposes of this review, we combined groups 3 and 4, only presenting them separately for the subgroup analysis by nutrient. We compared the combined group with group 1
Outcomes	1. Anaemia 2. Haemoglobin 3. Iron deficiency 4. Ferritin 5. Serum iron 6. Total iron-binding capacity 7. Transferrin saturation (%) 8. Vitamin A 9. Adherence (75% of the doses)
Notes	**Comments:** 1. The study population was highly transitional with a high rate of migration. 2. Malaria endemicity was not reported. **Study start date:** March 1998 **Study end date:** September 1998 **Funding source:** supported by a grant from the Department for International Development, UK. Beximco Pharmaceutical Company, Dhaka, Bangladesh, provided the iron and folate preparation and the Opsonin Pharmaceutical Company, Barisal, Bangladesh, provided the vitamin A preparation **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** participants were randomly allocated to 1 of the study groups. Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	**Comment:** an independent person coded the preparations and the code was not broken until all data had been entered into the computer

Ahmed 2001 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** participants, personnel and outcome assessors were not aware of the treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** 289 out of 480 (60%) participants completed the study and the losses were unbalanced among groups: 41%, 44%, 38% and 35% for groups 1, 2, 3, & 4, respectively. Participants were lost to follow-up for the following reasons: 75% left their job or moved to another factory; 3% became pregnant; 5% refused to give a second blood sample; 12% were absent on the day of blood collection; and 5% did not take the supplements for the full 12-week supplementation period
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Unclear risk	**Comment:** some variability in the administration of the supplements, depending on the factory management. In some factories, supplements were given before lunch and in some they were given after lunch. Many participants came to work after having eaten little or no breakfast and ate only a small lunch. Distribution of mild, moderate and severe anaemia not shown

Angeles-Agdeppa 1997

Methods	**Design:** 3-arm, randomised, double-blind, placebo-controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** governmental senior high schools in East Jakarta, Indonesia **Sample size:** 363 girls **Age range:** 14-18 years **Baseline prevalence of anaemia:** 21% **Inclusion criterion:** presence of regular menstruation **Exclusion criteria:** apparently none
Interventions	Participants were allocated to 1 of 4 groups. 1. Group 1 (n = 92): participants received 60 mg of elemental iron, 250 μg (0.25 mg) of folic acid, 750 µg of retinol, and 60 mg of vitamin C on every school day of the week (Monday-Friday). 2. Group 2 (n = 92): participants received 60 mg of elemental iron + 500 µg (0.5 mg) of folic acid + 6000 µg of vitamin A (as retinol) + 60 mg of vitamin C only on

	Friday (Muslim prayer day) and placebos throughout the rest of the week. 3. Group 3 (n = 92): participants received 120 mg of elemental iron + 500 µg (0.5 mg) of folic acid + 6000 µg of vitamin A (as retinol) + 60 mg of vitamin C only on Friday (Muslim prayer day) and placebos throughout the rest of the week. 4. Group 4 (n = 92): participants received a placebo every school day. **Length of the intervention:** 12 weeks For the purposes of the review, we combined groups 2 and 3, splitting them only for the subgroup analysis by dose
Outcomes	1. Anaemia 2. Iron deficiency 3. Prevalence of low retinol 4. Haemoglobin 5. Ferritin 6. Retinol 7. Diarrhoea 8. Adverse side effects (nausea, vomiting, sleepiness) 9. Positive side effects (increased appetite)
Notes	**Comments:** 1. All participants were dewormed at the start of the study with a single 500-mg dose of mebendazole because 34% of a subsample of 104 participants were found to be infested with *Trichuris trichiura*. 2. Intervention was supervised during the first 8 weeks. During weeks 9-12 the supplements were provided on a take-home basis after the girls had received careful instruction on tablet intake (because the last 4 weeks of supplementation fell in the Muslim fasting month). 3. Compliance was monitored by retrieving plastic bags in which the tablets were provided and counting the number of tablets that remained. 4. Malaria endemicity was not reported. **Study start date:** 1995 **Study end date:** 1995 **Funding source:** supported by Kimia Farma, Jakarta, Indonesia, and the German-Indonesian Technical Cooperation (project number 85.2534.1-01.100) **Conflicts of interest:** not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment:** participants were randomly selected and then randomly assigned to 1 of the study groups. Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned, but study had a double-masked placebo design

Angeles-Agdeppa 1997 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** participants and personnel were not aware of the treatment; outcome assessors were not described but likely did not know the treatments. Supplements and placebos had the same red colour and shape, and were not distinguishable by sight
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** 75% of the participants completed the study and the losses were unbalanced among study groups: 30%, 24%, 30%, 19% for groups 1, 2, 3, & 4, respectively
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Unclear risk	**Comment:** intervention supervised during the first 8 weeks. During weeks 9-12 the supplements were provided on a take-home basis after the girls had received careful instruction on tablet intake (because the last 4 weeks of supplementation fell in the Muslim fasting month). Distribution of mild, moderate, and severe anaemia not shown

Beasley 2000

Methods	**Design:** 2-arm, randomised, single-blind, controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** rural area of Muheza District in villages of Misongeni, Ubembe and Kilometa Saba, Tanzania **Sample size:** 234 females **Age range:** 12-18 years **Baseline prevalence of anaemia**: 27% had a haemoglobin < 110 g/L **Inclusion criteria:** 1. any child aged between 12 and 18 years and living in the villages, irrespective of school attendance 2. completion of all baseline measurements 3. haemoglobin concentration > 70 g/L **Exclusion criterion:** haemoglobin concentration lower than 70 g/L
Interventions	Participants were allocated to 1 of 2 groups. 1. Group 1 (n = 50): women were given 120 mg of elemental iron (as 200 mg of ferrous sulphate) per week. 2. Group 2 (n = 57): women were given a control treatment - cyanocobalamin (vitamin B_{12}) (2 x 50 μg).

Beasley 2000 (*Continued*)

	Both groups were treated for infection with albendazol before the intervention **Length of the intervention:** 16 weeks, where supplementation was given at intervals of "at least once a week"
Outcomes	1. Anaemia 2. Serum ferritin and mean change 3. Haemoglobin and mean change 4. Weight and prevalence and intensity (parasites/200 WBC) of infection with P. *falciparum*
Notes	**Comments:** Malaria is holo-endemic in the study area. **Study start date:** April 1996 **Study end date:** August 1996 **Funding source:** support from the Wellcome Trust and the Department for International Development, UK **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** randomisation took place before anthelmintic treatment. Groups were matched for intensity of infection with hookworm and S. haematobium. Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** unclear for participants (although a control was used, it is unclear whether pills had the same appearance); personnel were aware of the treatment; outcome assessors did not know the treatment group
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** of the girls included in the study, 119 (51% of those recruited) received 12 doses of iron or control treatment and completed all follow-up measures. It is unclear why children dropped out of the study or failed to receive all 12 doses of treatment
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement

Other bias	Unclear risk	**Comment:** control was vitamin B12, which could have potentially improved anaemia status. However, macrocytosis was observed in only 8% of blood films taken at baseline. Distribution of mild, moderate, and severe anaemia not shown

Dos Santos 1999

Methods	**Design:** 2-arm, randomised, blinded trial **Unit of randomisation:** individual level
Participants	**Location/setting:** low-income community in the city of Recife, Pernambuco, Brazil **Sample size:** 193 women **Age range:** 15-45 years **Baseline prevalence of anaemia:** not available; all were anaemic with haemoglobin between 75 g/L and 119 g/L **Inclusion criteria:** 1. mild to moderate anaemia (haemoglobin between 75 g/L and 119 g/L) 2. non-pregnant 3. with "regular" menstruation **Exclusion criteria:** 1. use of iron supplements during the last thirty days 2. haematological diseases 3. renal diseases
Interventions	Participants were allocated to 1 of 2 groups. 1. Group 1 (n = 96): women were given 60 mg of elemental iron (as ferrous sulphate) daily. 2. Group 2 (n = 97): women were given 60 mg of elemental iron (as ferrous sulphate) once a week. **Length of the intervention:** 12 weeks
Outcomes	1. Haemoglobin 2. Mean corpuscular volume 3. Adherence (optimal) 4. Weight
Notes	**Comments:** 1. Article translated into English from Portuguese. 2. Malaria endemicity was not reported. **Study start date:** not available **Study end date:** not available **Funding source:** not available **Conflicts of interest:** not available
Risk of bias	

Dos Santos 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** women were randomly allocated to the treatments by drawing of lots
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** participants were aware of the treatments; personnel staff in charge of haematological measurements did not know the study hypothesis, objectives and treatments received by the participants; not described for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** 150 out of 187 (80.2%) participants completed the study but the losses were unbalanced among groups; 26.0% and18.5% for groups 1 & 2, respectively
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Low risk	**Comment:** no evidence of other bias

Februhartanty 2002

Methods	**Design:** 3-arm, single-blind, community trial **Unit of randomisation:** individual level
Participants	**Setting/location:** junior high schools in Kupang, East Nusa Tenggara, in the eastern part of Indonesia **Sample size:** 150 postmenarchal adolescent girls, students from 2 different public high schools. 100 were selected from 1 school and allocated randomly to placebo or weekly groups and a further 50 adolescent student girls recruited at random from a different public high school and allocated to the menstruation group **Age range:** ~ 14-15 years **Baseline prevalence of anaemia:** 58% **Inclusion criteria:** postmenarchal adolescent girls from two different high schools located in relatively similar urban areas **Exclusion criteria:** none stated
Interventions	Participants were allocated to 1 of 3 groups. 1. Group 1 (n = 50): girls received a tablet containing 60 mg of elemental iron (as ferrous sulphate) and 250 μg (0.25 mg) of folic acid every Wednesday. 2. Group 2 (n = 50): girls received a placebo tablet every Wednesday. 3. Group 3 (n = 50): girls were given an iron tablet each day for 4 consecutive days (during menstruation). **Length of the intervention:** 16 weeks

Februhartanty 2002 (*Continued*)

	For the purposes of this review, we compared groups 1 and 2 only
Outcomes	1. Haemoglobin 2. Ferritin
Notes	**Comments:** 1. For participants attending morning classes, tablets were taken in the morning. For participants attending afternoon classes, tablets were taken in the afternoon. To control parasitic infestation, all participants were given a single dose of 500 mg of mebendazole 3 days before supplementation. 2. Due to unfavourable environmental conditions in the study area during late November 1998, the 16th-week tablets for the placebo and weekly groups were taken in the 17th week. The second blood collection was delayed by around 5 days. 3. Malaria area **Study start date:** August 1998 **Study end date:** December 1998 **Funding source:** SEAMEO-TROPMED Regional Center for Community Nutrition, Jakarta **Conflicts of interest:** not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment:** participants were allocated randomly only to placebo or weekly groups. Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** participants were not aware of treatments; not described for personnel or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** final data set consisted of 48 participants in each study group (4% dropout per group). Common reasons for dropping out were refusal to undergo blood collection, absent from class on the day of blood collection, and transfer to another school
Selective reporting (reporting bias)	Unclear risk	**Comment:** after excluding extreme values (serum ferritin changes of more than 50 μg/L), a complete data set of serum ferritin levels covered 34 participants in the placebo group and 31 participants in the weekly group

Februhartanty 2002 (*Continued*)

Other bias	High risk	**Comment:** higher prevalence of anaemia in the weekly group. Distribution of mild, moderate, and severe anaemia not shown

Gilgen 2001

Methods	**Design:** 4-arm, randomised, double-blind trial **Unit of randomisation:** individual level
Participants	**Setting/location:** North-East Bangladesh **Sample size:** 553 non-pregnant and non-breastfeeding tea pluckers **Age range:** 14-66 years of age (mean age = 39.6 years) **Baseline prevalence of anaemia:** 85.7% **Inclusion criteria:** female tea pluckers, non-pregnant and non-breastfeeding **Exclusion criteria:** pregnant and breastfeeding women
Interventions	Participants were allocated to 1 of 4 groups. 1. Group 1 (n = 139): participants received a weekly supplement containing 200 mg of elemental iron (as ferrous fumarate) and 200 μg (0.2 mg) of folic acid. 2. Group 2 (n = 143): participants received anthelmintic treatment on 2 occasions, at the beginning of the trial and 12 weeks later (using a single dose of 40 mg of albendazole). 3. Group 3 (n = 130): participants received a weekly supplement containing 200 mg of elemental iron (as ferrous fumarate) and 200 μg (0.2 mg) of folic acid + single dose of albendazole 400 mg on 2 occasions. 4. Group 4 (n = 141): participants received placebos for both iron supplementation (weekly) and antihelminthic treatment (beginning and 12 weeks later). **Length of the intervention:** 24 weeks For the purposes of this review, we only compared groups 1 and 4
Outcomes	1. Haemoglobin 2. Ferritin 3. Labour productivity 4. Helminth infections 5. Adverse side effects (giddiness, dizziness, nausea, bouts of vomiting, diarrhoea, and stomach pains) 6. Positive side effects (well-being, feeling stronger and more energetic, feeling relief from stomach pains, anorexia, diarrhoea)
Notes	**Comments:** 1. We could not extract data on work productivity as they did not include standard deviations. There were no significant differences in the number of days plucked on pruned, unpruned and young tea bushes between the study groups. 2. Of 139 women in the iron-supplemented group, 87 (62.2%) reported an improvement in well-being after 24 weeks of iron supplementation. Nearly half (46.6%) felt stronger and more energetic and 15.2% felt relief from stomach pains, anorexia, and diarrhoea. In the placebo group, 51.1% felt better after the study with 38.9% feeling stronger and more energetic, and 6.4% feeling relief from stomach

	pains, anorexia, and diarrhoea. 3. No screening for malaria parasites was performed as malaria is not known to be endemic in the study region. **Study start date:** November 1995 **Study end date:** March 1997 **Funding source:** UNICEF and The Nestle Foundation. D Gilgen received bursaries from Lucy Cavendish College, Cambridge, the Cambridge Philosophical Society and the University of Cambridge **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** participants were randomly assigned to 1 of the study groups. The random number generator in SPSS (Version 7.5) was used to create 4 groups of equal size and the process was repeated until there was no statistically significant difference between the randomised groups in mean age, years of plucking experience, productivity of the previous plucking season, haemoglobin and ferritin values, and prevalence and egg counts of *Ascaris, Trichuris* and hookworms.
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** study described as double-blind. Participants and personnel were not aware of the treatments; not described for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** not mentioned
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Low risk	**Comment:** no evidence of other bias

Gonzalez-Rosendo 2002

Methods	**Design:** 3-arm, randomised clinical trial **Unit of randomisation:** individual level
Participants	**Setting/location:** 15 public schools from rural areas in Morelos, Mexico **Sample size:** 637 adolescents girls, mixed anaemic and non-anaemic **Age range:** 12-18 years **Baseline prevalence of anaemia:** 28% **Inclusion criteria:** adolescent girls signed-up in the selected schools **Exclusion criteria:** adolescents diagnosed with gastritis or taking supplements
Interventions	Participants were allocated to 1 of 3 groups. 1. Group 1 (n = 169): girls received 60 mg of elemental iron (as ferrous sulphate) on week days (Monday-Friday). 2. Group 2 (n = 172): girls received 60 mg of elemental iron (as ferrous sulphate) once a week (Monday). 3. Group 3 (n = 170): girls received no treatment. This group comprised non-anaemic women only. **Length of the intervention:** 16 weeks For the purposes of this review, we compared groups 1 and 2 only
Outcomes	1. Anaemia 2. Haemoglobin 3. Haematocrit 4. Adherence 5. Weight 6. Height 7. Circumference of waist and hip
Notes	**Comments:** 1. We had the article translated from Spanish into English. 2. Prior to the study, adolescents with parasitaemia were treated with 400 mg of albendazol. 3. Teachers administered the supplements and supervised adherence to the intervention. 4. On average, the group receiving weekly iron supplementation consumed 81% of the total doses while women in the daily group consumed 56%. 5. Malaria endemicity was not reported. **Study start date:** not available **Study end date:** not available **Funding source:** not available **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** participants were randomly assigned to either the weekly or daily group by using a computer-generated random se-

Gonzalez-Rosendo 2002 (*Continued*)

		quence
Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding (performance bias and detection bias) All outcomes	High risk	**Comment:** participants, personnel and outcome assessors were aware of the treatments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** not described; apparently there were no losses to follow-up
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Unclear risk	**Comment:** distribution of mild, moderate, and severe anaemia not shown

Gupta 2014

Methods	**Design:** 3-arm, randomised controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** 9 selected schools in Shimla district of Himachal Pradesh, India **Sample size:** 331 adolescent girls with mild to moderate anaemia **Age range:** aged 10-19 years **Baseline prevalence of anaemia:** not available **Inclusion criteria:** anaemic adolescent girls from selected schools **Exclusion criteria:** refusal to participate
Interventions	Participants were allocated to 1 of 3 groups. 1. Group 1 (n = 108): girls received a tablet containing 100 mg of elemental iron (i.e. 335 mg ferrous sulphate) and 500 µg of folic acid once a week. They received a total of 52 doses spread over a 1-year period. 2. Group 2 (n = 112): girls received the same tablet twice a week. They received a total of 104 tablets spread over a 1-year period. 3. Group 3 (n = 111): girls received the same tablet daily over a 3-month period. **Length of the intervention:** 1 year For the purposes of this review, we combined groups 1 and 2 to make a single pair-wise comparison with group 3
Outcomes	1. Haemoglobin 2. Ferritin
Notes	**Comments:** 1. A school-based intervention. The tablets were distributed by the class teacher immediately after school recess break to ensure they were not taken on an empty stomach. 2. Malaria endemicity: not mentioned **Study start date:** not available

Gupta 2014 (*Continued*)

	Study end date: not available **Funding source:** Indian Council of Medical Research, New Delhi **Conflicts of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** study girls were assigned to the 3 intervention groups by lottery method
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	**Comment:** participants, personnel and outcome assessors aware of the treatments; iron-folic acid tablets were the same for the 3 intervention groups
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** not described; apparently there were no losses to follow-up
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	High risk	**Comment:** missing information on self-reported side effects (vomiting, loose stools, and constipation) that was recorded and is not shown by intervention groups. Distribution of mild, moderate, and severe anaemia not shown

Hall 2002 (C)

Methods	**Design:** 2-arm, cluster-randomised trial **Unit of randomisation:** school level (60 schools, 30 per arm; approximately 20 randomly selected children (10 boys and 10 girls) in each school)
Participants	**Setting/location:** rural informal community schools in the Kolondieba district of Mali, Africa **Sample size:** 552 girls **Age range:** 6-19 years (mean age = 11.4 years) **Baseline prevalence of anaemia:** ~ 55% **Inclusion criteria:** children that could read and write (for a separate study of educational achievements) **Exclusion criterion:** any child with severe anaemia (haemoglobin = 80 g/L or lower)

Hall 2002 (C) (*Continued*)

Interventions	Schools were allocated to 1 of 2 groups. 1. Group 1 (n = 271) at follow-up (number randomised not clear): children received 65 mg elemental iron (as 200 mg of ferrous sulphate) and 250 μg (0.25 mg) of folic acid once a week. 2. Group 2 (n = 281) at follow-up (number randomised not clear): no treatment. **Length of the intervention:** 10 weeks
Outcomes	1. Anaemia 2. Haemoglobin
Notes	**Comments:** 1. All children in every school were treated for parasitic infections at baseline using albendazole, and given vitamin A to treat night blindness. Supplements were given by the teachers and 83% of children were given all 10 tablets and 91% received at least 9 tablets. 2. Malaria is endemic in Mali, although the study was done in the dry season when transmission is less intense than in the wet season. 3. The study also included data for boys but we did not include these data in this review. 4. For the analyses, we only included the estimated effective sample size. Authors provided the ICC (0.0698) and design effect (2.22) to adjust data by the effect of clustering. The analyses only included the estimated effective sample size. **Study start date:** January 2000 **Study end date:** not available **Funding source:** Save the Children, USA, and Helen Keller International, Mali **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** 60 schools were randomly assigned to either a treatment or a comparison group by using a computer-generated random number list (information communicated by the author)
Allocation concealment (selection bias)	Low risk	**Comment:** not reported; however, since the intervention was allocated at school level, selection bias at individual level was unlikely
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Comment:** not reported for participants, personnel or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** 93% children followed up

Hall 2002 (C) (*Continued*)

Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Unclear risk	**Comment:** distribution of moderate and mild anaemia not shown

Jalambo 2018

Methods	**Design:** 3-arm, randomised controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** secondary schools in Gaza. 1 or 2 class(es) were selected randomly from grades 10, 11, and 12 in the selected schools, according to the population of the governorate **Sample size:** 131 adolescent school girls with iron deficiency or iron deficiency anaemia **Age range:** 15-19 years **Baseline prevalence of anaemia:** not available **Inclusion criteria:** unmarried and non-pregnant adolescent girls with iron deficiency and iron-deficiency anaemia (mild and moderate) **Exclusion criteria:** 1. severe anaemia (haemoglobin < 8 g/dL) 2. suffering from acute or chronic infections that could affect their haemoglobin and ferritin levels at the time of the blood sampling 3. had anaemia other than iron-deficiency anaemia 4. were underweight 5. were on medication 6. were diagnosed with thalassaemia trait
Interventions	Participants were allocated to 1 of 3 groups. 1. Group 1 (n = 45): received 200 mg of ferrous fumarate once a week for 3 months; this was given by the researchers during school hours. 2. Group 2 (n = 44): received iron supplementation (200 mg of ferrous fumarate once a week for 3 months) with nutrition education (9 nutritional education sessions (1.5 hours/session) for 3 months. 3. Group 3 (n = 42): control. **Length of the intervention:** 3 months For the purposes of this review, we used groups 1 and 3.
Outcomes	1. Haemoglobin 2. Ferritin 3. Malonyl dialdehyde
Notes	**Comments:** 1. Researchers provided the supplements. There is no mentioned of how supervision was done or compliance registered. 2. Malaria endemicity: not known. **Study start date:** October 2015 **Study end date:** April 2016

Jalambo 2018 (*Continued*)

	Funding source: none **Conflicts of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** schools, grades and girls were randomly selected; however, the method was not mentioned
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Comment:** not reported for participants, personnel or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** not described; apparently there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	**Comment:** apparently there was no selective reporting
Other bias	Low risk	**Comment:** distribution of moderate and mild anaemia not shown

Jayatissa 1999 (C)

Methods	**Design:** 3-arm, double-blinded, placebo-controlled clinical trial **Unit of randomisation:** class level
Participants	**Setting/location:** schools in the district of Colombo, Sri Lanka **Sample size:** 690 adolescents **Age range:** 10-17 years (mean age = 11.4 years) **Baseline prevalence of anaemia:** 21.1% **Inclusion criteria:** adolescent girl from each grade from years 6 to 10 was randomly selected **Exclusion criteria:** 1. chronic infectious diseases 2. cardiopathies 3. taken supplements or medications containing iron during the previous month 4. haemoglobin level less than 100 g/L with a blood picture showing any other kind of anaemia
Interventions	Classes were allocated to 1 of 4 groups. 1. Group 1 (n = 243): participants received a daily dose of 60 mg elemental iron (as ferrous sulphate) and 250 μg (0.25 mg) of folic acid in a combined tablet (iron/folate) and 100 mg of vitamin C, 5 days per week, Monday-Friday. 2. Group 2 (n = 230): participants received the same dose of iron/folate and vitamin

Jayatissa 1999 (C) (*Continued*)

	C, but only once a week on Monday, and they were given a placebo replacement for the iron/folate and vitamin C for the other 4 days. 3. Group 3 (n = 217): participants received a placebo replacement for iron/folate and vitamin C, 5 days per week, Monday-Friday. **Length of the intervention:** 8 weeks
Outcomes	1. Anaemia 2. Haemoglobin 3. Ferritin (only in a subsample) 4. Adverse side effects (side effects reported included constipation, sleepiness, abdominal pain, rash, and nausea)
Notes	**Comments:** 1. Ferritin measurements were obtained from only 1 school; we did not include this information. 2. Malaria endemicity was not reported. 3. We adjusted the results of this study to account for the effect of clustering in the data; we used the estimated effective sample size in the analyses. **Study start date:** not available **Study end date:** not available **Funding source:** WHO representative and its staff in Sri Lanka **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** it is stated that treatments were randomly allocated by classes. Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	**Comment:** not reported; however, since the intervention was allocated at class level, selection bias at individual level is unlikely
Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** supplements and placebos had the same colour and shape and were not distinguishable by sight. Girls, teachers, and interviewers were not aware of differences among the treatment regimens
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** dropout rate was 4.5%. The reasons for dropping out were side effects (16 girls, 52%), leaving school (10 girls, 32%), or doctor's advice not to take the tablet with other treatment (5 girls, 16%)
Selective reporting (reporting bias)	Unclear risk	**Comment:** ferritin samples were taken from a randomly selected subsample

Jayatissa 1999 (C) (*Continued*)

Other bias	Low risk	**Comment:** study appears to be free of other bias

Joshi 2013

Methods	**Design:** 2-arm, randomised controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** Urban Health and Training Centre in urban slum area in India **Sample size:** 120 anaemic adolescent girls. All girls who visited the Urban Health and Training Centre during the study period were interviewed as per pre-tested proforma and had their haemoglobin assessed. Those with haemoglobin < 12 g/dL and who consented were included in the study **Age range:** 10-19 years **Baseline prevalence of anaemia:** all were anaemic; 61.6% = mild anaemic, 36.6% = moderate anaemic, 1.66% = severe anaemic **Inclusion criteria:** adolescent girls with haemoglobin < 12 g/dL consenting for this study **Exclusion criteria:** 1. pregnancy 2. chronic conditions 3. history of acute illness like malaria in recent time (< 3 months)
Interventions	All included participants were dewormed at the start of the study and 15 days later with 400 mg of albendazole, and given related health education in separate sessions. Girls were randomly allocated to 1 of 2 groups 1. Group 1 (n = 60): received a daily tablet containing 300 mg of ferrous fumarate, 15 mcg of vitamin B12, and 1.5 mg of folic acid. 2. Group 2 (n = 60): received a weekly tablet containing 300 mg of ferrous fumarate, 15 mcg of vitamin B12, and 1.5 mg of folic acid. **Length of the intervention:** 3 months
Outcomes	1. Haemoglobin 2. Anaemia 3. Adverse reactions
Notes	**Comments:** 1. Compliance of the designated schedule was checked from time to time through home visits and interviews by field workers/supervisors/investigators. Empty cartons were also collected from them for assessment of IFA intake. After a 1-month lag postintervention, all study participants were interviewed for compliance to the intervention and an adverse drug reaction profile was created. **Study start date:** June 2011 **Study end date:** October 2012 **Funding source:** not available **Conflicts of interest:** not available

Risk of bias

Joshi 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** randomisation done using computer-generated block randomisation
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned. Every adolescent girl with haemoglobin < 12 g/dL selected for inclusion in the study was allocated randomly to either group by a laboratory technician until the required quota of 60 participants in each group was reached
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Comment:** not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** not described; apparently there were no losses to follow-up
Selective reporting (reporting bias)	High risk	**Comment:** missing information on compliance at individual level, which was recorded through home visits and postintervention interviews
Other bias	Low risk	**Comment:** study appeared to be free of other bias

Kianfar 2000

Methods	**Design:** 2 × 4, randomised controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** 4 high schools in urban areas of Zahedan and Rasht, Iran **Sample size:** 523 female adolescents (selected from students in grades 1-3) **Age range:** not reported (mean age = 16.1 years) **Baseline prevalence of anaemia:** 48.5% **Inclusion criterion:** written consent secured from participants' families **Exclusion criteria:** no exclusion criteria listed
Interventions	Participants were allocated to 1 of 4 groups. 1. Group 1 (n = 92): adolescents were given a daily tablet containing 50 mg of elemental iron (as 150 mg of ferrous sulphate) at least 1 hour after dinner and before sleeping to be taken with water on Wednesdays. 2. Group 2 (n = 112): adolescents were given a twice-weekly tablet containing 50 mg of elemental iron (as 150 mg of ferrous sulphate) at least 1 hour after dinner and before sleeping to be taken with water on Wednesdays and Saturday. 3. Group 3 (n = 171): adolescents were given a once-weekly tablet containing 50 mg of elemental iron (as 150 mg of ferrous sulphate) at least 1 hour after dinner and before

	sleeping to be taken with water on Wednesdays. 4. Group 4 (n = 148): adolescents received no intervention. **Length of the intervention:** 3 months For the purposes of this review, we combined groups 2 and 3, only presenting their individual results in the subgroup analysis by scheme
Outcomes	1. Haemoglobin 2. Serum ferritin 3. Serum transferrin 4. Anaemia 5. Iron deficiency (ferritin < 12 ng/mL) 6. Side effects 7. Adherence Data in each group reported only by anaemia status (anaemic, non-anaemic), so we combined them within each group to include the trial's information
Notes	**Comments:** 1. Adherence ranged between 70 and 90%. There were no differences in the incidence of side effects between supplementation regimens. 2. Malaria endemicity was not reported. **Study start date:** 1996-1997, during a 3-month period **Study end date:** 1996-1997, during a 3-month period **Funding source:** Undersecretariat for Research, Ministry of Health and Medical Education, Chancellors of Zahedan and Rasht Medical Universities, as well as Miss A Houshiar-Rad and F Nasseri, and Mr A Rashidi M Kar Andish and M Karajibani **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** participants stratified by anaemia status were randomly allocated to the groups. Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** participants were aware of the treatment; staff did not know the treatment group; not reported for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** 88/92 (95.6%), 108/112 (96.4%), 168/171 (98.2%), 145/148 (97.9%) of the participants finished the study in groups 1, 2, 3, and 4, respectively
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement

Other bias	Low risk	**Comment:** study appeared to be free of other bias

Leenstra 2009

Methods	**Design:** 2 × 2, randomised controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** 10 schools in the City of Kisumu in Nyanza Province, western Kenya **Sample size:** 279 non-pregnant school girls with mild-to-moderate anaemia (haemoglobin < 70 g/L but > 120 g/L) **Age range:** 12-18 years **Baseline prevalence of anaemia:** ~ 30% (iron deficiency = ~ 40%) **Inclusion criteria:** school girls aged 12-18 years, from public primary schools **Exclusion criteria:** 1. severe anaemia (haemoglobin < 70 g/L) 2. signs of xerophthalmia 3. pregnancy 4. disease requiring hospitalisation
Interventions	Participants were allocated to 1 of 4 groups. 1. Group 1 (n = 68): participants received 120 mg of oral iron (2 ferrous sulphate tablets of 200 mg each) and 25,000 IU (8.3 mg) of retinol (vitamin A) in gelatin capsule once a week. 2. Group 2 (n = 70): participants received iron (as group 1) and vitamin A placebo once a week. 3. Group 3 (n = 70): participants received vitamin A with iron placebo once a week. 4. Group 4 (n = 71): participants received placebo only (no iron nor vitamin A). **Length of the intervention:** 5 months For the purposes of this review, we compared groups 2 and 4 only
Outcomes	1. Haemoglobin (estimated from graph 1 in the paper) 2. Malaria 3. Parasitaemia 4. Morbidity 5. Side effects
Notes	**Comments:** 1. The intervention was supervised except during the school holidays. 2. Approximately 26% of 15-19 year old girls were affected by HIV. 3. Girls receiving iron were more likely to report constipation or dark stools (rate ratio = 2.2 (95% CI 1.1 to 4.4) than girls receiving iron placebo (rate ratio = 6.4 (95% CI 1.0 to 41.5). There was no difference between groups regarding the occurrence of potential side effects as nausea, vomiting, or diarrhoea (data not shown). 4. Malaria transmission in this urban area is largely uncharacterised, but is perennial with highest transmission during peak rainfall from April-July and October-December. **Study start date:** April 1998 **Study end date:** November 1998

	Funding source: The Netherlands Foundation for the Advancement of Tropical Research (WOTRO) **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** balanced block randomisation (block size 12). Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	**Comment:** placebo-controlled trial. Individual packs were left for girls in the study schools. Active and placebo supplements were manufactured by Laboratory and Allied Limited (Nairobi, Kenya) and the key was only revealed after completion of the study
Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** participants, personnel, and outcome assessors were not aware of the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** 249 out of 279 participants completed the study (89%). Loss to follow-up appeared balanced across groups and reasons were explained. Analyses were done on an intention-to-treat basis
Selective reporting (reporting bias)	Unclear risk	**Comment:** data on several outcomes described as non-significant but not shown (side effects including vomiting and diarrhoea)
Other bias	Unclear risk	**Comment:** groups appeared similar at baseline. Most of the results for the 4 randomised groups were presented in graphs which were difficult to interpret (and have not been included in our data and analysis tables). Data on several outcomes were described as non-significant but were not shown (side effects, including vomiting and diarrhoea). Placebo figures were not reported. Distribution of mild, moderate, and severe anaemia not shown

Mozaffari 2010 (C)

Methods	**Design:** 2-arm, cluster-randomised, community-based supplementation trial **Unit of randomisation:** school level
Participants	**Setting/location:** high schools in Yazd City in central Iran **Sample size:** 200 high school girls **Age range:** 14-16 years **Baseline prevalence of anaemia:** ~ 13% **Inclusion criteria:** first grade adolescent girls in each high school **Exclusion criteria:** 1. hepatic or neural diseases 2. received or donated blood within the previous 2 weeks
Interventions	Participants were allocated to 1 of 2 groups: 1. Group 1 (n = 100): girls received 30 mg of elemental iron (as ferrous sulphate) on the first working day of each week. 2. Group 2 (n = 100): girls received no intervention. **Length of the intervention:** 16 weeks For the purposes of this review, we analysed both groups.
Outcomes	1. Height 2. Weight 3. Anaemia 4. Iron deficiency 5. Haemoglobin 6. RBC 7. MCV 8. MCH 9. MCHC 10. Ferritin values 11. Side effects
Notes	**Comments:** 1. Supplements were distributed among the participants each week by the school health officer under the supervision of the school master. 2. Compliance and side effects were assessed by asking the supplemented students about consumption and any possible adverse reactions. 3. **Quote:** "The good organization and supervision of the trial with lack of side effects yielded a compliance rate of 96% that can justify the desirable achieved results" (data not shown). 4. Malaria endemicity was not reported. 5. We adjusted the results of this study to account for the effect of clustering in the data; we used the estimated effective sample size in the analyses. **Study start date:** October 2007 **Study end date:** November 2008 **Funding source:** Department of Research Administration, Shahid Sadoughi University of Medical Sciences, Yazd, Iran **Conflicts of interest:** none declared
Risk of bias	

Mozaffari 2010 (C) (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** study described as a community-based randomised trial. Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	**Comment:** not mentioned; however, since this is a cluster trial, selection bias at individual level is unlikely
Blinding (performance bias and detection bias) All outcomes	High risk	**Comment:** participants, personnel, and outcome assessors were aware of the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** 4 girls from the iron-supplemented group and 3 girls from the non-supplemented group dropped out on grounds of travel, illness, or some personal reasons
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Low risk	**Comment:** study appeared to be free of other bias

Muro 1999 (C)

Methods	**Design:** 3-arm, cluster-randomised, community-based, controlled trial **Unit of randomisation:** school level
Participants	**Setting/location:** 5 schools in Dar-es-Salaam, Tanzania **Sample size:** 237 adolescent girls **Age range:** 14-17 years **Baseline prevalence of anaemia:** ~ 48% **Inclusion criteria:** 1. menarche 2. written informed consent from the girls and their parents 3. anaemic and non-anaemic girls **Exclusion criterion:** girls suffering from infection with fever at the time of the interview
Interventions	Participants were allocated to 1 of 3 groups. 1. Group 1 (n = 78): girls received 65 mg of elemental iron plus 250 μg (0.25 mg) of folic acid once a week, as well as communication sessions. 2. Group 2 (n = 39): girls received 65 mg of elemental iron and 250 μg (0.25 mg) of folic acid once a week. 3. Group 3 (n = 120): girls received no intervention. **Length of the intervention:** 8 weeks

Muro 1999 (C) (*Continued*)

	For the purposes of this review, we compared groups 2 and 3 only
Outcomes	1. Anaemia 2. Side effects 3. Compliance (only for those who took the supplements)
Notes	**Comments:** 1. Full compliance, measured during the third week by positive iron stool tests, was 60-100% and declined to 40-87% at the 5th week. Self-reported compliance tended to be higher. 2. Supplements were distributed by the school teacher and a supplementation record book was provided to each class leader for the weekly collection of information about ingestion of the tablet, eventual side effects, illness, and absenteeism throughout the whole supplementation period. The reported side effects were: increased appetite, stomach irritation, increase in activity, and less sleepiness. 3. Malaria endemic area. 4. We adjusted the results of this study to account for the effect of clustering in the data; the estimated effective sample size was used in the analyses. **Study start date:** August 1996 **Study end date:** November 1996 **Funding source:** not available **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** each group should have contained a similar number of girls. However, this goal was not reached, because after the schools had been randomly assigned to the 3 groups, the parents of the girls in school 4, who were assigned to receive iron supplementation without communication, did not approve of their daughters receiving iron tablets. The girls from this school were added to the non-intervention group
Blinding (performance bias and detection bias) All outcomes	High risk	**Comment:** participants and personnel were aware of the treatment; outcome assessors seemed to be aware of the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** 100% of participants finished the treatment

Muro 1999 (C) (*Continued*)

Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Low risk	**Comment:** study appeared to be free of other bias

Nguyen 2008

Methods	**Design:** 4-arm, randomised double-blind, controlled trial **Unit of randomisation:** individual level
Participants	**Settinglocation:** Concepción, Chiquirichapa, in the western highlands of Guatemala **Sample size:** 459 healthy women **Age range:** 15 to 49 years **Baseline prevalence of anaemia:** prevalent, but percentage not reported **Inclusion criteria:** non-pregnant, non-lactating, anaemic (mild or moderate) women **Exclusion criteria:** 1. pregnancy 2. lactation (having had a child within the last 3 months) 3. consumption of folic acid supplements 4. chronic diseases that interfere with folic acid metabolism 5. severe anaemia
Interventions	Participants were allocated to 1 of 4 groups. 1. Group 1 (n = 114): participants received a weekly supplement containing 5000 µg (5 mg) of folic acid, 120 mg of iron, 30 mg of zinc, and 16.8 µg of vitamin B12. 2. Group 2 (n = 115): participants received a weekly supplement containing 2800 µg (2.8 mg) of folic acid, 120 mg of iron, and 16.8 µg of vitamin B_{12}. 3. Group 3 (n = 114): participants received a daily supplement containing 400 µg (0.4 mg) of folic acid, 60 mg of iron, 15 mg of zinc, and 2.4 µg of vitamin $B_{12.}$ 4. Group 4 (n = 116): participants received a daily supplement containing 200 µg (0.2 mg) of folic acid, 60 mg of iron, and 2.4 µg of vitamin $B_{12.}$ The weekly-dose groups received 6 placebos and 1 active pill on the 3rd day of the week. Daily records were kept to track the participants' health **Length of the intervention:** 12 weeks For the purposes of this review, we combined groups 1 and 2 and compared them with groups 3 and 4, which we also combined
Outcomes	1. Depression status 2. Body mass index 3. Serum and RBC folate 4. Adverse side effects (gastric complaint, head ache, nausea) 5. Hospitalisation
Notes	**Comments:** 1. Compliance was assessed by trained field workers from the community, who visited each woman 7 days a week, to deliver and observe the ingestion of the supplements for the entire 12-week supplementation period. All women received 7

	pills per week. 2. Malaria endemicity was not reported. **Study start date:** March 2006 **Study end date:** June 2006 **Funding source:** not available **Conflict of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** computer-generated random numbers used to assigned women to 1 of the treatment groups
Allocation concealment (selection bias)	Low risk	**Comment:** code allocation was kept secure at Emory University and was only revealed after completion of the study
Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** participants, personnel and outcome assessors were not aware of the treatment. All supplements were identical in appearance and taste, and were coded with lot numbers at the factory, corresponding to 1 of 4 treatment arms
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** of the 459 women randomised to 1 of the treatment groups, 369 completed the 12-week study protocol: 1. Group 1: 8 women withdrew from the study. Reasons: 1 = new pregnancy; 1 = prevented by husband; 3 = hospitalisations; 2 = gastric complaints; 1 = side effects such as headache and nausea 2. Group 2: 7 women withdrew from the study. Reasons: 1 = moved; 1 = hospitalisation; 1 = inconvenienced by daily visits; 2 = gastric complaints; 2 = side effects such as headache and nausea 3. Group 3: 17 women withdrew from the study. Reasons: 3 = new pregnancies; 2 = moved; 3 = prevented by husband; 2 = hospitalisations; 6 = gastric complaints; 1 = didn't like the visits 4. Group 4: 5 women withdrew from the study. Reasons: 2 = new pregnancies; 1 = moved; 1 = inconvenienced by daily visits; 1 = gastric complaint

Nguyen 2008 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Low risk	**Comment:** study appeared to be free of other bias

Rezaeian 2014

Methods	**Design:** 2-arm, randomised, blinded, clinical controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** high school students in Shirvan, Khorasan, Iran **Sample size:** 200 female high school students (anaemic and not anaemic); enrolled from the general population **Age range:** 14-18 years **Baseline prevalence of anaemia:** not available **Inclusion criteria:** anaemic and non-anaemic girls **Exclusion criteria:** students with high levels of haemoglobin (≥ 16 g/dL)
Interventions	Participants were allocated to 1 of 2 groups: 1. Group 1 (n = 100): morning shift control group (no treatment). 2. Group 2 (n = 100): afternoon shift, whether anaemic or not, received a 50 mg ferrous-sulphate tablet every Wednesday and Saturday. **Length of the intervention:** 16 weeks
Outcomes	1. Sociodemographics 2. Haemoglobin 3. Haematocrit 4. Mean corpuscular volumen 5. Attention score
Notes	**Comments:** distribution of the supplements, compliance and side effects were not mentioned **Study start date:** not available **Study end date:** not available **Funding source:** Vice Chancellor of the Islamic Azad University of Bojnourd, Iran **Conflicts of interest:** not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Comment:** the high school was selected using a simple draw method from the 4 female high schools in Shirvan, Khorasan, Iran, that enrolled students from the general population. Simple draw method was also used to determine whether the

Rezaeian 2014 (*Continued*)

		morning of afternoon shift was assigned as the control or intervention group. Using systematic random sampling, 25 students were selected from each age group
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** the examiner did not know whether the individual tested belonged to the case or control group. The person in charge of the data analysis did not know whether the data belonged to the control or case group. Although the participants were aware of whether they had or had not consumed the supplement, the nature of the study indicators used were objective or approximately objective (blood tests and attention scores), so it is unlikely that the participant's awareness of the consumption of the supplement would have had a major effect on the results
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** missing data of dropouts and withdrawals, and compliance
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Low risk	**Comment:** missing data on complete blood count and demographics

Riuvard 2006

Methods	**Design:** 2-arm, randomised controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** Internal Medicine Department, CHU de (University Hospital of) Clermont-Ferrand, France **Sample size:** 24 women **Age range:** 18 to 30 years **Baseline prevalence of anaemia:** not available **Inclusion criteria:** 1. iron deficiency (ferritin < 15 ug/L) 2. haemoglobin above 100 g/L 3. no significant health disorder **Exclusion criteria:** 1. gastrointestinal symptoms 2. previous intolerance to iron treatment, ongoing treatment with minerals or other

	micronutrients 3. C-reactive protein above 10 mg/L 4. Alanine Amino Transaminase > 1.5 of the normal value 5. presence of anti-hepatitis C or anti-HIV antibodies 6. presence of haemoglobin antigen
Interventions	Participants were allocated to 1 of 2 groups. 1. Group 1 (n = 13): women received 50 mg of iron as ferrous chloride daily. 2. Group 2 (n = 11): women received 50 mg of iron as ferrous chloride twice weekly. **Length of the intervention:** 3 months
Outcomes	1. Haemoglobin 2. Serum ferritin 3. Serum soluble transferrin receptor/TfR 4. Serum iron 5. Plasma transferrin 6. Oxidative stress
Notes	**Comments:** 1. On day 10 (D10) and on day 90 (D90) of Fe supplementation, blood samples were obtained, and women received about 5 mg of 57Fe orally, and blood was sampled at different times over 24 hours. The 57Fe absorption was evaluated by calculating the areas under the curves (AUC). 2. Malaria-free area. **Study start date:** not available **Study end date:** not available **Funding source:** supported, in part, by a grant from UCB Pharma (France) **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** participants were randomly assigned to 1 of the study groups with the aid of a randomisation table
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	**Comment:** participants, personnel, and outcome assessors were aware of the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** 3 participants withdrew from the study: 2 from group 1 and 1 from group 2
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement

Riuvard 2006 (*Continued*)

Other bias	Low risk	**Comment:** study appeared to be free of other bias

Roschnik 2003 (C)

Methods	**Design:** 2-arm, cluster-randomised trial **Unit of randomisation:** school level (40 schools) and stratified by sponsorship status
Participants	**Setting/location:** 40 primary schools in the Mangochi District, Malawi **Sample size:** 752 boys and girls (from 1160 randomised) **Age range:** for 371 girls; ~ 7-8 years (standard 2 grade) and ~ 12-15 years (standard 6 grade) **Baseline prevalence of anaemia:** around 54% **Inclusion criteria:** registered children **Exclusion criteria:** not available
Interventions	371 girls were randomly allocated to 1 of 2 groups. 1. Group 1 (n = 184 at follow-up): participants received 65 mg of elemental iron (as 200 mg of ferrous sulphate) and 250 μg (0.25 mg) of folic acid once a week. 2. Group 2 (n = 187 at follow-up): participants received no intervention. **Length of the intervention:** 15 weeks
Outcomes	1. Haemoglobin concentration 2. Bilharzia infection 3. School attendance 4. Test scores 5. Dropout rate* 6. Repetition rate* *(at school level)
Notes	**Comments:** 1. A famine occurred in the region at the time of the study. 2. Each study group included 10 sponsorship schools and 10 non-sponsorship schools, 10 coastal, and 10 upland schools. All children in coastal intervention and comparison schools, where the prevalence of bilharzia was over 50%, were dewormed with praziquantel (600 mg) just after the baseline survey. 3. A vitamin A capsule (200,000 IU) was given to all children in standard 2 and below. 4. 63% of children took 10 iron tablets or more. 5. Malaria endemicity was not reported. 6. We adjusted the results of this study to account for the effect of clustering in the data; we used the estimated effective sample size in the analyses. **Study start date:** July 2001 **Study end date:** not available **Funding source:** not available **Conflicts of interest:** not available

Risk of bias

Roschnik 2003 (C) (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** 40 primary schools in the Mangochi District were randomly divided into the intervention (1^{st} iron group) and comparison group (2^{nd} iron group). Each group included 10 sponsorship schools and 10 non-sponsorship schools. Method of sequence generation not specified
Allocation concealment (selection bias)	Low risk	**Comment:** not reported; however, since the intervention was allocated at school level, selection bias at individual level is unlikely
Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** not mentioned; however, as randomisation was at class level, it is unlikely that participants were blinded. Not reported for personnel or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** 1280 were randomised, 1160 had haemoglobin levels at baseline and 752 were followed up. 41.2% children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Unclear risk	**Comment:** children attending sponsored schools responded better to the treatment

Shah 2002

Methods	**Design:** 3-arm, randomised controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** government girls school of the Dharan Municipality, an urban foothill town in Nepal **Sample size:** 209 girls **Age range:** 11 to 18 years **Baseline prevalence of anaemia:** 48% **Inclusion criteria:** girls aged 11 to 18 years **Exclusion criteria:** 1. any chronic illnesses (e.g. asthma, rheumatic heart disease) 2. receiving any long-term allopathic or indigenous drug treatments 3. girls who had been hospitalised for any severe illness within the past 2 weeks

Interventions	Participants were allocated to 1 of 3 groups. 1. Group 1 (n = 67): participants received 70 mg of elemental iron (as 350 mg of ferrous sulphate) and 1500 μg (1.5 mg) of folic acid on a fixed day, once a week. 2. Group 2 (n = 70): participants received daily supplementation with tablets containing 70 mg of elemental iron (as 350 mg of ferrous sulphate) and 1500 μg (1.5 mg) of folic acid, once a day for 90 to 100 days (~ 14 weeks). 3. Group 3 (n = 72): participants received no treatment during the study period. **Length of the intervention:** 90 to 100 days (~ 14 weeks)
Outcomes	1. Anaemia (defined as haematocrit 36%) 2. Mean haematocrit and net change in haematocrit 3. Adherence. This was the only outcome we included in this review
Notes	**Comments:** 1. Daily supplements were given to parents on a weekly basis, and they were asked to maintain a record of its consumption. A study investigator supervised intake of weekly supplements. 2. **Quote:** "Drop-outs because of poor compliance were almost double in the daily supplementation group as compared with the weekly group, and persistent adverse effects were also limited to the daily supplementation group. However, because there were fewer participants, the impact of a daily vs weekly schedule on the adverse effects of iron therapy could not be confidently demonstrated" (data not shown). 3. Malaria endemicity was not reported. **Study start date:** March 1998 **Study end date:** March 1999 **Funding source:** Research Committee of BP Koirala Institute of Health Sciences, Dharan **Conflicts of interest:** not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Comment:** participants randomly assigned to 1 of 3 groups. Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	**Comment:** participants, personnel, and outcome assessors were aware of the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** of the 209 girls who met the inclusion criteria, 181 completed the study (87%); losses were balanced among groups. Severe adverse effects, non-compliance to treatment, and non-availability for final haematocrit measurement were listed as

Shah 2002 (*Continued*)

		reasons for losses. Numbers of participants who left for each reason was not documented
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	High risk	**Comment:** participants in the daily regimen group were not supervised and only asked to maintain a record of the supplements consumption, while those in the weekly group were supervised by an investigator

Shobha 2003

Methods	**Design:** 3 × 2 randomised controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** Andhra Pradesh Social Welfare Residential School, located in Ranga Reddy district, India **Sample size:** 244 females **Age range:** 13 to 15 years **Baseline prevalence of anaemia:** 83% **Inclusion criteria:** not available **Exclusion criteria:** not available
Interventions	Adolescents were allocated to 1 of 2 groups. 1. Group 1 (n = 102): participants received 60 mg of iron and 500 μg (0.5 mg) of folic acid daily. 2. Group 2 (n = 101): participants received 60 mg of iron and 500 μg (0.5 mg) of folic acid twice a week, every Wednesday and Saturday. **Length of the intervention:** 84 days
Outcomes	1. Haemoglobin (stratified by anaemia status*) 2. Attendance 3. Morbidity 4. Adherence 5. Side effects For the purposes of this review, we pooled all girls in group 1, independently of the degree of anaemia, and did the same for group 2 *Based on initial haemoglobin levels, participants were classified as normal (higher than 120 g/L), mildly anaemic (100-119.9 g/L), moderately anaemic (80-99.9 g/L), or severely anaemic (80 g/L), as per the WHO standard
Notes	**Comments:** 1. The participants were dewormed with a single dose of 400 mg of albendazole 1 week prior to supplementation. 2. Supplementation was carried out under the strict supervision of the investigator

Shobha 2003 (*Continued*)

	and the supplement was administered around 4.00 pm, 3 hours after lunch and 3 hours before dinner. **Study start date:** not available **Study end date:** not available **Funding source:** none **Conflicts of interest:** none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** participants stratified by grade of anaemia (mild, moderate, or severe) and randomly divided into study groups. Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	**Comment:** not mentioned for participants, personnel, or outcome assessors. However, there was no placebo for girls under the once weekly regimen (for the rest of the days), while the girls under the intermittent regimen took a tablet every day in the same school
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** not mentioned
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Unclear risk	**Comment:** distribution of mild, moderate, and severe anaemia not shown

Soekarjo 2004 (C)

Methods	**Design:** 4-arm, cluster-randomised, school-based supplementation trial **Unit of randomisation:** class level
Participants	**Setting/location:** 4 rural or urban schools selected from 2 districts (Bangkalan and Sampang) on the island of Madura, representing both main school types in Indonesia **Sample size:** 1460 postmenarchal adolescents **Age range:** 12-15 years **Baseline prevalence of anaemia:** 22.9%-26.1% **Inclusion criteria:** school students **Exclusion criteria:** not available

Soekarjo 2004 (C) (*Continued*)

Interventions	15 intervention schools. All children (n = 2990) received supplements and were divided into 3 groups according to their grade 1. Group 1 (n = 489): students received 10,000 IU of vitamin A. 2. Group 2 (n = 516): students took 60 mg of elemental iron (as ferrous sulphate) and 250 μg (0.25 mg) of folic acid once a week. 3. Group 3 (n = 533): students received weekly doses of 10,000 IU of vitamin A, 60 mg of elemental iron, 250 μg (0.25 mg) of folic acid. A fourth group (9 schools; n = 923) did not receive the intervention **Length of the intervention:** 3 months Given that it was unclear how the 9 schools were allocated to receive no intervention, and that the 3 intervention groups were allocated at random to each intervention, we only compared groups 1 and 3
Outcomes	1. Haemoglobin concentration (stratified subsequently by sex, pubertal status, and anaemia status) 2. Compliance 3. Side effects. We only included data for pubescent girls
Notes	**Comments:** 1. This study also included data for boys, which we did not use in this review. 2. Children took 9 tablets under the supervision of trained field workers (1-2 field workers per ~ 50 students). 5 tablets were distributed at school with instructions to be taken once a week on a fixed day at home during Ramadan and school holidays. 3. All pupils were aware of the supplements they were taking and were told iron would improve health and prevent/cure anaemia. 4. Self-reported compliance and side effects were recorded at the end of the intervention from a random subsample of girls taking supplements (n = 413; 13.8%). Almost all respondents (90%-97%) claimed to have taken at least half of the tablets distributed under supervision. Without supervision, however, this proportion dropped to 50%-70%. 41% of the girls taking supplements reported gastrointestinal side effects. 5. Malaria endemicity was not reported. 6. We adjusted the results of this study to account for the effect of clustering in the data; we used the estimated effective sample size in the analyses. **Study start date:** October 1996 **Study end date:** May 1997 **Funding source:** Helen Keller International in cooperation with the Ministry of Health of the Government of Indonesia as part of the GIRLS (Gizi: Intervensi Remaja Lewat Sekolah/Nutrition Intervention for Adolescents through Schools) Project **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** adolescents from 15 schools were randomly selected to receive weekly supplements, while adolescents in the other 9 schools served as controls. In each of the schools receiving supplements, each of

Soekarjo 2004 (C) (*Continued*)

		the 3 grades was randomly allocated to receive 1 of the 3 supplementation regimens. Method of sequence generation not mentioned
Allocation concealment (selection bias)	Low risk	**Comment:** not mentioned; however, since this is a cluster trial, selection bias at individual level is unlikely
Blinding (performance bias and detection bias) All outcomes	High risk	**Comment:** participants were aware of the treatment; but randomisation was done at class levels. Likely that personnel and outcome assessors were also aware of the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** 4810 out of 5116 participants (96%) completed the study. Losses were mainly caused by absenteeism on several consecutive days during the end-line data collection. There was no difference in dropout rate between the 4 groups
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Low risk	**Comment:** study appeared to be free of other bias

Zavaleta 2000

Methods	**Design:** 3-arm, double-blind, placebo-controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** public secondary school in Villa El Salvador, a peri-urban shanty town in Lima, Peru **Sample size:** 312 adolescent girls **Age range:** 12-18 years **Baseline prevalence of anaemia:** ~ 19% **Inclusion criteria:** 1. living in community for at least 6 months 2. healthy, nulliparous, menstruating regularly in the last three months 3. haemoglobin lower than 80 g/L **Exclusion criterion:** multi-vitamin/mineral supplement intake in the last 6 months
Interventions	Participants were allocated to 1 of 3 groups. 1. Group 1 (n = 98): girls were given a tablet containing 60 mg of elemental iron as ferrous sulphate 2 days of the week and a placebo on the other 3 days of the week, Monday-Friday. 2. Group 2 (n = 101): girls were given a tablet containing 60 mg of elemental iron as

	ferrous sulphate 5 days of the week, Monday-Friday. 3. Group 3 (n = 97): girls were given a placebo 5 days of the week, Monday-Friday. All tablets had the same brick colour and shape. **Length of the intervention:** 17 weeks
Outcomes	1. Anaemia 2. Haemoglobin 3. Serum ferritin 4. Free erythrocyte protoporphyrin We were not able to use continuous data for haemoglobin because standard deviations and number of cases and controls were not reported at follow-up. Changes in haemoglobin levels by initial anaemia status in adolescents were presented in graphs (final haemoglobin concentrations for daily, intermittent, and control groups were 123.7 g/L, 120 g/L and 110.4 g/L, respectively)
Notes	**Comments:** 1. Supplements were administered daily, at school, between meals, together with a sweetened flavoured drink without ascorbic acid, and under close supervision of a field worker. 2. Girls took 94% of the expected dose of 85 pills, and the median consumption was 80 tablets in the 3 groups. Few girls in the 3 groups reported side effects (e.g. gastrointestinal problems or headache) during the intervention, and there was no significant difference in the frequency of side effects reported by any group. **Study start date:** August 1996 **Study end date:** December 1996 **Funding source:** not available **Conflicts of interest:** not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** participants randomly assigned to treatments. Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	**Comment:** all tablets had the same brick colour and shape and were distributed in coded blister packages
Blinding (performance bias and detection bias) All outcomes	Low risk	**Comment:** all tablets looked similar and were administered in coded packages. Participants and personnel were not aware of the treatment; not described for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** a total of 312 girls started the study and 16 (5.1%) dropped out. Of these 16, 8 moved to another school, 2 disliked

Zavaleta 2000 (*Continued*)

		the tablets, 4 complained of side effects and withdrew, and 2 were absent at the time of final evaluation
Selective reporting (reporting bias)	Unclear risk	**Comment:** insufficient information to permit judgement
Other bias	Low risk	**Comment:** study appeared to be free of other bias

AUC:areaunderthecurve

Fe: iron
IFA: iron and folic acid
MCH: mean corpuscular haemoglobin
MCHC: mean corpuscular haemoglobin concentration
MCV: mean corpuscular volume
RBC: red blood cells
SEAMEO-TROPMED: Southeast Asian Ministers of Education Tropical Medicine and Public Health Network
TfR: transferrin receptor
UNICEF: United Nations International Children's Emergency Fund
UCB: Union Chimique Belge
WBC: white blood cells
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmed 2005	Randomised, double-blind clinical trial conducted in Bangladesh. Anaemic (haemoglobin less than 120 g/L) girls (n = 197) aged 14-18 years old from rural schools in Dhaka District were entered into a randomised double-blind trial and received twice-weekly supplements of iron and folic acid or multiple micronutrients (15 micronutrients, including iron and folic acid for 12 weeks). Found that twice-weekly multiple micronutrients supplementation for 12 weeks significantly improved the status of the micronutrients assessed, but was not more efficacious than supplementation with iron and folic acid alone in improving the haematologic status of anaemic adolescent girls. We excluded the study because the authors did not compare intermittent iron supplementation versus daily supplementation or placebo and hence it was outside the scope of this review
Ahmed 2010	Randomised, double-blind trial conducted in Bangladesh. Anaemic adolescent girls (n = 324) aged 11-17 years, attending rural schools, were given once- or twice-weekly multiple micronutrient supplements or twice-weekly iron-folic acid supplements, containing 60 mg of elemental iron/dose in both supplements, for 52 weeks. Both once- and twice-weekly multiple micronutrient supplements significantly improved riboflavin, vitamin A, and vitamin C status compared with iron-folic acid supplements. Overall, once-weekly multiple micronutrient supplements was less efficacious than twice-weekly multiple micronutrient supplements in improving iron, riboflavin, red blood cell folate, and vitamin A levels. Micronutrient

(*Continued*)

	supplementation beyond 26 weeks was likely important in sustaining improved micronutrient status. We excluded the study because the authors did not compare intermittent iron supplementation versus daily supplementation or placebo and hence it was outside the scope of this review
Ahmed 2012	Randomised, double blind controlled trial with 324 adolescent girls to investigate the effect of long-term once-weekly and twice-weekly UNIMMAP dose using a double dose of all nutrients except for folic acid. 3 supplementation groups: 1) double UNIMMAP dose and a placebo once weekly; 2) double UNIMMAP dose twice weekly; 3) routine standard dose of iron-folic acid twice weekly. An equal number of 324 rural school girls aged 11-17 years old were randomly assigned to each intervention group. Blood samples were collected at baseline, 26 and 52 weeks. MMN-1 was found to be less effective than MMN-2 in improving iron, vitamins A and B2 and folic acid status. Receiving MMN beyond 26 weeks showed little additional benefit in improving micronutrients status. In conclusion, given twice weekly for 26 weeks, MMN supplements improved micronutrient status effectively with no significant increase in haemoglobin concentration compared with iron-folic acid alone in non-anaemic adolescent Bangladeshi girls. We excluded the study because the comparison was outside the scope of this review
Bansal 2016	Community-based, randomised, double-blind controlled trial conducted among anaemic adolescent girls (n = 446) 11-18 years of age. Sought to assess and compare the impact of weekly iron-folic acid supplementation with or without vitamin B12 on reduction in prevalence of anaemia and blood concentrations of haemoglobin, ferritin, folic acid, and vitamin B12. Weekly supervised supplementation was given for 26 weeks. Group A (n = 222): iron (100 mg), folic acid (500 mcg) and placebo; Group B (n = 224) : iron (100 mg), folic acid (500 mcg) and cyanocobalamin (500 mcg for 6 weeks and 15 mcg for 20 weeks). Haemoglobin, serum ferritin, folic acid and vitamin B12 levels were assessed at baseline and after intervention. A total of 373 participants completed 26 weeks of supplementation successfully. The study showed that iron-folic acid supplementation with or without vitamin B12 was an effective method of curing anaemia. We excluded the study because the comparison was outside the scope of this review
Beaton 1999	A report based on the analysis of 22 completed trials of iron supplementation. The major objective of the analysis was to determine, to the extent possible, the situations in which the apparent efficacy of intermittent supplementation was maximised. We excluded the report because it was a review
Berger 2005	Community-based trial in all 19 communes of the Thanh Mien district in the Hai Duong province in Hanoi, Vietnam. Women were informed by the social marketing campaign about the benefits of taking preventive iron folic-acid supplementation before and during pregnancy, combined with improved diets. Women recruited were married, nulliparous and planning to have a child. They were allocated to 2 treatments according to their pregnancy status at baseline: daily supplements containing 60 mg of elemental iron + 250 μg (0.25 mg) of folic acid to pregnant women or weekly intervention to non-pregnant women. We excluded the study because it was not randomised and did not have a control group
Bruner 1996	Double-blind, placebo-controlled clinical trial that assessed the effects of iron supplementation on cognitive function in adolescent girls (n = 716) with non-anaemic iron deficiency. Girls who enrolled at 4 high schools in Baltimore, USA, were screened for non-anaemic iron deficiency (serum ferritin = 12 μg/L or less with normal haemoglobin). 98 (13.7%) girls had non-anaemic iron deficiency, 81 of whom were enrolled in the trial. Participants were randomly assigned oral ferrous sulphate (650 mg twice daily) or placebo for 8 weeks. The effect of iron treatment was assessed by questionnaires and haematological and cognitive tests, which were done before treatment started and repeated after the intervention. Authors used 4 tests of attention and memory to measure cognitive functioning. Intention-to-treat and per-protocol analyses were done. Of the 81 enrolled girls with non-anaemic iron deficiency, 78 (96%) completed the study (39 in each group). 5 girls (3 = control, 2 = treatment) developed anaemia during the intervention and were

(*Continued*)

	excluded from the analyses. Thus, 73 girls were included in the per-protocol analysis. Ethnic distribution, mean age, serum ferritin concentrations, haemoglobin concentrations, and cognitive test scores of the groups did not differ significantly at baseline. Postintervention haematological measures of iron status were significantly improved in the treatment group (serum ferritin = 27.3 vs 12.1 μg/L, P < 0.001). Regression analysis showed that girls who received iron performed better on a test of verbal learning and memory than girls in the control group (P < 0.02). In this urban population of non-anaemic, iron-deficient adolescent girls, iron supplementation improved verbal learning and memory. We excluded the study because the authors did not compare intermittent iron supplementation versus daily supplementation or placebo and hence the study was outside the scope of this review
Casey 2009	Distribution of weekly iron and folic acid supplementation and deworming were integrated with routine health services and made available to 52,000 women. Demographic data and blood and stool samples were collected at baseline and 3- and 12-month post-implementation surveys using a population-based, stratified, multi-stage cluster sampling design. Authors concluded that a free, universal, weekly iron and folic acid supplementation programme with regular deworming was associated with reduced prevalence and severity of anaemia, iron deficiency, and hookworm infection when made available to Vietnamese women over a 12-month period. We excluded the study because it was not randomised and did not have a control group
Cook 1995	Study designed to examine inhibition in absorption from iron taken on the previous day by measuring iron absorption from 50 mg of radiolabeled ferrous sulphate in 23 female volunteer participants divided into 2 groups. In the first group, a labelled ferrous sulphate supplement was given with water, and in the second group it was given with a rice-based meal. In both groups, absorption was measured in a randomised fashion twice in each participant, once with daily and once with weekly supplementation. Those tested for daily supplementation were given an iron supplement daily for 6 days before testing whereas those tested for weekly supplementation were given no iron for 6 days before testing. When the labelled iron supplement was given with water only, absorption averaged 8.5% with daily and 9.8% with weekly administration compared with 2.3% and 2.6%, respectively, when given with food. The 13% lower absorption observed with daily administration in both groups was not statistically significant (P > 0.20). These results indicated that there was no significant absorptive advantage in giving iron less often than once daily. We excluded the study because it was not a controlled trial
Crape 2005	A social marketing programme promoting weekly iron-folic acid supplementation improved haemoglobin levels in women of reproductive age in Cambodia. Supplementation was increasingly effective among women of higher socioeconomic status. We excluded the study because it was not randomised and did not have a control group
Deshmukh 2008	Effectiveness trial of a weekly, iron supplementation regimen through the government health system among urban slum, rural, and tribal girls of Nashik district, India. Participants were adolescent girls (14-18 years old) who were given supplements containing 100 mg of iron and 500 μg (0.5 mg) of folic acid and were trained for three hours every day for three days. The overall prevalence of anaemia came down significantly to 54.3% from 65.3%. We excluded the study because it was not randomised and did not have a control group, and hence was outside the scope of this review
Dwividi 2006	Review of programmes in India of weekly iron supplementation to control anaemia in adolescent girls. Programmes, implemented in 13 states with varying coverage, targeted 2 different groups: girls in school and girls out of school. The objective of the review was to summarise and analyse the status/characteristics of the various adolescent anaemia programmes in India, summarise and analyse the results of the impact assessments that have already been conducted, and to estimate and analyse the costs of the programmes.

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	From results, it was evident that weekly iron/folic acid supplementation in adolescents girls led to a marked decrease in the prevalence of anaemia. In some cases, a large long-term impact (70%, 2 years) was reported. Reasons for the small but significant decrease in the prevalence of anaemia included low compliance and a possible multicausality of anaemia as deficiency in other vitamins and minerals or genetic causes. It could also be that a larger reduction in anaemia prevalence may be achieved only after prolonged supplementation. Supplementation programmes should continue until other sources of iron intake become available, be it from natural dietary sources or from fortified foods, or both. Programmes targeting out-of-school girls can be successful as the interventions targeting these girls also resulted in significant decreases in anaemia prevalence. Success factors included: ensuring compliance; counselling not only the beneficiaries but the community; ensuring continuous tablet supply and regular monitoring; among others. It is clear that if well conceived, the supplementation component of an overall package of services for the adolescent girl costs very little. We excluded this record because it was a review
Horjus 2005	Pre-post study to assess the programme effectiveness of 2 school-based weekly iron-folic acid supplementation regimens: 5 months versus 8 months. In both groups, participant girls received 60 mg of elemental iron and 400 µg (0.4 mg) of folic acid. All girls received a single dose of mebendazole at the beginning of the study and at 6 months. The study found that school-based weekly supplementation is a feasible and effective intervention to prevent seasonal drops in haemoglobin concentration and increases in anaemia prevalence. We excluded the study because it was not randomised and the comparisons did not fit the scope of this review
Jackson 2003	Randomised trial to ascertain whether short-term supplementation with iron was effective in reducing anaemia. Assigned 608 girls with mild-to-moderate anaemia from high schools to 3 treatment groups. Supplementation included 60 mg of iron per week, 3500 μg (3.5 mg) of folic acid per week, iron + folic acid (same dose), and a control group. In conclusion, 8 weeks of supplements given on a weekly basis were well tolerated and caused few symptoms, and the regimen was effective in reducing anaemia by 30-40%. We excluded the study because the control group was not randomised and included it non-anaemic classmates (with normal haemoglobin values)
Joseph 2013	To assess if weekly iron-folic acid dose (150 mg of ferrous sulphate + 0.5 mg of folic acid along with vitamin C (100 mg)) in the workplace could reduce the prevalence of anaemia. The study setting was 7 apparel manufacturing factories and it lasted 16 weeks. A sample of 515 workers were included and given a single dose of albendazole before the supplementation period. Haemoglobin levels of a randomly-selected sample of workers were tested before and after the intervention. Found that the workplace might be an ideal location for weekly iron supplementation to tackle anaemia effectively and possibly improve working efficiency. We excluded the study because it was not a randomised controlled trial
Kätelhut 1996	Randomised effectiveness study to investigate whether a supplement containing iron and folic acid, vitamin A, and vitamin C would be more effective than a supplement containing only iron and a smaller amount of folic acid in improving the iron status of young women. A total of 84 menstruating anaemic and non-anaemic girls were included and randomly assigned to 2 groups. Group 1 received weekly supplements containing 60 mg of elemental iron + 500 mcg folic acid + 20,000 IU vitamin A and 60 mg ascorbic acid for 5 weeks. Group 2 received weekly supplements containing only 60 mg of elemental iron and 250 mcg of folic acid. Haemoglobin, mean cell volume, and serum ferritin increased in both groups, confirming that weekly supplementation was effective in improving iron status in a short time. We excluded the study because the comparison was outside the scope of this review

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López de Romaña 2006	Cluster trial conducted in Peru among women and adolescent girls of childbearing age and children under 5 years of age, to assess the impact of a campaign on the growth of children and on anaemia among children and among women and adolescent girls of childbearing age. Weekly multi-micronutrient supplementation was provided for 8 weeks in communities with a high prevalence of stunting; control households were selected from communities with a lower prevalence of stunting. There were no significant effects of weekly multi-micronutrient supplementation on anaemia or growth. We excluded the study because it was not randomised
Moretti 2015	Authors conducted 3 separate studies with the aim of measuring acute iron-induced increase in hepcidin. They used a cross-over design study to assess iron status markers. In study 1, participants were randomly assigned to take 2 iron challenges either as a single dose or as 2 doses given on consecutive days; hepcidin response was assessed after 48 hours. In study 2, 2 single doses of 60 mg of elemental iron were administered on 2 consecutive days and, similarly hepcidin response was assessed after 48 hours. In study 3, the effect of administering 60 mg of iron twice daily during 24 hours on hepcidin levels and iron absorption was assessed. The duration of hepcidin response supported alternate days of supplementation. We excluded the study because the setting, population and intervention were outside the scope of this review
Pasricha 2009	Multi-stage, cluster-sampling study. A programme of weekly iron and folic acid supplementation and deworming every 4 months for all women of reproductive age living in Yen Bai province, Vietnam, was implemented by active distribution through the existing primary health structure. Women received ferrous sulphate and folic acid tablets. After 3 months, anaemia prevalence fell to 58/221 (26.2%), and the mean haemoglobin change was + 3.5 g/L (95% CI 0.9 to 6.6). We excluded the study because it was not randomised and did not have a control group, and hence was outside the scope of this review
Perrin 2002	We excluded this record because it was a commentary paper on Shah 2002
Ramakrishnan 2012	Double-blind, randomised controlled trial with 5011 women, to evaluate whether providing additional, pre-pregnancy, weekly iron-folic acid or multiple micronutrient supplements improves iron status and anaemia during pregnancy and early postpartum, compared to folic acid only. Women were provided with weekly supplements containing either only 2800 mcg of folic acid (control group), 60 mg iron + 2800 mcg of folic acid, or 15 micronutrients with similar amounts of iron and folic acid. All women who became pregnant (n = 1813) in each of the 3 groups received daily supplements (60 mg of iron + 400 mcg of folic acid) through delivery. Haematological indicators were assessed at baseline (pre-pregnancy), during pregnancy, postpartum, and in cord blood. We excluded the study because, although supplements were given during pre-pregnancy, no outcomes on pre-pregnancy (i.e. menstruating women) were reported, only pregnancy and postpartum
Sen 2012	Randomised, efficacy controlled trial to assess the impact of iron-folic acid supplementation on hemanitic status and growth of school girls. The trial was conducted in primary urban schools with girls (aged 9-13 years) only. 4 schools were randomly assigned to either treatment or control: 100 mg of elemental iron + 0.5 mg of folic acid once weekly, twice weekly, daily, and no treatment in the control group. Haemoglobin levels increased significantly in all intervention schools, with higher increases among anaemic girls. Twice-weekly supplementation was comparable to daily supplementation with regard to impact on haemoglobin and growth, at less cost and greater feasibility. We excluded the study because it did not include menstruating girls: girls who attained their menarche (n = 18), prior to or during the study, were excluded from the analysis though they received the supplements

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Shah 2016	Community-based, cross-sectional study in 5 tribal villages in India to describe the burden of anaemia. The study included adolescent boys (n = 127) and girls (n =117) aged 10-19 years. They were provided weekly with iron-folic acid supplements containing 100 mg of elemental iron and 500 mcg of folic acid, along with the distribution of abendazole tablets for bi-annual deworming. Awareness sessions were conducted for mothers and adolescents. Results showed a significant reduction in anaemia of all severity among adolescents boys and girls. We excluded the study because it was not a randomised controlled trial
Siddiqui 2003	Study to compare improvement in haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin and ferritin levels in children (aged 5-10 years) and women of reproductive age (15-45 years of age) , who were supplemented orally with single and double doses of ferrous sulphate daily and once weekly. 20 children received 200 mg of ferrous sulphate daily and 20 received the same dose once weekly for 2 months. 10 women received 300 mg of ferrous sulphate daily, 10 received the same dose once weekly, and 10 received 600 mg of ferrous sulphate once weekly for 1 month. All parameters improved significantly in children who received 200 mg of ferrous sulphate daily and weekly. Similarly, the parameters improved significantly in women who received 300 mg of ferrous sulphate daily and 600 mg of ferrous sulphate weekly. In conclusion, weekly supplementation of iron was far better at controlling iron deficiency anaemia, due to cost-effectiveness and better compliance. We excluded the study because it was not randomised and did not have a control group, and hence was outside the scope of this review
Taylor 2001	Randomised controlled trial with 428 primary school students stratified into 6 groups by age, sex, and intervention, with the objective of measuring the effect of different anthelmintic treatments and iron supplementation regimens provided twice at 6-monthly intervals for 1 year. Half of the students received iron supplementation (200 mg of ferrous fumarate weekly for 10 weeks). Students received 2 anthelmintic regimens, either 400 mg of albendazole plus 40 mg/kg of praziquantel or 400 mg of albendazole on 3 consecutive days plus 40 mg/kg of praziquantel, or placebo. 12 months after treatment there was a significant increase in haemoglobin levels (P = 0.02) among pupils receiving triple-dose albendazole, praziquantel and ferrous fumarate; students receiving no anthelmintic treatment showed a significant decrease, as did pupils who received triple-dose albendazole and praziquantel but no iron. We excluded the study because postmenarchal girls were excluded from the study due to risk of pregnancy and treatments were not secure during pregnancy (at the moment, the safety of albendazole during pregnancy has not been established)
Tee 1999	Study that investigated whether long-term, weekly iron and folic acid supplements administered at school would improve haemoglobin and ferritin concentrations in adolescent girls, including those with mild-to-moderate anaemia and haemoglobin concentrations indicating borderline anaemia. 266 girls with haemoglobin concentrations of 80-119.9 g/L (group A) and 358 girls with haemoglobin concentrations of 120-130 g/L (group B) who were otherwise healthy took part; group C did not receive supplements but was not followed-up. All 266 girls in group A and 268 (out of 358) girls in group B were randomly assigned to receive either 60 mg or 120 mg of elemental iron plus 3500 μg (3.5 mg) of folic acid weekly for 22 weeks. 90 of the girls in group B were randomly assigned to receive only 5000 μg (5 mg) of folic acid weekly. Authors concluded that long-term, weekly iron-folic acid supplementation was a practical, safe, effective, and inexpensive method for improving iron nutrition in adolescent school girls. We excluded the study because girls in both arms were given iron on a weekly basis
Vir 2008	Study performed in school and non-school girls aged 11-18 years that aimed to assess the effectiveness of weekly iron-folic acid supplementation in reducing the prevalence of anaemia in adolescent girls. The project provided weekly iron-folic acid tablets, family life education, and deworming tablets every 6 months to 150,700 adolescent school and non-school girls of a total district population of 3,647,834. Groups were not evaluated simultaneously. In 4 years, the overall prevalence of anaemia was reduced from 73.3% to 25.

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	4%. Haemoglobin levels and anaemia prevalence were influenced significantly at 6 months. No difference in the impact on haemoglobin or anaemia prevalence was observed between supervised and unsupervised girls. We excluded the study because it was not randomised and did not have a control group
Viteri 1999	Randomised, double-blind trial involving 239 healthy, menstruating women, older than 18 years of age (some anaemic and some iron deficient) from the University of California, Berkely community, USA. Exclusion criteria: blood donation during the previous 6 months, pregnancy, pregnancy terminated during the previous year, lactating, meno-metrorrhagia, having a chronic condition interfering with normal iron metabolism, currently taking or having taken therapeutic iron during the last 6 months, and predicted impossibility to comply with the experimental protocol. Group 1 received 60 mg of elemental iron + 250 µg (0.25 mg) of folic acid daily for 3 months and 250 µg (0.25 mg) of folic acid weekly for 4 months. Group 2 received 60 mg of elemental iron + 250 µg (0.25 mg) of folic acid daily for 3 months and 60 mg of elemental iron + 250 µg (0.25 mg) of folic acid weekly (same dose) for 4 months. Group 3 received 250 µg (0.25 mg) of folic acid daily for 3 months and 250 µg (0.25 mg) of folic acid (same dose) weekly for 4 months. We excluded the study because the intervention groups did not match the comparisons of interest in this review

CI:confidenceintervals

MMN: multiple micronutrients
N: number
UNIMMAP: United Nations International Multiple Micronutrient Preparation
VS: versus

Characteristics of studies awaiting assessment *[ordered by study ID]*

Brabin 2014

Methods	**Design:** randomised, double-blind, controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** highly malarious areas in Africa **Sample size:** ~ 1800 young women of childbearing age (enrolled prior to their first pregnancy) **Age range:** not reported (median = 16 years) **Inclusion criteria:** not available **Exclusion criteria:** not available
Interventions	Women were allocated to 1 of 2 groups. 1. Group 1: 60 mg of iron + 2.8 mg of folic acid. 2. Group 2: 2.8 mg of folic acid (control). Supplements were given under the observation of field workers during weekly home visits. Women who remained non-pregnant continued weekly iron-folic acid supplementation for 18 months. Those who became pregnant continued weekly iron-folic acid supplementation until the first antenatal visit by the study team
Outcomes	1. Anaemia 2. Perceptions 3. Knowledge

Brabin 2014 (*Continued*)

Notes	**Comment:** This was the qualitative report of the randomised controlled trial. It was missing the quantitative results that may be included in the review, when available **Study start date:** April 2011 **Study end date:** June 2013 **Funding source:** National Institutes of Health (NIH) and Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) **Conflicts of interest:** not available

Malhotra 2013

Methods	**Design:** 4-arm, randomised controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** outside Delhi, India **Sample size:** 140 adolescent girls **Age range:** 14-19 years **Inclusion criteria:** not available **Exclusion criteria:** not available
Interventions	Participants were allocated to1 of 4 groups. 1. Group 1: no intervention (control). 2. Group 2: girls received a tablet with 60 mg of elemental iron and 0.5 mg of folic acid (IFA supplementation). 3. Group 3: girls received a tablet with 60 mg of elemental iron and 0.5 mg of folic acid plus nutrition education (IFA supplementation + NE). 4. Group 4: girls received nutrition education (NE).
Outcomes	1. Anthropopmetric measures 2. Dietary data 3. Haemoglobin 4. Knowledge, attitude and practices (KAP) regarding anaemia, both at baseline and at 12 weeks
Notes	**Comment:** Population was mixed anaemic and non-anaemic girls. Available abstract did not provide quantitative data for extraction for meta-analysis **Study start date:** not available **Study end date:** not available **Funding source:** Indian Council of Medical Research, New Delhi **Conflicts of interest:** none declared

Olsen 2000

Methods	**Design:** 2 × 2, randomised, double-blind, placebo-controlled trial **Unit of randomisation:** individual level
Participants	**Setting/location:** in the villages of Asino, Ohala and Pith-Kodhiambo, which lie in the Kisumu district of Nyanza province, Western Kenya **Sample size:** school children (from schools with highest prevalence of helminth infections) **Age range:** 8-18 years **Inclusion criteria:** moderately low blood concentrations of haemoglobin (i.e. 80-130 g/L if a child aged 4-14 years

Olsen 2000 (*Continued*)

	or a non-pregnant female aged > 14 years of age, and 80-135 g/L if male and aged > 14 years) **Exclusion criteria:** 1. Signs of micronutrient deficiencies 2. Haemoglobin concentrations below 80 g/L 3. Signs of other acute disease 4. pregnant female These participants were offered relevant treatment.
Interventions	877 children were randomly allocated to 1 of 2 groups. 1. Group 1: multi-micronutrient supplementation. 2. Group 2: identical-looking placebo. Additionally, each participant was independently randomised to: multi-helminth chemotherapy or identical looking placebo **Length of the intervention:** 4 weeks
Outcomes	1. Malaria 2. Haemoglobin 3. Helminth infections 4. Serum retinol 5. Weight 6. Height
Notes	**Comment:** We were unable to obtain the data for girls separately. **Study start date:** November 1994 **Study end date:** January 1996 **Fundind source:** Institute for Health Research and Development financially supported this work and SmithKline Beecham in Nairobi generously supplied the albendazole used **Conflict of interest:** not available

Sharma 2000

Methods	**Design:** 3-arm, randomised experimental trial **Unit of randomisation:** individual level
Participants	**Setting/location:** poor communities in urban areas of Delhi and rural parts of Bharatpu **Sample size:** 270 adolescent girls **Age range:** not available **Inclusion criterion:** haemoglobin levels of > 12 g/dL **Exclusion criteria:** not available
Interventions	Participants were allocated to 1 of 4 groups. 1. Group 1 (n = 83): girls received 1 tablet with 100 mg of elemental iron plus 500 μg (0.5 mg) of folic acid once a week. 2. Group 2 (n = 95): girls received 1 tablet with 100 mg of elemental iron, 500 μg (0.5 mg) of folic acid and 25 mg of vitamin C once a week. 3. Group 3 (n = 37): girls received 1 tablet of iron-folic acid (100 mg of elemental iron + 500 μg (0.5 mg) of folic acid) daily. 4. Group 4 (n = 55): urban control group (unclear if received no intervention or a placebo). **Length of the intervention:** 6 months

Sharma 2000 (*Continued*)

	For the purposes of this review, we combined groups 1 and 3, separating them only for the subgroup analysis by composition
Outcomes	1. Anthropopmetric measures 2. Anaemia 3. Change in haemoglobin
Notes	**Comment:** 1. In school, tablets were distributed weekly to the participants by a research worker immediately after lunch time so that they were not taken on an empty stomach. The intake of the tablets by the participants was assured by a helper. In the rural area, 2 field workers were responsible for the distribution and ensuring intake of tablets by the participants only after brunch. 2. Malaria endemicity was not reported. 3. Student awaiting assessment until receiving more information about the study design and groups as it was unclear the number of people leaving in rural/urban areas and there was a clear imbalance between study arms. 4. Age of participants was not available to see if the study met inclusion criteria. 5. We attempted to contact the authors to obtain further information on this trial but received no response at the time of publication. **Study start date:** not available **Study end date:** not available **Funding source:** not available **Conflicts of interest:** not available

IFA:ironandfolicacid

KAP: knowledge, attitudes and practices
NE: nutrition education

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2017/11/010453

Trial name or title	Efficacy of once a week versus daily iron supplementation for control of anaemia in school-going adolescent girls: a randomised clinical trial
Methods	Randomised controlled trial. 2-arm study design
Participants	**Setting:** selected schools of higher primary and high schools of Handignur PHC **Target sample size:** 588 **Participants:** anaemic adolescent girls **Age:** 12-16 years old **Inclusion criteria:** 1. studying in selected schools of higher primary and high schools of Handignur PHC and consented to participate in the study 2. attained menarche 3. mild to moderate anaemia (haemoglobin less than 12 g/dL) 4. age group 12 to 16 years

CTRI/2017/11/010453 (*Continued*)

	Exclusion criteria: 1. severely anaemic girls (i.e. haemoglobin less than 8 gm/dL) - referred to hospital for treatment 2. history of any bleeding disorders 3. known cases of systemic diseases 4. not attending the school regularly
Interventions	Participants were allocated to 1 of the following groups: 1. **Intervention (n = not available):** girls receive 1 tablet with 200 mg of ferrous sulphate once a week. 2. **Control (n = not available):** girls receive 1 tablet with 200 mg of ferrous sulphate per day. **Length of the intervention:** 3 months
Outcomes	**Primary outcomes:** 1. Haemoglobin 2. Anaemia
Starting date	October 2017 **Current status:** not known
Contact information	**Name:** Dr Sangeeta A Moreshwar **Affilitation:** PD Bharatesh College of Nursing, Halaga, Belgaum, India **Email:** smoreshwar@yahoo.co.in
Notes	**Funding source:** not available **Conflicts of interest:** not available

DATA AND ANALYSES

Comparison 1. Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anaemia (All)	11	3135	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.49, 0.87]
2 Anaemia (by supplement composition)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Iron alone	2	292	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.09, 2.13]
2.2 Iron plus folic acid	8	1871	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.52, 0.97]
2.3 Iron plus multiple micronutrients	3	972	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.25, 1.07]
3 Anaemia (by anaemia status at baseline)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Anaemic	1	222	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.30, 0.52]
3.2 Mixed/Unknown	10	2913	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.55, 0.93]
4 Anaemia (by iron status at baseline): Mixed/Unknown	11	3135	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.49, 0.87]
5 Anaemia (dose of elemental iron per week in the intermittent group)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 60 mg of iron or less per week	5	1855	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.43, 1.10]
5.2 More than 60 mg of iron per week	7	1280	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.42, 0.91]
6 Anaemia (by duration of supplementation)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 3 months or less	6	2176	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.44, 1.00]
6.2 More than 3 months	5	959	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.34, 1.04]
7 Anaemia (by malaria endemicity)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 No malaria/Unknown	9	2937	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.41, 0.86]
7.2 Malaria	2	290	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.56, 1.30]
8 Haemoglobin in g/L (All)	15	2886	Mean Difference (IV, Random, 95% CI)	5.19 [3.07, 7.32]
9 Haemoglobin in g/L (by supplement composition)	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Iron alone	6	893	Mean Difference (IV, Random, 95% CI)	7.16 [3.40, 10.92]
9.2 Iron plus folic acid	8	1671	Mean Difference (IV, Random, 95% CI)	3.56 [1.11, 6.01]
9.3 Iron plus multiple micronutrients	2	322	Mean Difference (IV, Random, 95% CI)	7.94 [2.37, 13.52]
10 Haemoglobin in g/L (by anaemia status at baseline)	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 Anaemic	3	439	Mean Difference (IV, Random, 95% CI)	7.21 [3.05, 11.37]
10.2 Mixed/Unknown	12	2447	Mean Difference (IV, Random, 95% CI)	4.71 [2.30, 7.13]
11 Haemoglobin in g/L (by iron status at baseline)	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 Iron deficient	1	87	Mean Difference (IV, Random, 95% CI)	4.80 [1.42, 8.18]

11.2 Mixed/Unknown	14	2725	Mean Difference (IV, Random, 95% CI)	5.59 [3.47, 7.72]
12 Haemoglobin in g/L (by dose of elemental iron per week in the intermittent group)	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 60 mg of iron or less per week	6	971	Mean Difference (IV, Random, 95% CI)	5.21 [2.06, 8.36]
12.2 More than 60 mg of iron per week	10	1915	Mean Difference (IV, Random, 95% CI)	5.24 [2.43, 8.04]
13 Haemoglobin in g/L (by duration of supplementation)	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 3 months or less	7	1387	Mean Difference (IV, Random, 95% CI)	6.37 [3.37, 9.37]
13.2 More than 3 months	8	1499	Mean Difference (IV, Random, 95% CI)	3.95 [1.28, 6.63]
14 Haemoglobin in g/L (by malaria endemicity)	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 No malaria/Unknown	12	2389	Mean Difference (IV, Random, 95% CI)	5.63 [3.18, 8.09]
14.2 Malaria	3	497	Mean Difference (IV, Random, 95% CI)	3.04 [0.52, 5.56]
15 Iron deficiency (All)	3	624	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.24, 1.04]
16 Ferritin in µg/L (All)	7	1067	Mean Difference (IV, Random, 95% CI)	7.46 [5.02, 9.90]
17 Ferritin in µg/L (by supplement composition)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
17.1 Iron alone	3	291	Mean Difference (IV, Random, 95% CI)	6.01 [3.89, 8.13]
17.2 Iron plus folic acid	3	455	Mean Difference (IV, Random, 95% CI)	5.87 [3.23, 8.52]
17.3 Iron plus multiple micronutrients	2	321	Mean Difference (IV, Random, 95% CI)	11.05 [2.94, 19.17]
18 Ferritin in µg/L (by anaemia status at baseline)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
18.1 Anaemic	2	309	Mean Difference (IV, Random, 95% CI)	6.17 [4.47, 7.88]
18.2 Mixed/Unknown	5	758	Mean Difference (IV, Random, 95% CI)	9.15 [4.36, 13.95]
19 Ferritin in µg/L (by iron status at baseline)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 Iron deficient	1	87	Mean Difference (IV, Random, 95% CI)	5.79 [3.55, 8.03]
19.2 Mixed/Unknown	6	980	Mean Difference (IV, Random, 95% CI)	8.32 [4.97, 11.66]
20 Ferritin in µg/L (by dose of elemental iron per week in the intermittent group)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 60 mg of iron or less per week	3	269	Mean Difference (IV, Random, 95% CI)	12.37 [7.06, 17.69]
20.2 More than 60 mg of iron per week	5	798	Mean Difference (IV, Random, 95% CI)	6.60 [4.30, 8.91]
21 Ferritin in µg/L (by duration of supplementation)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 3 months or less	3	518	Mean Difference (IV, Random, 95% CI)	8.32 [4.38, 12.26]
21.2 More than 3 months	4	549	Mean Difference (IV, Random, 95% CI)	6.31 [2.82, 9.81]
22 Ferritin in µg/L (by malaria endemicity)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
22.1 No malaria/Unknown	5	895	Mean Difference (IV, Random, 95% CI)	7.74 [4.79, 10.69]
22.2 Malaria	2	172	Mean Difference (IV, Random, 95% CI)	6.79 [0.48, 13.10]
23 Iron deficiency anaemia (All)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
24 All cause morbidity (All)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25 Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26 Any adverse side effects	3	630	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.31, 12.72]

27 Adherence	2	417	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.96, 1.02]
28 Prevalence of malaria parasitaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
29 Any malaria parasitaemia (Incidence rate; per 1000 person months)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
30 High density malaria parasitaemia (parasites 200/wbc)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
31 Clinical malaria	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 2. Intermittent iron supplementation versus daily iron supplementation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anaemia (All)	8	1749	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.93, 1.29]
2 Anaemia (by supplement composition)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Iron alone	3	690	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.97, 1.99]
2.2 Iron plus folic acid	4	861	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.81, 1.30]
2.3 Iron plus multiple micronutrients	1	198	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.30, 2.46]
3 Anaemia (by anaemia status at baseline)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Anaemic	2	270	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.76, 1.16]
3.2 Mixed/Unknown	6	1479	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.01, 1.47]
4 Anaemia (by iron status at baseline): Mixed/Unknown	7	1629	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.01, 1.45]
5 Anaemia (by dose of elemental iron per week in the intermittent group)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 60 mg of iron or less per week	4	614	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.82, 1.85]
5.2 More than 60 mg of iron per week	5	1135	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.85, 1.35]
6 Anaemia (by duration of supplementation)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 3 months or less	4	631	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.77, 1.16]
6.2 More than 3 months	4	1118	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.99, 1.54]
7 Anaemia (by malaria endemicity)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 No malaria/Unknown	7	1629	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.01, 1.45]
7.2 Malaria	1	120	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.73, 1.14]
8 Haemoglobin in g/L (All)	10	2127	Mean Difference (IV, Random, 95% CI)	0.43 [-1.44, 2.31]
9 Haemoglobin in g/L (by supplement composition)	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Iron alone	4	671	Mean Difference (IV, Random, 95% CI)	0.31 [-1.15, 1.78]
9.2 Iron plus folic acid	4	1138	Mean Difference (IV, Random, 95% CI)	0.39 [-4.18, 4.96]

9.3 Iron plus multiple micronutrients	2	318	Mean Difference (IV, Random, 95% CI)	0.84 [-1.08, 2.76]
10 Haemoglobin in g/L (by anaemia status at baseline)	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 Anaemic	4	804	Mean Difference (IV, Random, 95% CI)	2.82 [1.56, 4.09]
10.2 MIxed/Unknown	6	1323	Mean Difference (IV, Random, 95% CI)	-1.14 [-3.15, 0.87]
11 Haemoglobin in g/L (by iron status at baseline)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 Iron deficient	1	21	Mean Difference (IV, Random, 95% CI)	-1.0 [-7.94, 5.94]
11.2 Mixed/Unknown	8	1986	Mean Difference (IV, Random, 95% CI)	0.36 [-1.77, 2.49]
12 Haemoglobin in g/L (by dose of elemental iron per week in the intermittent group)	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 60 mg of iron or less per week	6	843	Mean Difference (IV, Random, 95% CI)	1.14 [-0.34, 2.62]
12.2 More than 60 mg of iron per week	5	1284	Mean Difference (IV, Random, 95% CI)	-0.34 [-3.44, 2.76]
13 Haemoglobin in g/L (by duration of supplementation)	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 3 months or less	7	1059	Mean Difference (IV, Random, 95% CI)	1.36 [0.19, 2.53]
13.2 More than 3 months	3	1068	Mean Difference (IV, Random, 95% CI)	-0.72 [-5.41, 3.98]
14 Haemoglobin in g/L (by malaria endemicity)	11		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 No malaria/Unknown	10	2416	Mean Difference (IV, Random, 95% CI)	0.17 [-1.65, 1.98]
14.2 Malaria	1	120	Mean Difference (IV, Random, 95% CI)	2.0 [-1.40, 5.40]
15 Iron deficiency (All)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16 Ferritin in µg/L (All)	4	988	Mean Difference (IV, Random, 95% CI)	-6.07 [-10.66, -1.48]
17 Ferritin in µg/L (by duration of supplementation)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
17.1 3 months or less	2	219	Mean Difference (IV, Random, 95% CI)	-17.42 [-23.44, -11.41]
17.2 More than 3 months	2	769	Mean Difference (IV, Random, 95% CI)	-1.05 [-3.59, 1.48]
18 Ferritin in µg/L (by anaemia status at baseline)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
18.1 Anaemic	1	331	Mean Difference (IV, Random, 95% CI)	0.10 [-0.73, 0.93]
18.2 Mixed/Unknown	3	657	Mean Difference (IV, Random, 95% CI)	-11.32 [-22.61, -0.02]
19 Ferritin in µg/L (by iron status at baseline)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 Iron deficient	1	21	Mean Difference (IV, Random, 95% CI)	-14.8 [-22.99, -6.61]
19.2 Mixed/Unknown	3	967	Mean Difference (IV, Random, 95% CI)	-3.80 [-8.08, 0.47]
20 Ferritin in µg/L (by dose of elemental iron per week in the intermittent group)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 60 mg or iron or less per week	2	123	Mean Difference (IV, Random, 95% CI)	-16.29 [-23.09, -9.48]
20.2 More than 60 mg of iron per week	3	865	Mean Difference (IV, Random, 95% CI)	-2.08 [-5.44, 1.29]
21 Ferritin in µg/L (by supplement composition)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 Iron alone	1	21	Mean Difference (IV, Random, 95% CI)	-14.8 [-22.99, -6.61]

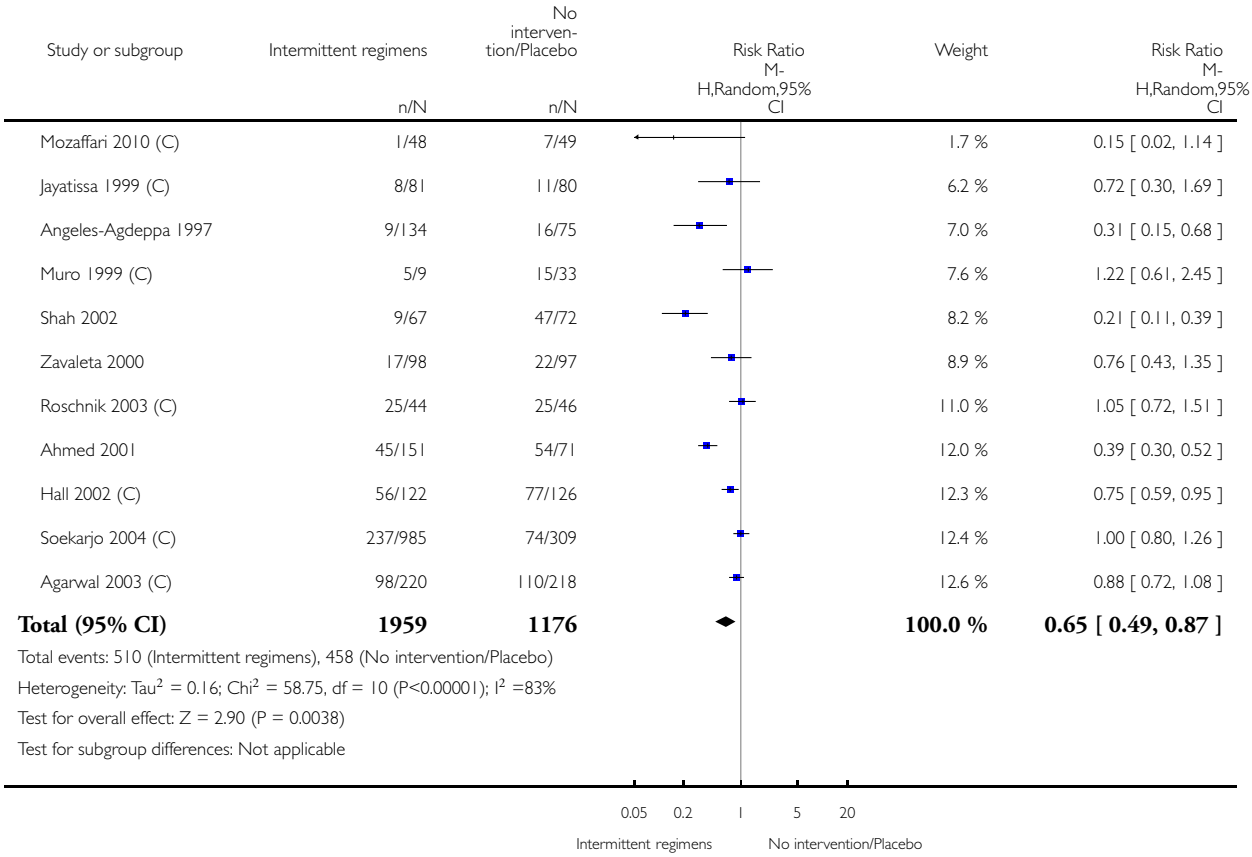
21.2 Iron plus folic acid	2	769	Mean Difference (IV, Random, 95% CI)	-1.05 [-3.59, 1.48]
21.3 Iron plus multiple micronutrients	1	198	Mean Difference (IV, Random, 95% CI)	-18.5 [-27.37, -9.63]
22 Ferritin in µg/L (by malaria endemicity): No malaria/Unknown	4	988	Mean Difference (IV, Random, 95% CI)	-8.27 [-16.21, -0.32]
23 Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
24 Any adverse side effects	6	1166	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.21, 0.82]
25 Depression	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26 Adherence	4	507	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.99, 1.09]

Analysis 1.1. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 1 Anaemia (All).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 1 Anaemia (All)

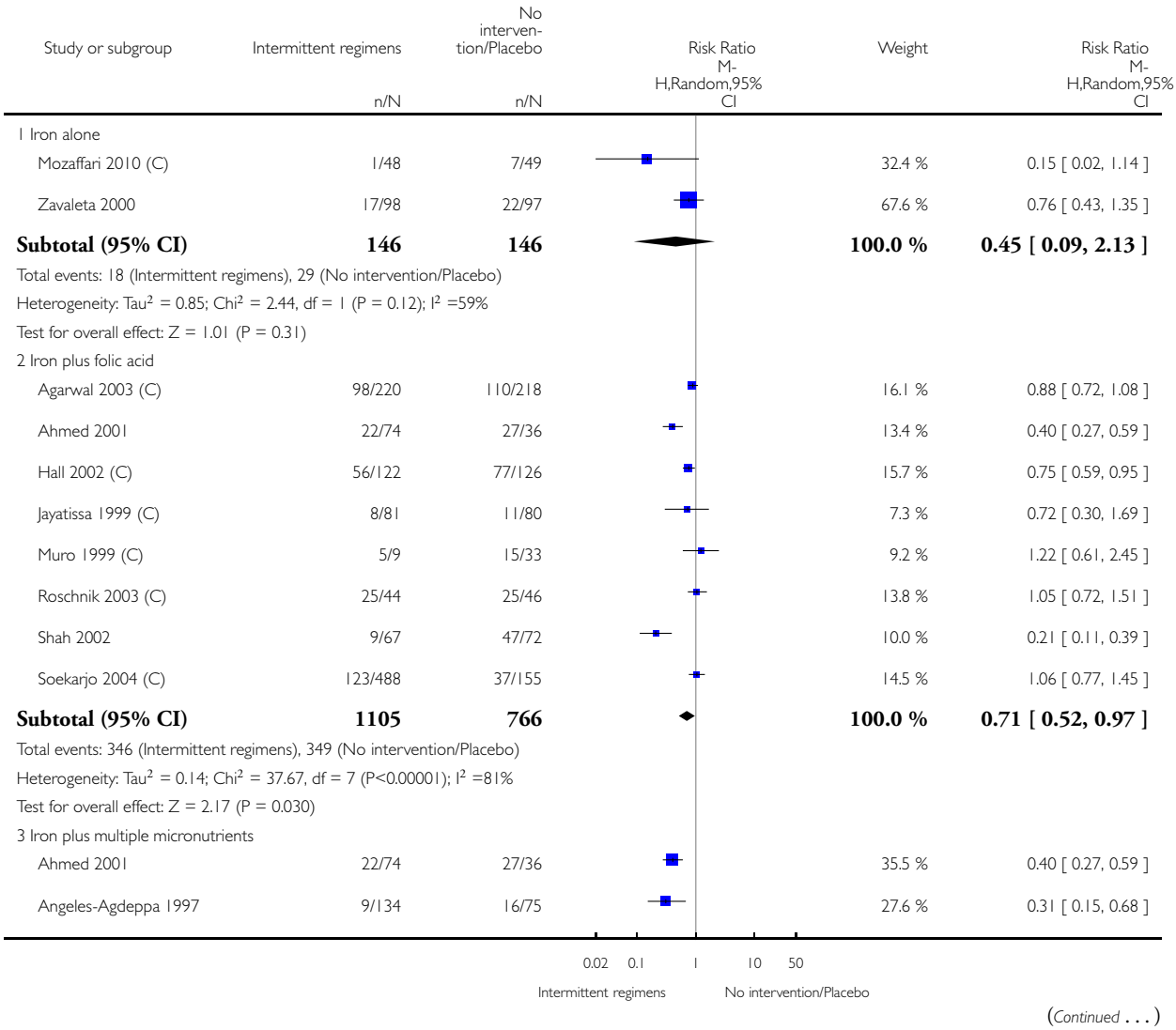


Analysis 1.2. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 2 Anaemia (by supplement composition).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 2 Anaemia (by supplement composition)



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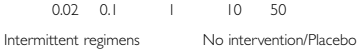
Study or subgroup	Intermittent regimens n/N	No intervention/Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Soekarjo 2004 (C)	114/497	37/156		36.8 %	0.97 [0.70, 1.34]
Subtotal (95% CI)	**705**	**267**		**100.0 %**	**0.52 [0.25, 1.07]**
Total events: 145 (Intermittent regimens), 80 (No intervention/Placebo)					
Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 15.29$, df = 2 (P = 0.00048); $I^2 = 87\%$					
Test for overall effect: Z = 1.78 (P = 0.076)					
Test for subgroup differences: $Chi^2 = 0.90$, df = 2 (P = 0.64), $I^2 = 0.0\%$					



Analysis 1.3. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 3 Anaemia (by anaemia status at baseline).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 3 Anaemia (by anaemia status at baseline)

Study or subgroup	Intermittent regimens n/N	No intervention/Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Anaemic					
Ahmed 2001	45/151	54/71		100.0 %	0.39 [0.30, 0.52]
Subtotal (95% CI)	**151**	**71**		**100.0 %**	**0.39 [0.30, 0.52]**
Total events: 45 (Intermittent regimens), 54 (No intervention/Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.62 (P < 0.00001)					
2 Mixed/Unknown					
Agarwal 2003 (C)	98/220	110/218		15.7 %	0.88 [0.72, 1.08]
Angeles-Agdeppa 1997	9/134	16/75		7.1 %	0.31 [0.15, 0.68]
Hall 2002 (C)	56/122	77/126		15.1 %	0.75 [0.59, 0.95]

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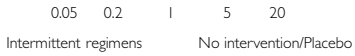
Study or subgroup	Intermittent regimens n/N	No intervention/Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Jayatissa 1999 (C)	8/81	11/80		6.2 %	0.72 [0.30, 1.69]
Mozaffari 2010 (C)	1/48	7/49		1.5 %	0.15 [0.02, 1.14]
Muro 1999 (C)	5/9	15/33		7.9 %	1.22 [0.61, 2.45]
Roschnik 2003 (C)	25/44	25/46		12.9 %	1.05 [0.72, 1.51]
Shah 2002	9/67	47/72		8.7 %	0.21 [0.11, 0.39]
Soekarjo 2004 (C)	237/985	74/309		15.2 %	1.00 [0.80, 1.26]
Zavaleta 2000	17/98	22/97		9.6 %	0.76 [0.43, 1.35]
Subtotal (95% CI)	**1808**	**1105**		**100.0 %**	**0.71 [0.55, 0.93]**

Total events: 465 (Intermittent regimens), 404 (No intervention/Placebo)

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 35.21$, df = 9 (P = 0.00005); $I^2 = 74\%$

Test for overall effect: Z = 2.47 (P = 0.013)

Test for subgroup differences: $Chi^2 = 9.38$, df = 1 (P = 0.00), $I^2 = 89\%$

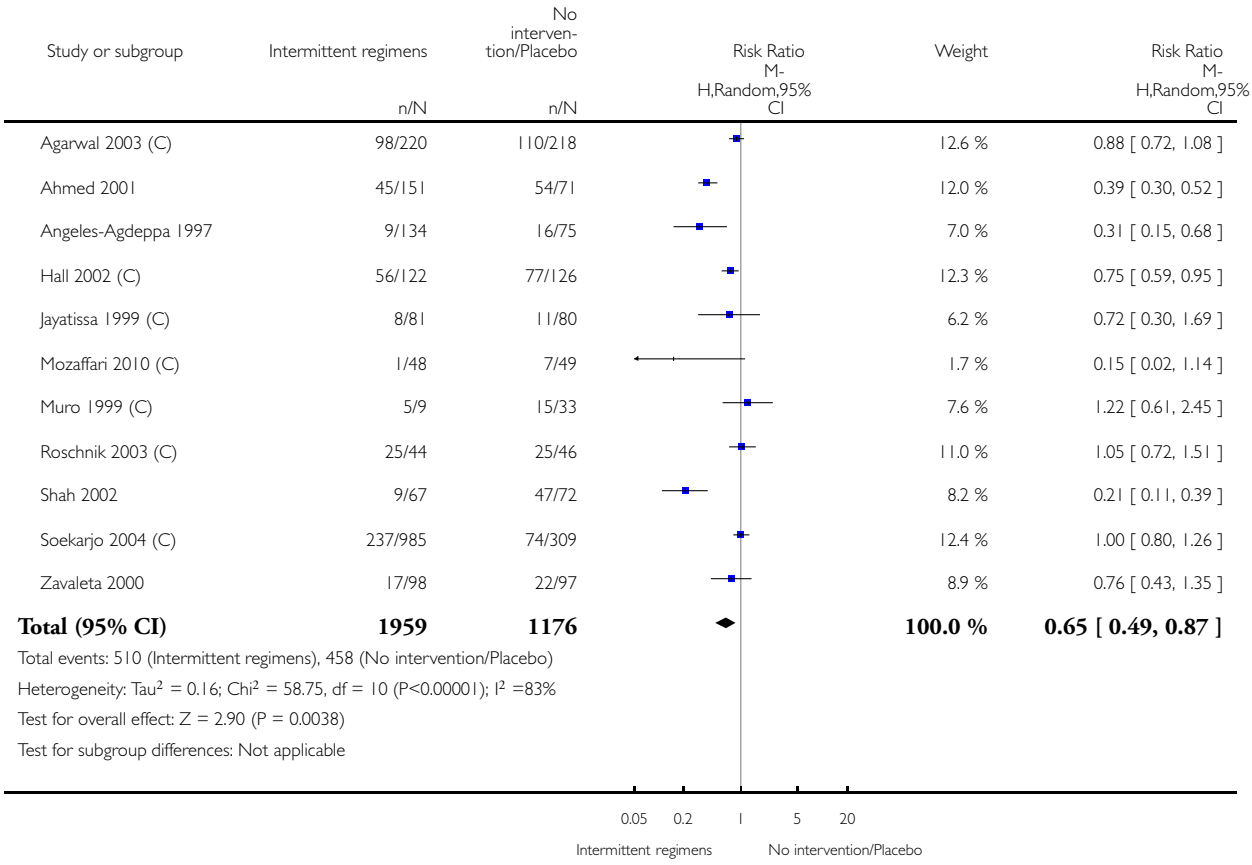


Analysis 1.4. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 4 Anaemia (by iron status at baseline): Mixed/Unknown.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 4 Anaemia (by iron status at baseline): Mixed/Unknown

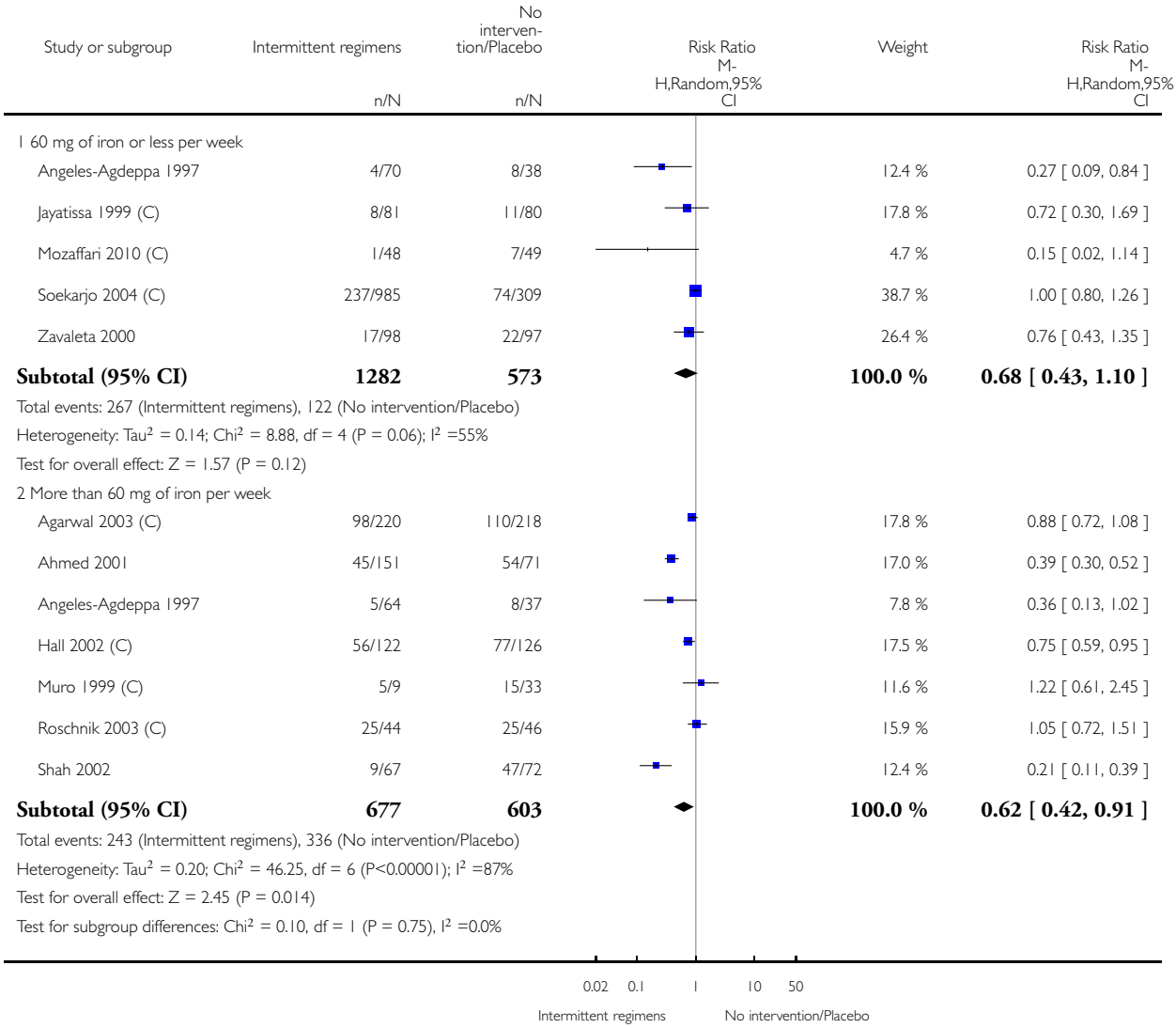


Analysis 1.5. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 5 Anaemia (dose of elemental iron per week in the intermittent group).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 5 Anaemia (dose of elemental iron per week in the intermittent group)

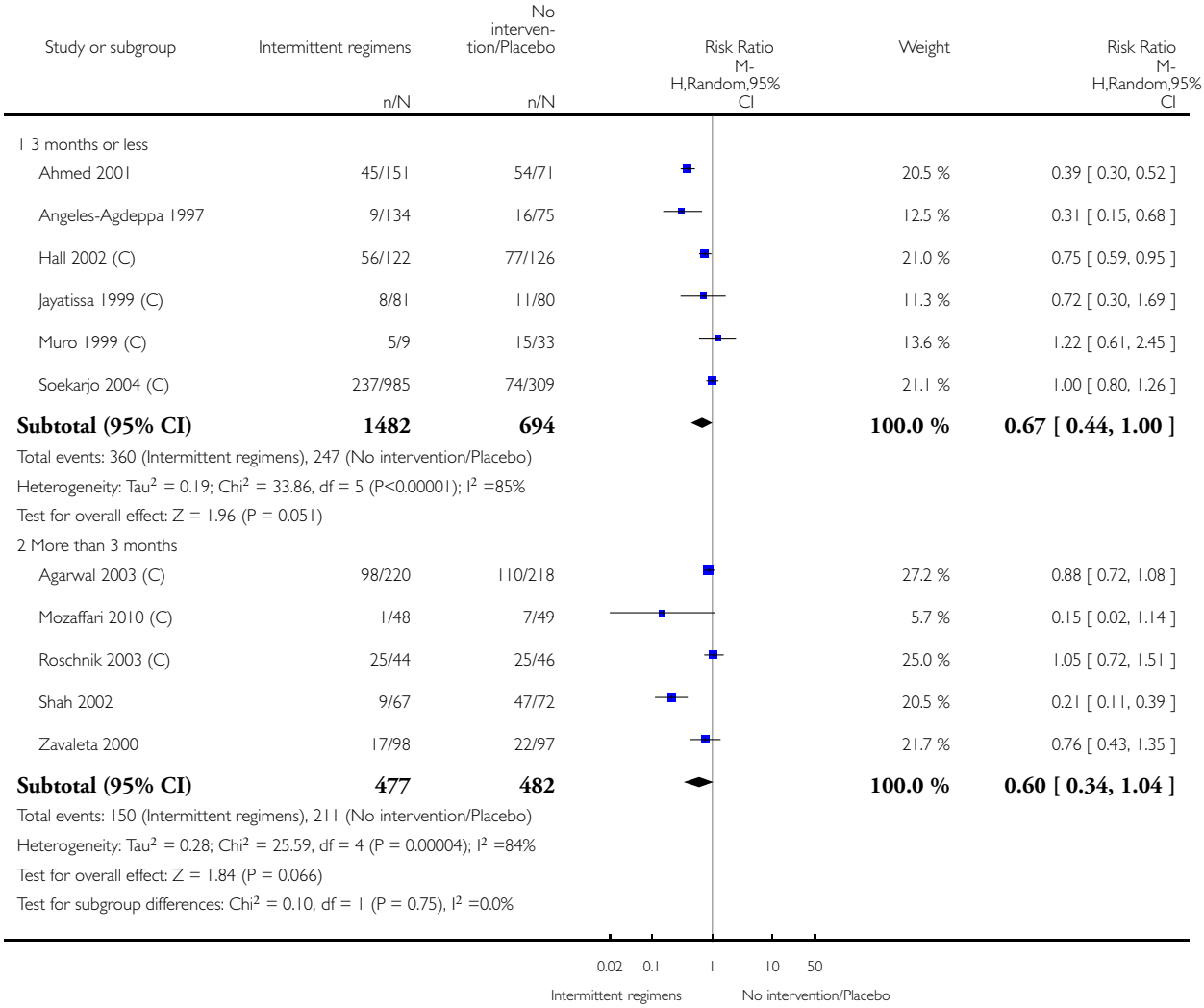


Analysis 1.6. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 6 Anaemia (by duration of supplementation).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 6 Anaemia (by duration of supplementation)

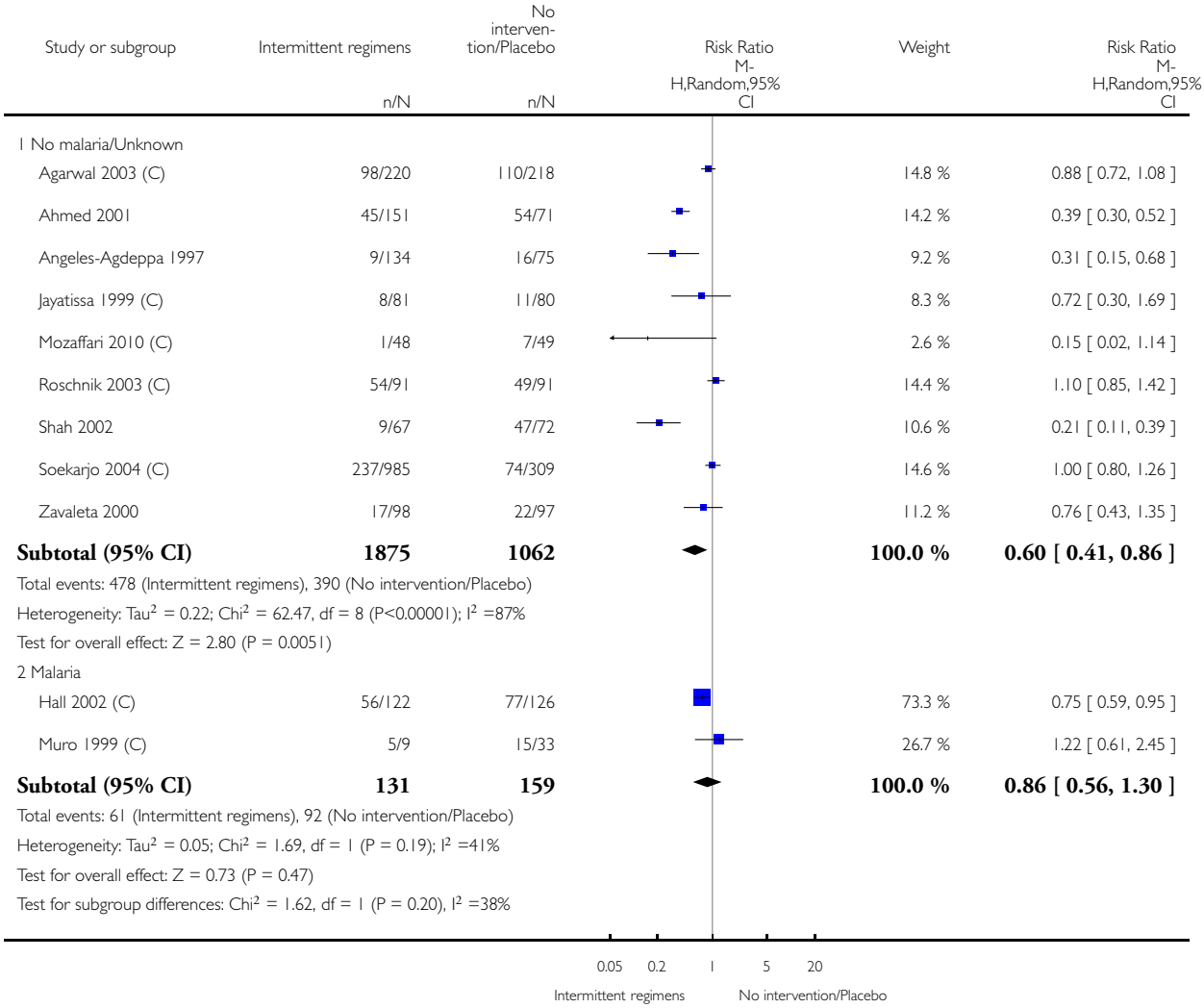


Analysis 1.7. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 7 Anaemia (by malaria endemicity).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 7 Anaemia (by malaria endemicity)



Analysis 1.8. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 8 Haemoglobin in g/L (All).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 8 Haemoglobin in g/L (All)

Study or subgroup	Intermittent regimens		No intervention/Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Roschnik 2003 (C)	44	113.3 (14.2)	46	114.7 (14)		5.1 %	-1.40 [-7.23, 4.43]
Soekarjo 2004 (C)	127	-3.7 (30.5)	122	-4.4 (11.8)		5.2 %	0.70 [-5.00, 6.40]
Leenstra 2009	64	134 (12.2)	66	128.5 (19.7)		5.3 %	5.50 [-0.11, 11.11]
Mozaffari 2010 (C)	48	145.6 (12)	49	133.2 (12.5)		5.8 %	12.40 [7.52, 17.28]
Februhartanty 2002	48	126.2 (12.7)	48	120.4 (9.2)		6.1 %	5.80 [1.36, 10.24]
Gilgen 2001	139	5.52 (14.84)	141	-0.24 (14.81)		6.8 %	5.76 [2.29, 9.23]
Beasley 2000	57	119.4 (10.6)	62	118.5 (7.9)		6.9 %	0.90 [-2.48, 4.28]
Jalambo 2018	45	124.6 (6.4)	42	119.8 (9.3)		6.9 %	4.80 [1.42, 8.18]
Jayatissa 1999 (C)	81	131 (10)	80	131 (11)		7.0 %	0.0 [-3.25, 3.25]
Hall 2002 (C)	122	117 (12.4)	126	113 (13.1)		7.1 %	4.00 [0.83, 7.17]
Rezaeian 2014	100	125 (9.7)	100	112 (10)		7.4 %	13.00 [10.27, 15.73]
Ahmed 2001	151	122.5 (8)	71	112 (10)		7.4 %	10.50 [7.85, 13.15]
Angeles-Agdeppa 1997	134	130.3 (7.8)	75	125 (8.8)		7.6 %	5.30 [2.91, 7.69]
Agarwal 2003 (C)	220	118 (13)	218	116 (12)		7.6 %	2.00 [-0.34, 4.34]
Kianfar 2000	112	8.5 (9.2)	148	2 (8)		7.7 %	6.50 [4.36, 8.64]
Total (95% CI)	**1492**		**1394**			**100.0 %**	**5.19 [3.07, 7.32]**

Heterogeneity: $Tau^2 = 14.01$; $Chi^2 = 87.02$, df = 14 ($P<0.00001$); $I^2 = 84\%$

Test for overall effect: $Z = 4.79$ ($P < 0.00001$)

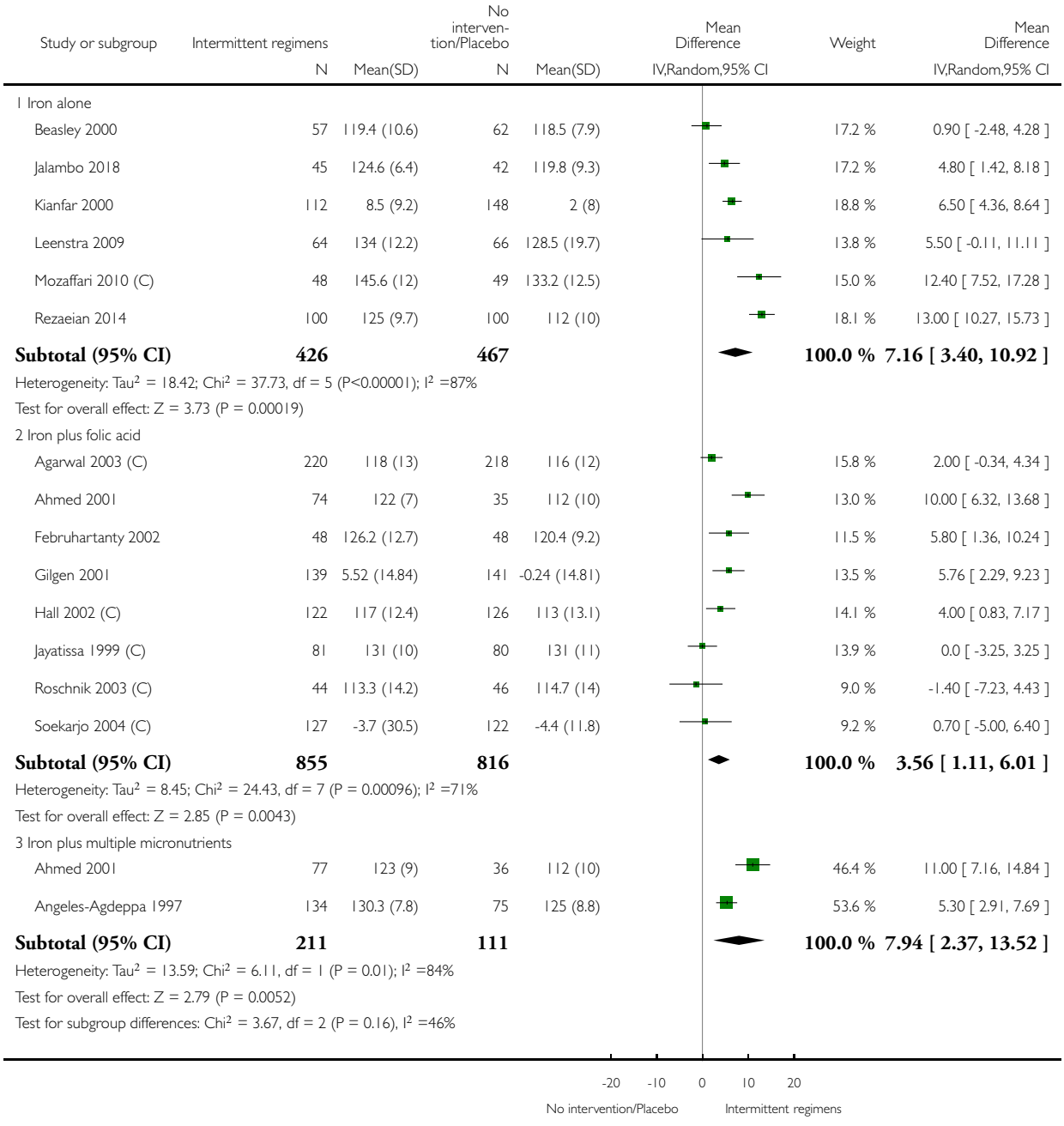
Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 9 Haemoglobin in g/L (by supplement composition).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 9 Haemoglobin in g/L (by supplement composition)



Analysis 1.10. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 10 Haemoglobin in g/L (by anaemia status at baseline).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 10 Haemoglobin in g/L (by anaemia status at baseline)

Study or subgroup	Intermittent regimens		No intervention/Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Anaemic							
Ahmed 2001	151	122.5 (8)	71	112 (10)		39.2 %	10.50 [7.85, 13.15]
Jalambo 2018	45	124.6 (6.4)	42	119.8 (9.3)		35.6 %	4.80 [1.42, 8.18]
Leenstra 2009	64	134 (12.2)	66	128.5 (19.7)		25.2 %	5.50 [-0.11, 11.11]
Subtotal (95% CI)	**260**		**179**			**100.0 %**	**7.21 [3.05, 11.37]**
Heterogeneity: Tau^2 = 9.69; Chi^2 = 7.62, df = 2 (P = 0.02); I^2 =74%							
Test for overall effect: Z = 3.39 (P = 0.00069)							
2 Mixed/Unknown							
Agarwal 2003 (C)	220	118 (13)	218	116 (12)		9.4 %	2.00 [-0.34, 4.34]
Angeles-Agdeppa 1997	134	130.3 (7.8)	75	125 (8.8)		9.4 %	5.30 [2.91, 7.69]
Beasley 2000	57	119.4 (10.6)	62	118.5 (7.9)		8.6 %	0.90 [-2.48, 4.28]
Februhartanty 2002	48	126.2 (12.7)	48	120.4 (9.2)		7.7 %	5.80 [1.36, 10.24]
Gilgen 2001	139	5.52 (14.84)	141	-0.24 (14.81)		8.5 %	5.76 [2.29, 9.23]
Hall 2002 (C)	122	117 (12.4)	126	113 (13.1)		8.8 %	4.00 [0.83, 7.17]
Jayatissa 1999 (C)	81	131 (10)	80	131 (11)		8.7 %	0.0 [-3.25, 3.25]
Kianfar 2000	112	8.5 (9.2)	148	2 (8)		9.6 %	6.50 [4.36, 8.64]
Mozaffari 2010 (C)	48	145.6 (12)	49	133.2 (12.5)		7.3 %	12.40 [7.52, 17.28]
Rezaeian 2014	100	125 (9.7)	100	112 (10)		9.1 %	13.00 [10.27, 15.73]
Roschnik 2003 (C)	44	113.3 (14.2)	46	114.7 (14)		6.4 %	-1.40 [-7.23, 4.43]
Soekarjo 2004 (C)	127	-3.7 (30.5)	122	-4.4 (11.8)		6.6 %	0.70 [-5.00, 6.40]
Subtotal (95% CI)	**1232**		**1215**			**100.0 %**	**4.71 [2.30, 7.13]**
Heterogeneity: Tau^2 = 14.64; Chi^2 = 72.31, df = 11 (P<0.00001); I^2 =85%							
Test for overall effect: Z = 3.83 (P = 0.00013)							
Test for subgroup differences: Chi^2 = 1.03, df = 1 (P = 0.31), I^2 =3%							

Analysis 1.11. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 11 Haemoglobin in g/L (by iron status at baseline).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 11 Haemoglobin in g/L (by iron status at baseline)

Study or subgroup	Intermittent regimens		No intervention/Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Iron deficient							
Jalambo 2018	45	124.6 (6.4)	42	119.8 (9.3)		100.0 %	4.80 [1.42, 8.18]
Subtotal (95% CI)	**45**		**42**			**100.0 %**	**4.80 [1.42, 8.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.79 (P = 0.0053)							
2 Mixed/Unknown							
Agarwal 2003 (C)	220	118 (13)	218	116 (12)		8.3 %	2.00 [-0.34, 4.34]
Ahmed 2001	151	122.5 (8)	71	112 (10)		8.0 %	10.50 [7.85, 13.15]
Angeles-Agdeppa 1997	134	130.3 (7.8)	75	125 (8.8)		8.2 %	5.30 [2.91, 7.69]
Beasley 2000	57	119.4 (10.6)	62	118.5 (7.9)		7.4 %	0.90 [-2.48, 4.28]
Februhartanty 2002	48	126.2 (12.7)	48	120.4 (9.2)		6.6 %	5.80 [1.36, 10.24]
Gilgen 2001	139	5.52 (14.84)	141	-0.24 (14.81)		7.4 %	5.76 [2.29, 9.23]
Hall 2002 (C)	122	117 (12.4)	126	113 (13.1)		7.6 %	4.00 [0.83, 7.17]
Jalambo 2018	45	124.6 (6.4)	42	119.8 (9.3)		7.4 %	4.80 [1.42, 8.18]
Kianfar 2000	112	8.5 (9.2)	148	2 (8)		8.4 %	6.50 [4.36, 8.64]
Leenstra 2009	64	134 (12.2)	66	128.5 (19.7)		5.6 %	5.50 [-0.11, 11.11]
Mozaffari 2010 (C)	48	145.6 (12)	49	133.2 (12.5)		6.2 %	12.40 [7.52, 17.28]
Rezaeian 2014	100	125 (9.7)	100	112 (10)		8.0 %	13.00 [10.27, 15.73]
Roschnik 2003 (C)	44	113.3 (14.2)	46	114.7 (14)		5.4 %	-1.40 [-7.23, 4.43]
Soekarjo 2004 (C)	127	-3.7 (30.5)	122	-4.4 (11.8)		5.5 %	0.70 [-5.00, 6.40]
Subtotal (95% CI)	**1411**		**1314**			**100.0 %**	**5.59 [3.47, 7.72]**
Heterogeneity: Tau^2 = 12.81; Chi^2 = 74.95, df = 13 (P<0.00001); I^2 =83%							
Test for overall effect: Z = 5.16 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.15, df = 1 (P = 0.70), I^2 =0.0%							

Analysis 1.12. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 12 Haemoglobin in g/L (by dose of elemental iron per week in the intermittent group).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 12 Haemoglobin in g/L (by dose of elemental iron per week in the intermittent group)

Study or subgroup	Intermittent regimens		No intervention/Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 60 mg of iron or less per week							
Angeles-Agdeppa 1997	70	130.5 (7.8)	38	124.6 (8.8)		18.0 %	5.90 [2.56, 9.24]
Februhartanty 2002	48	126.2 (12.7)	48	120.4 (9.2)		15.6 %	5.80 [1.36, 10.24]
Jayatissa 1999 (C)	81	131 (10)	80	131 (11)		18.2 %	0.0 [-3.25, 3.25]
Kianfar 2000	112	8.5 (9.2)	148	2 (8)		20.5 %	6.50 [4.36, 8.64]
Mozaffari 2010 (C)	48	145.6 (12)	49	133.2 (12.5)		14.7 %	12.40 [7.52, 17.28]
Soekarjo 2004 (C)	127	-3.7 (30.5)	122	-4.4 (11.8)		13.0 %	0.70 [-5.00, 6.40]
Subtotal (95% CI)	**486**		**485**			**100.0 %**	**5.21 [2.06, 8.36]**
Heterogeneity: Tau² = 11.41; Chi² = 22.25, df = 5 (P = 0.00047); I² =78%							
Test for overall effect: Z = 3.24 (P = 0.0012)							
2 More than 60 mg of iron per week							
Agarwal 2003 (C)	220	118 (13)	218	116 (12)		11.1 %	2.00 [-0.34, 4.34]
Ahmed 2001	151	122.5 (8)	71	112 (10)		10.9 %	10.50 [7.85, 13.15]
Angeles-Agdeppa 1997	64	130 (7.7)	37	124.6 (8.8)		10.2 %	5.40 [1.99, 8.81]
Beasley 2000	57	119.4 (10.6)	62	118.5 (7.9)		10.2 %	0.90 [-2.48, 4.28]
Gilgen 2001	139	5.52 (14.84)	141	-0.24 (14.81)		10.1 %	5.76 [2.29, 9.23]
Hall 2002 (C)	122	117 (12.4)	126	113 (13.1)		10.4 %	4.00 [0.83, 7.17]
Jalambo 2018	45	124.6 (6.4)	42	119.8 (9.3)		10.2 %	4.80 [1.42, 8.18]
Leenstra 2009	64	134 (12.2)	66	128.5 (19.7)		8.1 %	5.50 [-0.11, 11.11]
Rezaeian 2014	100	125 (9.7)	100	112 (10)		10.8 %	13.00 [10.27, 15.73]
Roschnik 2003 (C)	44	113.3 (14.2)	46	114.7 (14)		7.9 %	-1.40 [-7.23, 4.43]

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Study or subgroup	Intermittent regimens		No intervention/Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Subtotal (95% CI)	**1006**		**909**			**100.0 %**	**5.24 [2.43, 8.04]**
Heterogeneity: Tau² = 17.06; Chi² = 64.43, df = 9 (P<0.00001); I² =86%							
Test for overall effect: Z = 3.66 (P = 0.00026)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² =0.0%							

Analysis 1.13. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 13 Haemoglobin in g/L (by duration of supplementation).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 13 Haemoglobin in g/L (by duration of supplementation)

Study or subgroup	Intermittent regimens		No intervention/Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 3 months or less							
Ahmed 2001	151	122.5 (8)	71	112 (10)		14.5 %	10.50 [7.85, 13.15]
Angeles-Agdeppa 1997	134	130.3 (7.8)	75	125 (8.8)		14.8 %	5.30 [2.91, 7.69]
Hall 2002 (C)	122	117 (12.4)	126	113 (13.1)		13.8 %	4.00 [0.83, 7.17]
Jalambo 2018	45	124.6 (6.4)	42	119.8 (9.3)		13.6 %	4.80 [1.42, 8.18]
Jayatissa 1999 (C)	81	131 (10)	80	131 (11)		13.7 %	0.0 [-3.25, 3.25]
Kianfar 2000	112	8.5 (9.2)	148	2 (8)		15.1 %	6.50 [4.36, 8.64]
Rezaeian 2014	100	125 (9.7)	100	112 (10)		14.4 %	13.00 [10.27, 15.73]
Subtotal (95% CI)	**745**		**642**			**100.0 %**	**6.37 [3.37, 9.37]**
Heterogeneity: Tau² = 14.30; Chi² = 50.02, df = 6 (P<0.00001); I² =88%							
Test for overall effect: Z = 4.16 (P = 0.000031)							
2 More than 3 months							

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Study or subgroup	Intermittent regimens		No interven-tion/Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Agarwal 2003 (C)	220	118 (13)	218	116 (12)		16.5 %	2.00 [-0.34, 4.34]
Beasley 2000	57	119.4 (10.6)	62	118.5 (7.9)		14.5 %	0.90 [-2.48, 4.28]
Februhartanty 2002	48	126.2 (12.7)	48	120.4 (9.2)		12.5 %	5.80 [1.36, 10.24]
Gilgen 2001	139	5.52 (14.84)	141	-0.24 (14.81)		14.4 %	5.76 [2.29, 9.23]
Leenstra 2009	64	134 (12.2)	66	128.5 (19.7)		10.3 %	5.50 [-0.11, 11.11]
Mozaffari 2010 (C)	48	145.6 (12)	49	133.2 (12.5)		11.6 %	12.40 [7.52, 17.28]
Roschnik 2003 (C)	44	113.3 (14.2)	46	114.7 (14)		10.0 %	-1.40 [-7.23, 4.43]
Soekarjo 2004 (C)	127	-3.7 (30.5)	122	-4.4 (11.8)		10.2 %	0.70 [-5.00, 6.40]
Subtotal (95% CI)	**747**		**752**			**100.0 %**	**3.95 [1.28, 6.63]**

Heterogeneity: $Tau^2 = 9.83$; $Chi^2 = 23.43$, df = 7 (P = 0.001); $I^2 = 70\%$

Test for overall effect: Z = 2.90 (P = 0.0038)

Test for subgroup differences: $Chi^2 = 1.39$, df = 1 (P = 0.24), $I^2 = 28\%$

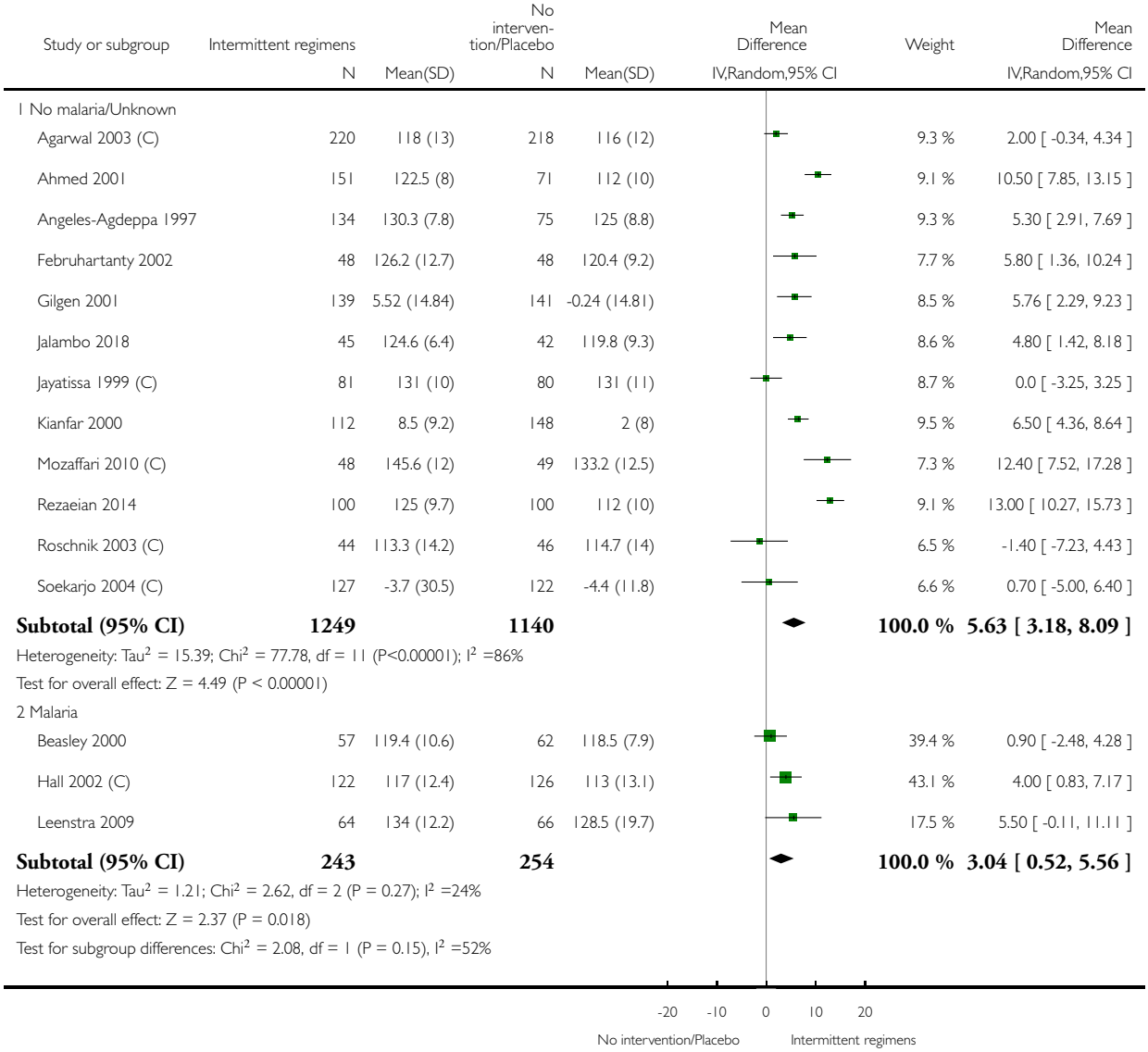
Analysis 1.14. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 14 Haemoglobin in g/L (by malaria endemicity).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 14 Haemoglobin in g/L (by malaria endemicity)

Study or subgroup	Intermittent regimens		No intervention/Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 No malaria/Unknown							
Agarwal 2003 (C)	220	118 (13)	218	116 (12)		9.3 %	2.00 [-0.34, 4.34]
Ahmed 2001	151	122.5 (8)	71	112 (10)		9.1 %	10.50 [7.85, 13.15]
Angeles-Agdeppa 1997	134	130.3 (7.8)	75	125 (8.8)		9.3 %	5.30 [2.91, 7.69]
Februhartanty 2002	48	126.2 (12.7)	48	120.4 (9.2)		7.7 %	5.80 [1.36, 10.24]
Gilgen 2001	139	5.52 (14.84)	141	-0.24 (14.81)		8.5 %	5.76 [2.29, 9.23]
Jalambo 2018	45	124.6 (6.4)	42	119.8 (9.3)		8.6 %	4.80 [1.42, 8.18]
Jayatissa 1999 (C)	81	131 (10)	80	131 (11)		8.7 %	0.0 [-3.25, 3.25]
Kianfar 2000	112	8.5 (9.2)	148	2 (8)		9.5 %	6.50 [4.36, 8.64]
Mozaffari 2010 (C)	48	145.6 (12)	49	133.2 (12.5)		7.3 %	12.40 [7.52, 17.28]
Rezaeian 2014	100	125 (9.7)	100	112 (10)		9.1 %	13.00 [10.27, 15.73]
Roschnik 2003 (C)	44	113.3 (14.2)	46	114.7 (14)		6.5 %	-1.40 [-7.23, 4.43]
Soekarjo 2004 (C)	127	-3.7 (30.5)	122	-4.4 (11.8)		6.6 %	0.70 [-5.00, 6.40]
Subtotal (95% CI)	**1249**		**1140**			**100.0 %**	**5.63 [3.18, 8.09]**
Heterogeneity: Tau^2 = 15.39; Chi^2 = 77.78, df = 11 (P<0.00001); I^2 =86%							
Test for overall effect: Z = 4.49 (P < 0.00001)							
2 Malaria							
Beasley 2000	57	119.4 (10.6)	62	118.5 (7.9)		39.4 %	0.90 [-2.48, 4.28]
Hall 2002 (C)	122	117 (12.4)	126	113 (13.1)		43.1 %	4.00 [0.83, 7.17]
Leenstra 2009	64	134 (12.2)	66	128.5 (19.7)		17.5 %	5.50 [-0.11, 11.11]
Subtotal (95% CI)	**243**		**254**			**100.0 %**	**3.04 [0.52, 5.56]**
Heterogeneity: Tau^2 = 1.21; Chi^2 = 2.62, df = 2 (P = 0.27); I^2 =24%							
Test for overall effect: Z = 2.37 (P = 0.018)							
Test for subgroup differences: Chi^2 = 2.08, df = 1 (P = 0.15), I^2 =52%							



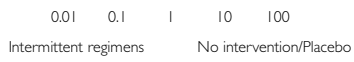
Analysis 1.15. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 15 Iron deficiency (All).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 15 Iron deficiency (All)

Study or subgroup	Intermittent regimens n/N	No intervention/Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ahmed 2001	99/151	66/71		38.4 %	0.71 [0.62, 0.80]
Angeles-Agdeppa 1997	9/134	27/75		28.7 %	0.19 [0.09, 0.38]
Mozaffari 2010 (C)	21/96	27/97		33.0 %	0.79 [0.48, 1.29]
Total (95% CI)	**381**	**243**		**100.0 %**	**0.50 [0.24, 1.04]**
Total events: 129 (Intermittent regimens), 120 (No intervention/Placebo)					
Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 17.52$, df = 2 (P = 0.00016); $I^2 = 89\%$					
Test for overall effect: Z = 1.86 (P = 0.062)					
Test for subgroup differences: Not applicable					



Analysis 1.16. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 16 Ferritin in µg/L (All).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 16 Ferritin in g/L (All)

Study or subgroup	Intermittent regimens		No intervention/Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Ahmed 2001	151	11.7 (9.9)	71	5 (9)		26.3 %	6.70 [4.08, 9.32]
Angeles-Agdeppa 1997	134	43.5 (24.5)	75	28 (18.6)		11.7 %	15.50 [9.59, 21.41]
Beasley 2000	50	46.3 (17)	57	41 (25.7)		7.2 %	5.30 [-2.87, 13.47]
Februhartanty 2002	31	34.6 (25.3)	34	25.6 (13.1)		5.2 %	9.00 [-0.94, 18.94]
Gilgen 2001	139	-0.33 (17.8)	141	-5.31 (21.21)		16.2 %	4.98 [0.40, 9.56]
Jalambo 2018	45	15.92 (5.43)	42	10.13 (5.25)		28.6 %	5.79 [3.55, 8.03]
Mozaffari 2010 (C)	48	35.59 (32.87)	49	23.73 (16.6)		4.8 %	11.86 [1.46, 22.26]
Total (95% CI)	**598**		**469**			**100.0 %**	**7.46 [5.02, 9.90]**

Heterogeneity: Tau² = 4.10; Chi² = 10.94, df = 6 (P = 0.09); I² =45%

Test for overall effect: Z = 6.00 (P < 0.00001)

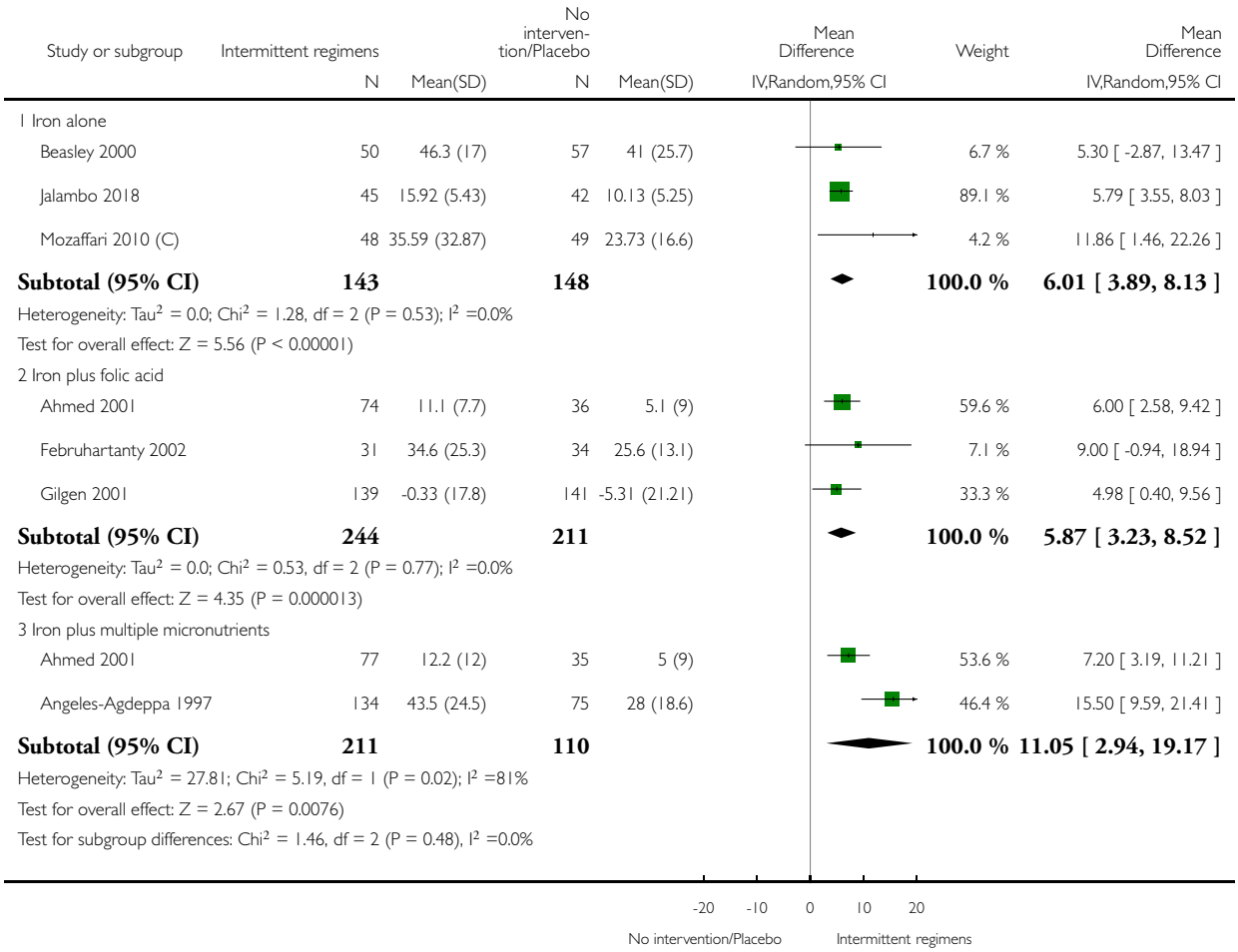
Test for subgroup differences: Not applicable

Analysis 1.17. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 17 Ferritin in µg/L (by supplement composition).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 17 Ferritin in g/L (by supplement composition)



Analysis 1.18. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 18 Ferritin in µg/L (by anaemia status at baseline).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 18 Ferritin in g/L (by anaemia status at baseline)

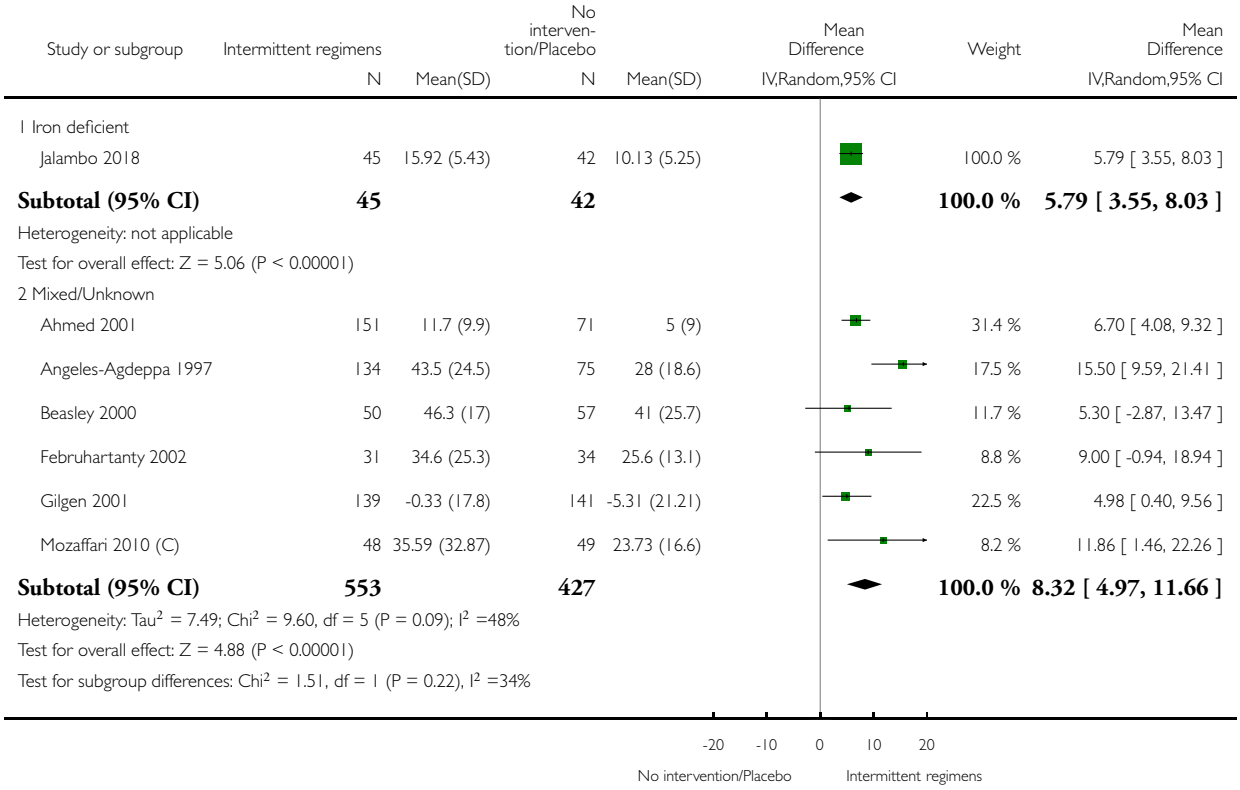
Study or subgroup	Intermittent regimens		No intervention/Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Anaemic							
Ahmed 2001	151	11.7 (9.9)	71	5 (9)		42.3 %	6.70 [4.08, 9.32]
Jalambo 2018	45	15.92 (5.43)	42	10.13 (5.25)		57.7 %	5.79 [3.55, 8.03]
Subtotal (95% CI)	**196**		**113**			**100.0 %**	**6.17 [4.47, 7.88]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.27$, df = 1 (P = 0.61); $I^2 = 0.0\%$							
Test for overall effect: Z = 7.10 (P < 0.00001)							
2 Mixed/Unknown							
Angeles-Agdeppa 1997	134	43.5 (24.5)	75	28 (18.6)		24.5 %	15.50 [9.59, 21.41]
Beasley 2000	50	46.3 (17)	57	41 (25.7)		18.3 %	5.30 [-2.87, 13.47]
Februhartanty 2002	31	34.6 (25.3)	34	25.6 (13.1)		14.6 %	9.00 [-0.94, 18.94]
Gilgen 2001	139	-0.33 (17.8)	141	-5.31 (21.21)		28.8 %	4.98 [0.40, 9.56]
Mozaffari 2010 (C)	48	35.59 (32.87)	49	23.73 (16.6)		13.8 %	11.86 [1.46, 22.26]
Subtotal (95% CI)	**402**		**356**			**100.0 %**	**9.15 [4.36, 13.95]**
Heterogeneity: $Tau^2 = 15.29$; $Chi^2 = 8.64$, df = 4 (P = 0.07); $I^2 = 54\%$							
Test for overall effect: Z = 3.74 (P = 0.00018)							
Test for subgroup differences: $Chi^2 = 1.32$, df = 1 (P = 0.25), $I^2 = 24\%$							

Analysis 1.19. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 19 Ferritin in µg/L (by iron status at baseline).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 19 Ferritin in g/L (by iron status at baseline)

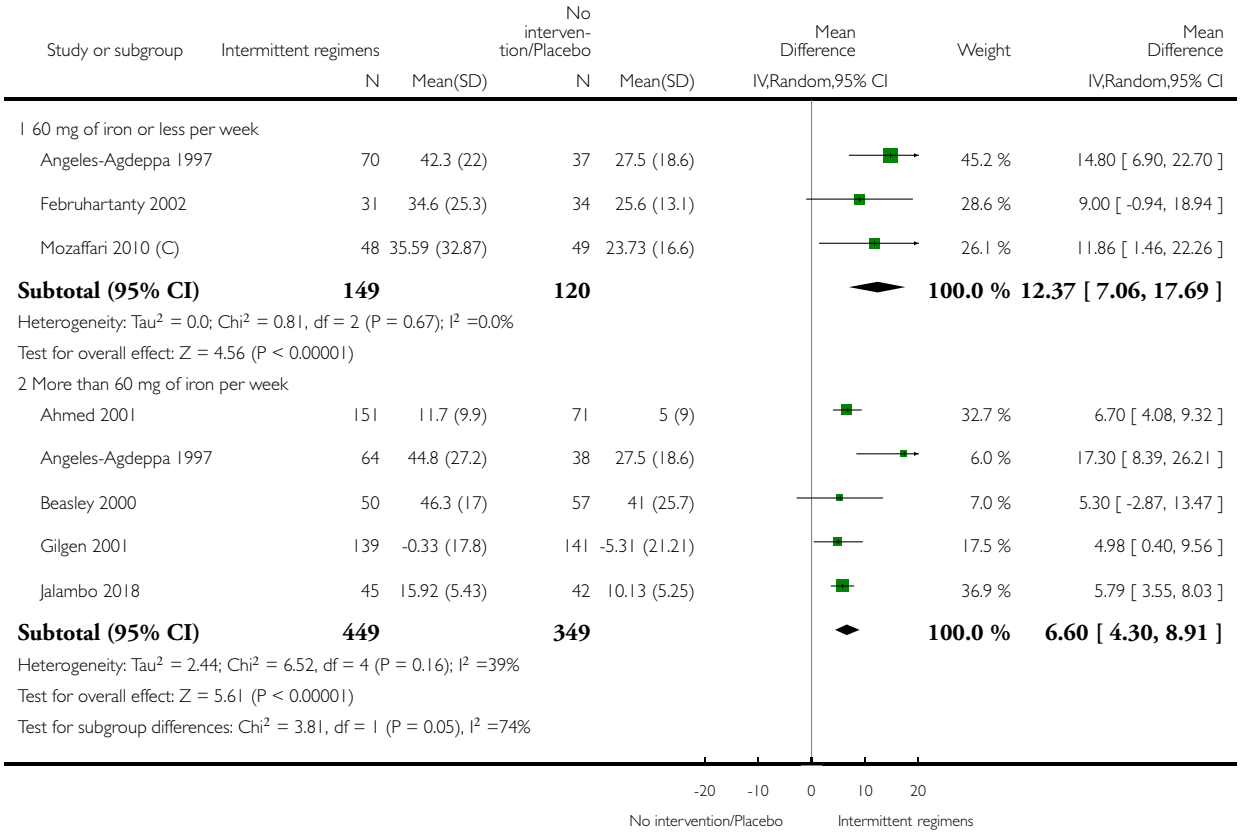


Analysis 1.20. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 20 Ferritin in µg/L (by dose of elemental iron per week in the intermittent group).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 20 Ferritin in g/L (by dose of elemental iron per week in the intermittent group)



Analysis 1.21. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 21 Ferritin in µg/L (by duration of supplementation).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 21 Ferritin in g/L (by duration of supplementation)

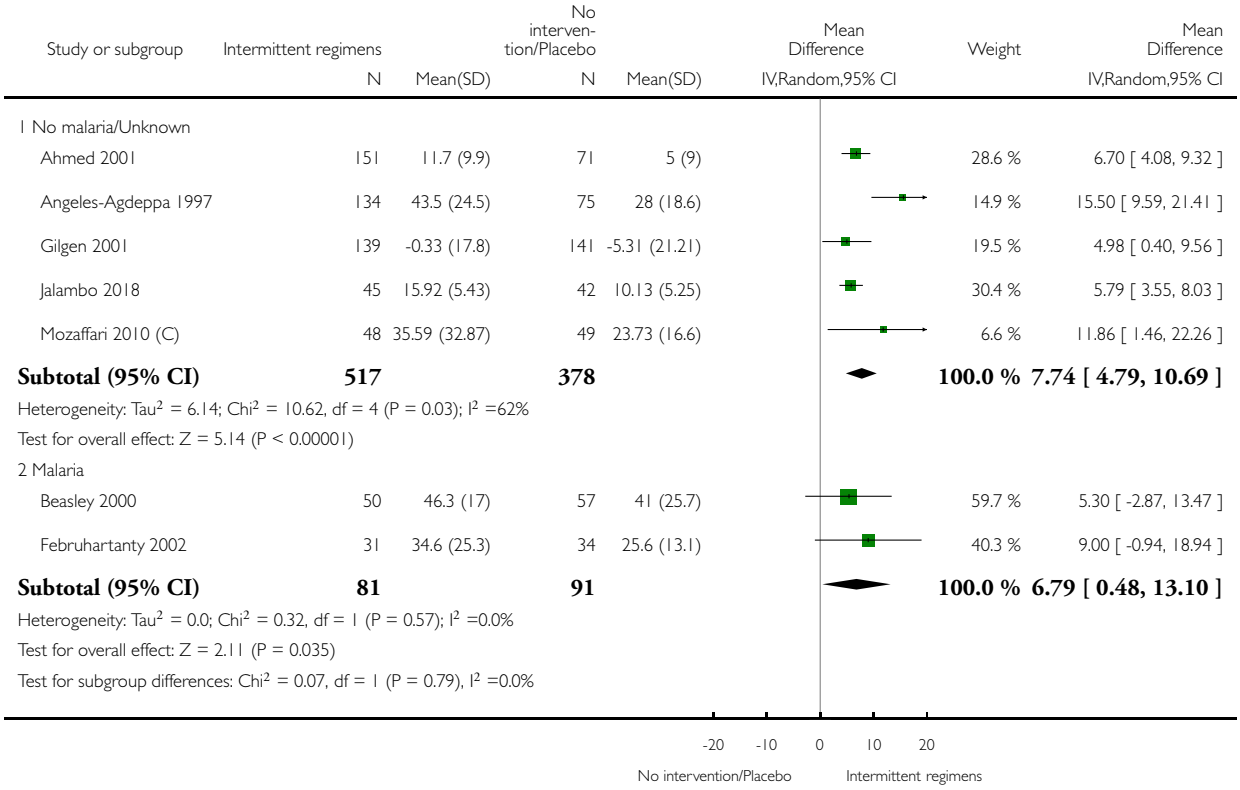
Study or subgroup	Intermittent regimens		No intervention/Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 3 months or less							
Ahmed 2001	151	11.7 (9.9)	71	5 (9)		37.9 %	6.70 [4.08, 9.32]
Angeles-Agdeppa 1997	134	43.5 (24.5)	75	28 (18.6)		22.5 %	15.50 [9.59, 21.41]
Jalambo 2018	45	15.92 (5.43)	42	10.13 (5.25)		39.6 %	5.79 [3.55, 8.03]
Subtotal (95% CI)	**330**		**188**			**100.0 %**	**8.32 [4.38, 12.26]**
Heterogeneity: Tau^2 = 8.89; Chi^2 = 9.10, df = 2 (P = 0.01); I^2 =78%							
Test for overall effect: Z = 4.14 (P = 0.000035)							
2 More than 3 months							
Beasley 2000	50	46.3 (17)	57	41 (25.7)		18.3 %	5.30 [-2.87, 13.47]
Februhartanty 2002	31	34.6 (25.3)	34	25.6 (13.1)		12.4 %	9.00 [-0.94, 18.94]
Gilgen 2001	139	-0.33 (17.8)	141	-5.31 (21.21)		58.1 %	4.98 [0.40, 9.56]
Mozaffari 2010 (C)	48	35.59 (32.87)	49	23.73 (16.6)		11.3 %	11.86 [1.46, 22.26]
Subtotal (95% CI)	**268**		**281**			**100.0 %**	**6.31 [2.82, 9.81]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.76, df = 3 (P = 0.62); I^2 =0.0%							
Test for overall effect: Z = 3.54 (P = 0.00040)							
Test for subgroup differences: Chi^2 = 0.56, df = 1 (P = 0.46), I^2 =0.0%							

Analysis 1.22. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 22 Ferritin in µg/L (by malaria endemicity).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 22 Ferritin in g/L (by malaria endemicity)

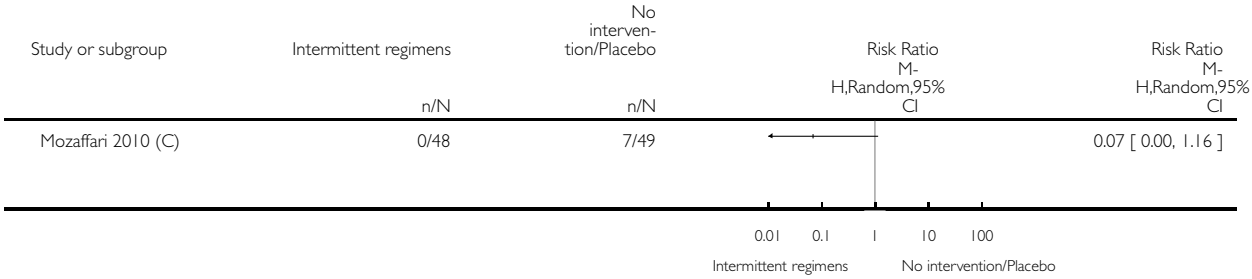


Analysis 1.23. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 23 Iron deficiency anaemia (All).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 23 Iron deficiency anaemia (All)

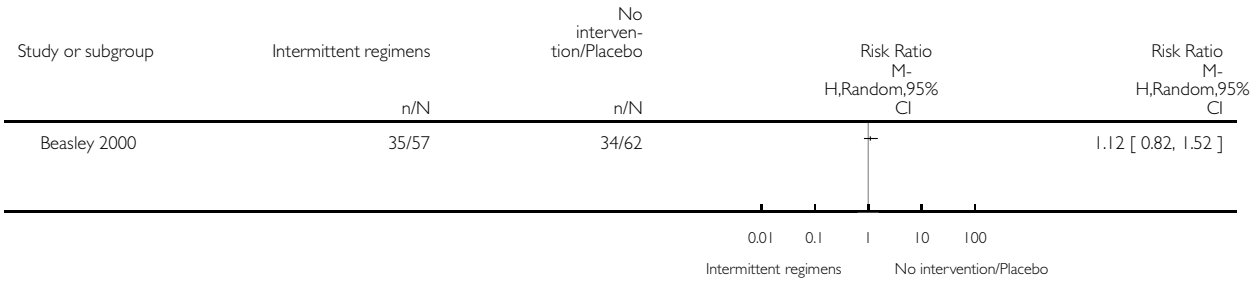


Analysis 1.24. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 24 All cause morbidity (All).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 24 All cause morbidity (All)

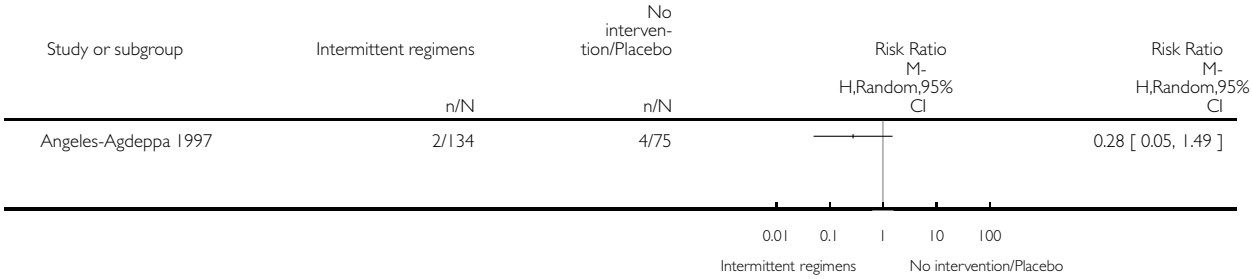


Analysis 1.25. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 25 Diarrhoea.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 25 Diarrhoea

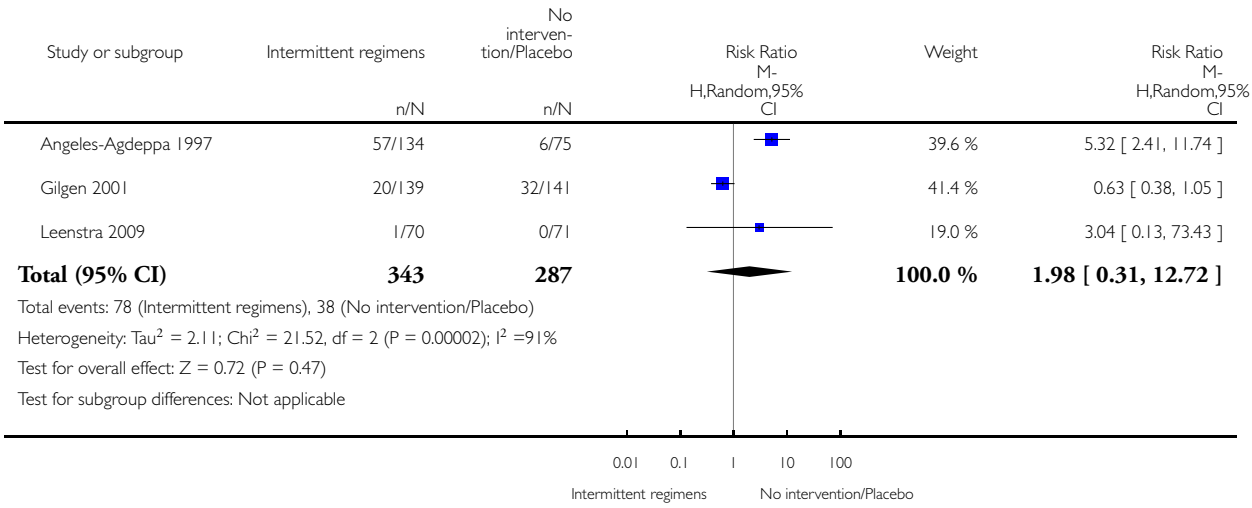


Analysis 1.26. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 26 Any adverse side effects.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 26 Any adverse side effects



Analysis 1.27. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 27 Adherence.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 27 Adherence

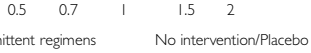
Study or subgroup	Intermittent regimens n/N	No intervention/Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ahmed 2001	148/151	71/71		81.5 %	0.98 [0.95, 1.01]
Zavaleta 2000	93/98	92/97		18.5 %	1.00 [0.94, 1.07]
Total (95% CI)	**249**	**168**		**100.0 %**	**0.99 [0.96, 1.02]**

Total events: 241 (Intermittent regimens), 163 (No intervention/Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.34$, df = 1 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Not applicable



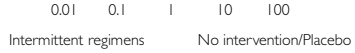
Analysis 1.28. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 28 Prevalence of malaria parasitaemia.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 28 Prevalence of malaria parasitaemia

Study or subgroup	Intermittent regimens n/N	No intervention/Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Beasley 2000	36/57	34/62		1.15 [0.85, 1.56]



Analysis 1.29. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 29 Any malaria parasitaemia (Incidence rate; per 1000 person months).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 29 Any malaria parasitaemia (Incidence rate; per 1000 person months)

Study or subgroup	Intermittent regimens n/N	No intervention/Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Leenstra 2009	43/124	31/125		1.40 [0.95, 2.06]

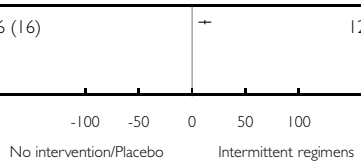
Analysis 1.30. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 30 High density malaria parasitaemia (parasites 200/wbc).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 30 High density malaria parasitaemia (parasites 200/wbc)

Study or subgroup	Intermittent regimens		No intervention/Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Beasley 2000	57	18 (17)	62	6 (16)		12.00 [6.06, 17.94]



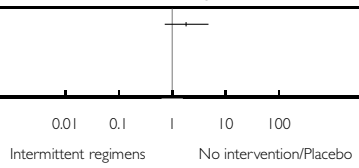
Analysis 1.31. Comparison 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo, Outcome 31 Clinical malaria.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 1 Intermittent iron supplementation (alone or with any other micronutrients) versus no supplementation or placebo

Outcome: 31 Clinical malaria

Study or subgroup	Intermittent regimens	No intervention/Placebo	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
Leenstra 2009	11/124	6/125		1.85 [0.71, 4.84]

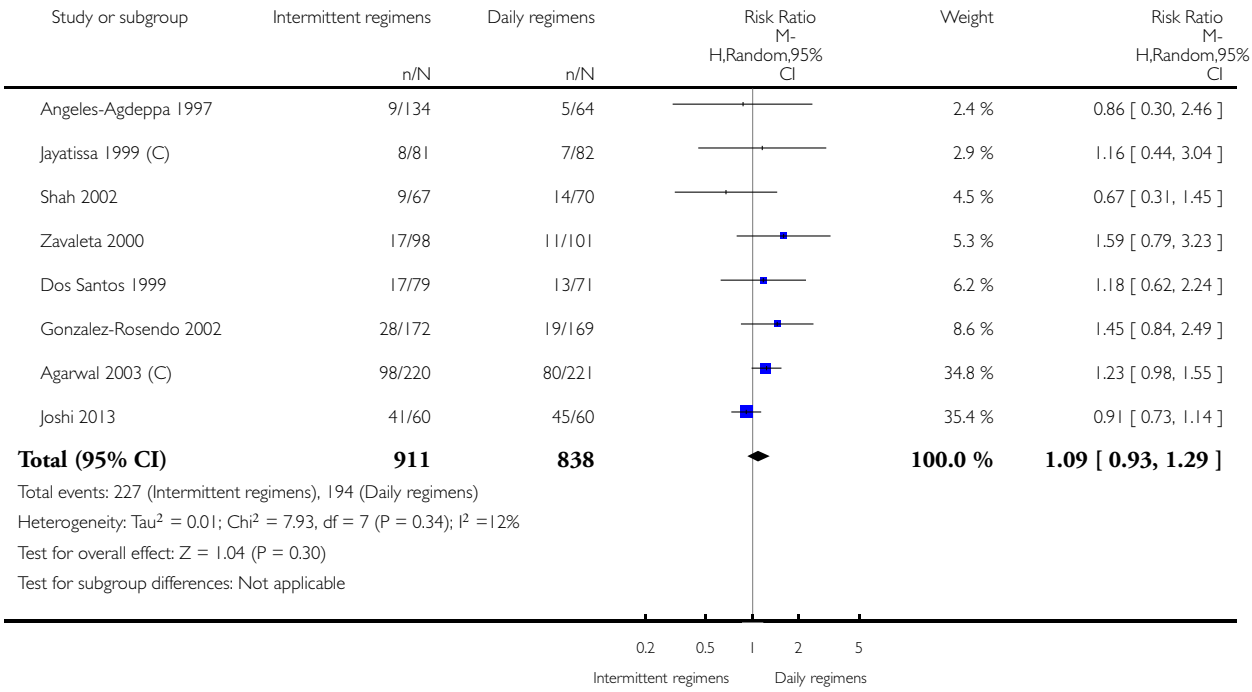


Analysis 2.1. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 1 Anaemia (All).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 1 Anaemia (All)

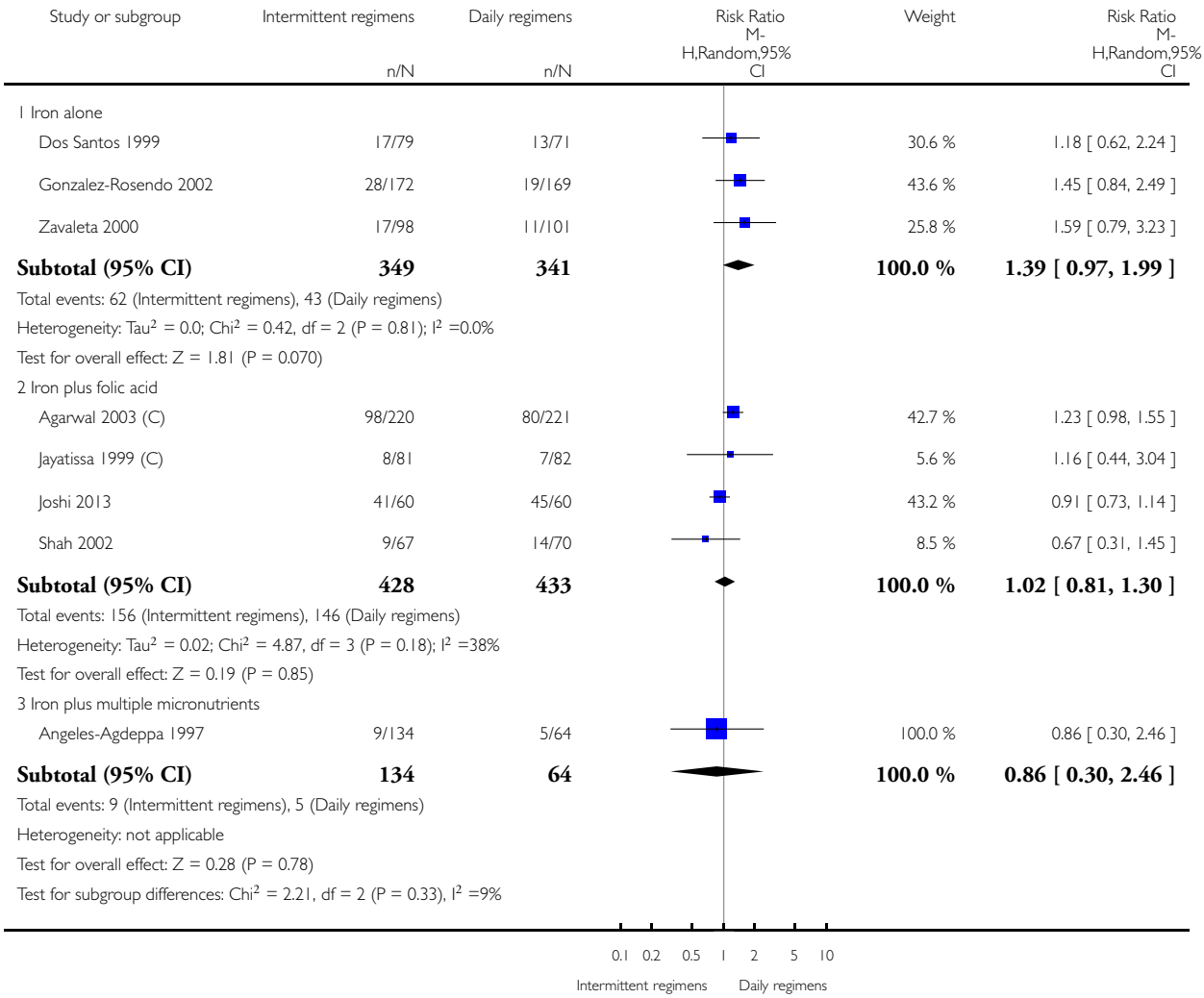


Analysis 2.2. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 2 Anaemia (by supplement composition).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 2 Anaemia (by supplement composition)

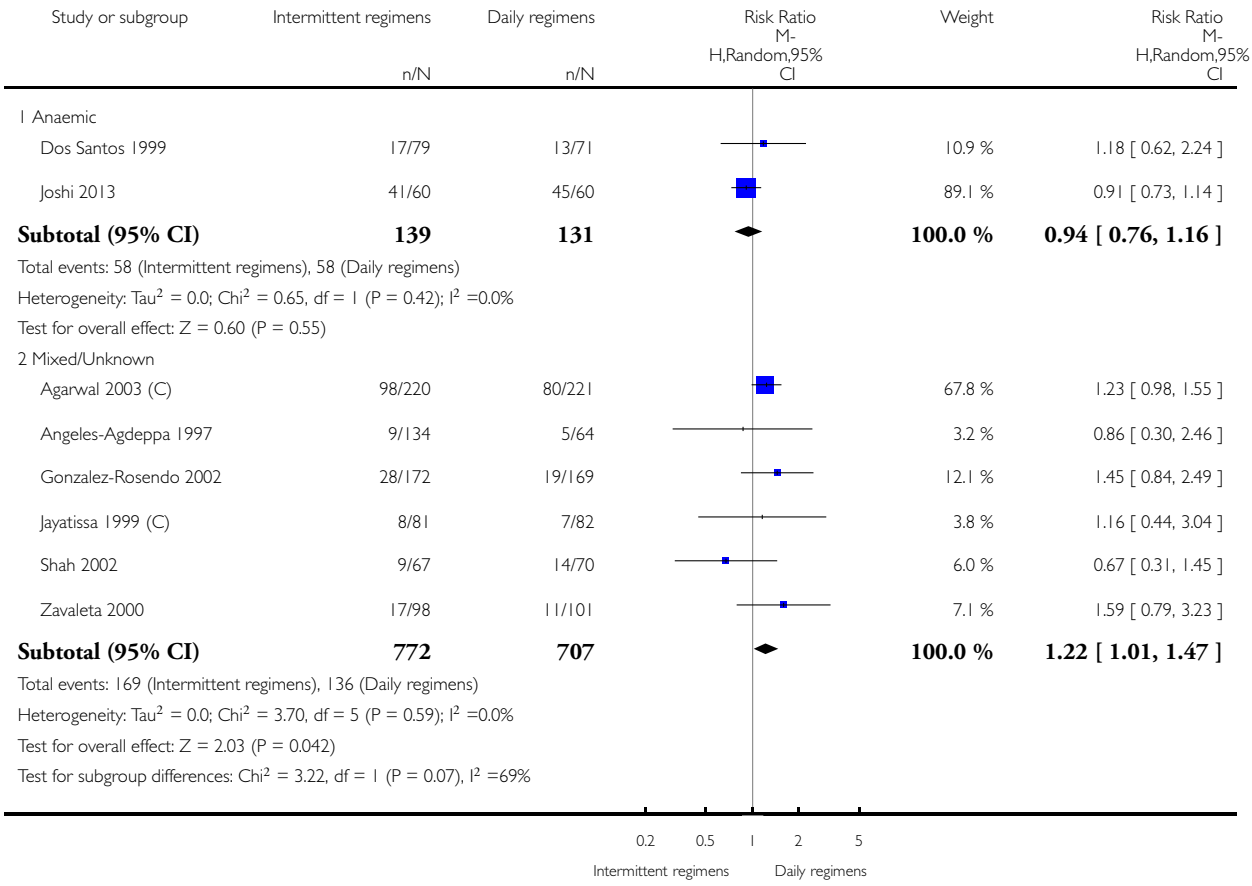


Analysis 2.3. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 3 Anaemia (by anaemia status at baseline).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 3 Anaemia (by anaemia status at baseline)



Analysis 2.4. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 4 Anaemia (by iron status at baseline): Mixed/Unknown.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 4 Anaemia (by iron status at baseline): Mixed/Unknown

Study or subgroup	Intermittent regimens n/N	Daily regimens n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Agarwal 2003 (C)	98/220	80/221		62.5 %	1.23 [0.98, 1.55]
Angeles-Agdeppa 1997	9/134	5/64		3.0 %	0.86 [0.30, 2.46]
Dos Santos 1999	17/79	13/71		7.8 %	1.18 [0.62, 2.24]
Gonzalez-Rosendo 2002	28/172	19/169		11.1 %	1.45 [0.84, 2.49]
Jayatissa 1999 (C)	8/81	7/82		3.5 %	1.16 [0.44, 3.04]
Shah 2002	9/67	14/70		5.6 %	0.67 [0.31, 1.45]
Zavaleta 2000	17/98	11/101		6.6 %	1.59 [0.79, 3.23]
Total (95% CI)	**851**	**778**		**100.0 %**	**1.21 [1.01, 1.45]**

Total events: 186 (Intermittent regimens), 149 (Daily regimens)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.71$, df = 6 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 2.09 (P = 0.037)

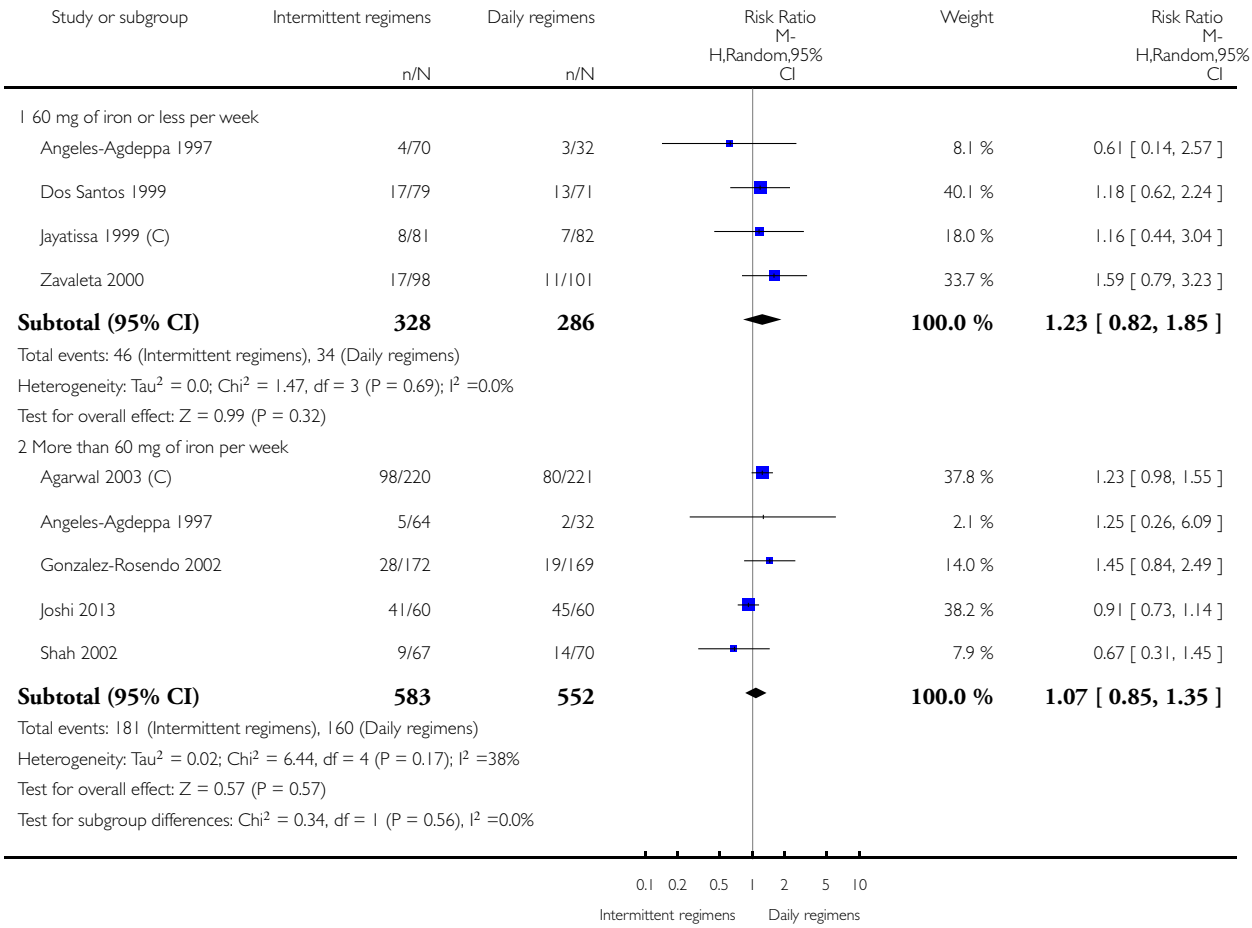
Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 5 Anaemia (by dose of elemental iron per week in the intermittent group).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 5 Anaemia (by dose of elemental iron per week in the intermittent group)

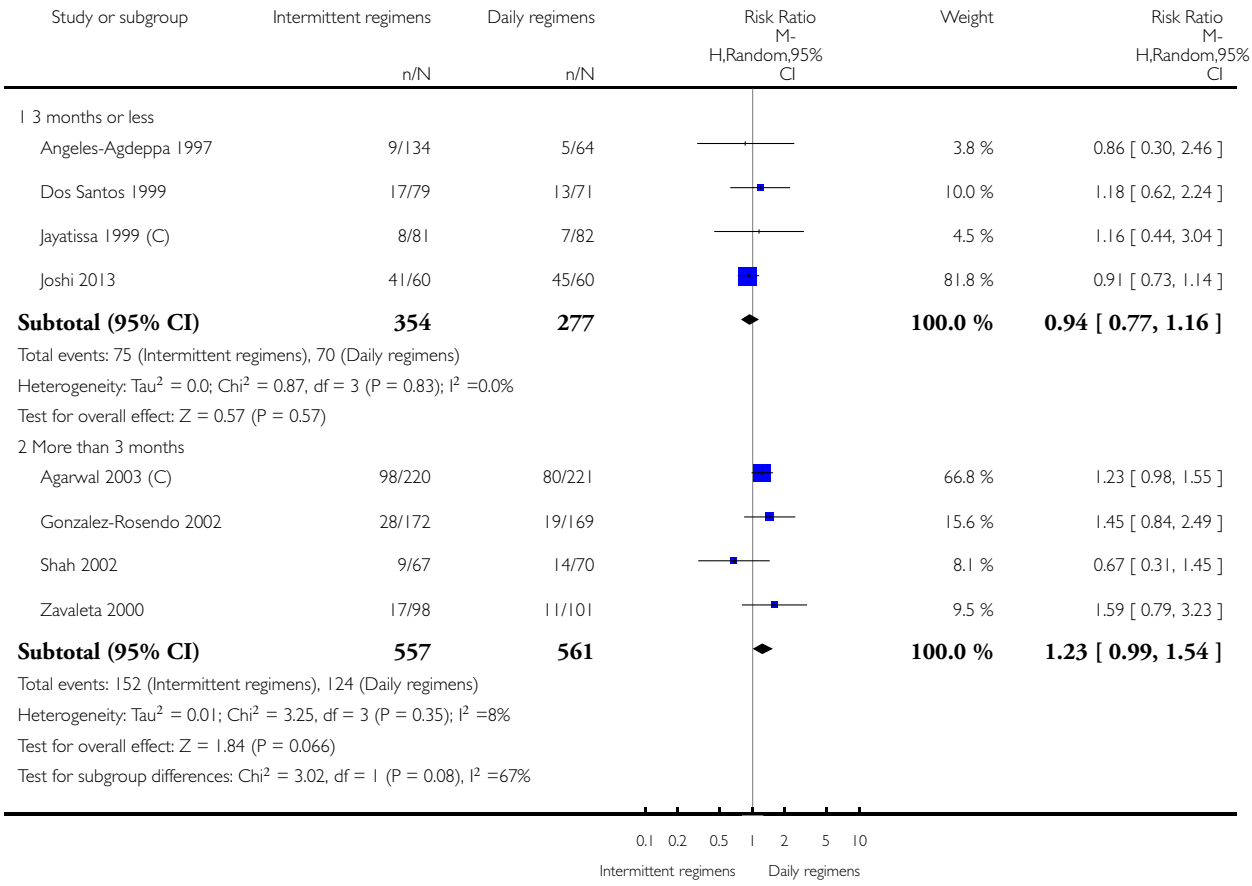


Analysis 2.6. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 6 Anaemia (by duration of supplementation).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 6 Anaemia (by duration of supplementation)

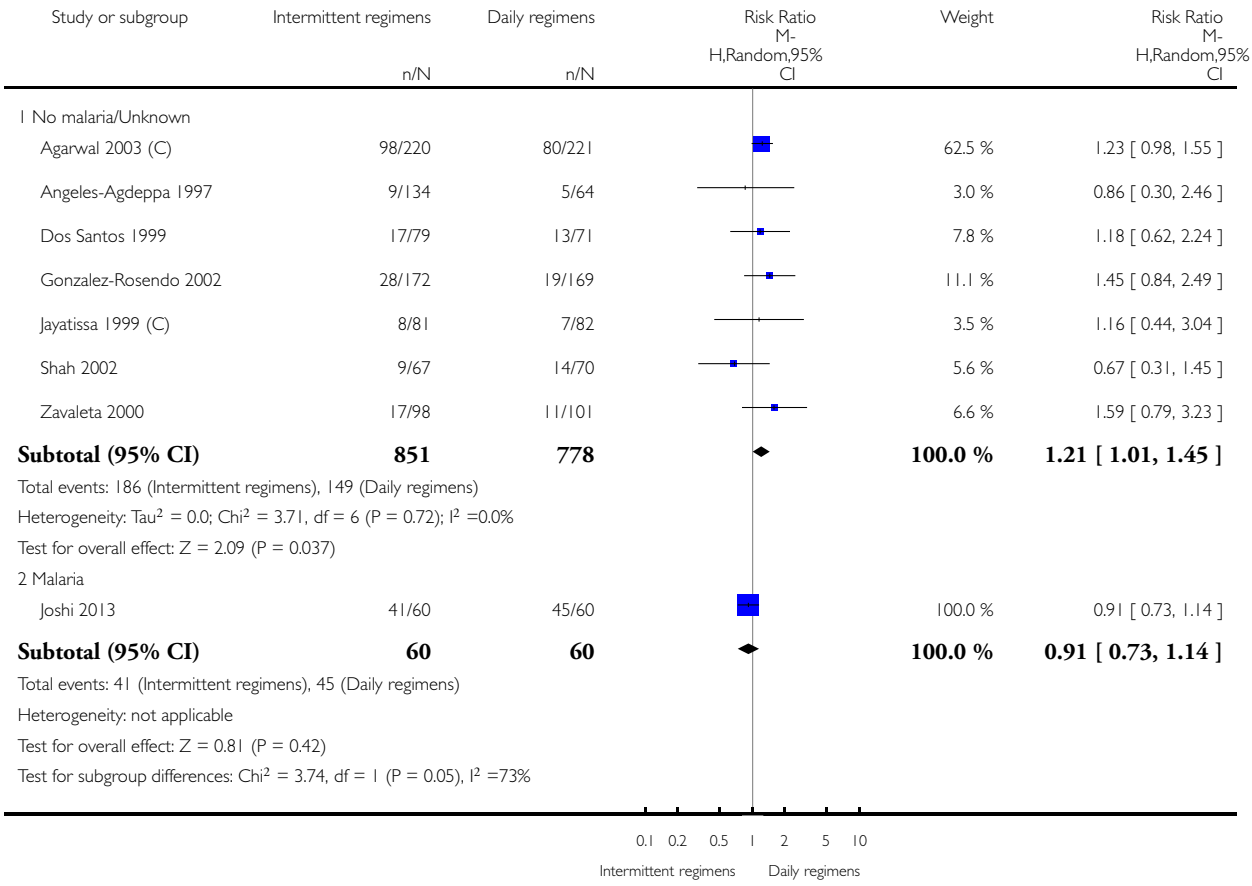


Analysis 2.7. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 7 Anaemia (by malaria endemicity).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 7 Anaemia (by malaria endemicity)



Analysis 2.8. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 8 Haemoglobin in g/L (All).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 8 Haemoglobin in g/L (All)

Study or subgroup	Intermittent regimens N	Mean(SD)	Daily regimens N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Agarwal 2003 (C)	220	118 (13)	221	123 (11)		11.8 %	-5.00 [-7.25, -2.75]
Angeles-Agdeppa 1997	134	130.3 (7.8)	64	130 (7.8)		11.6 %	0.30 [-2.02, 2.62]
Dos Santos 1999	79	118.3 (9.7)	71	116.2 (11.8)		9.5 %	2.10 [-1.38, 5.58]
Gonzalez-Rosendo 2002	145	131 (10)	151	132 (10)		11.7 %	-1.00 [-3.28, 1.28]
Gupta 2014	220	126 (29)	111	120 (23)		6.1 %	6.00 [0.26, 11.74]
Jayatissa 1999 (C)	81	131 (10)	82	132 (9)		10.5 %	-1.00 [-3.92, 1.92]
Joshi 2013	60	114 (9)	60	112 (10)		9.6 %	2.00 [-1.40, 5.40]
Kianfar 2000	112	8.5 (9.2)	92	7.4 (8.5)		11.4 %	1.10 [-1.33, 3.53]
Riuvard 2006	10	130 (9)	11	131 (7)		4.8 %	-1.00 [-7.94, 5.94]
Shobha 2003	102	122.9 (5.1)	101	120 (6)		12.9 %	2.90 [1.37, 4.43]
Total (95% CI)	**1163**		**964**			**100.0 %**	**0.43 [-1.44, 2.31]**

Heterogeneity: $Tau^2 = 6.45$; $Chi^2 = 40.60$, df = 9 ($P<0.00001$); $I^2 = 78\%$

Test for overall effect: Z = 0.45 (P = 0.65)

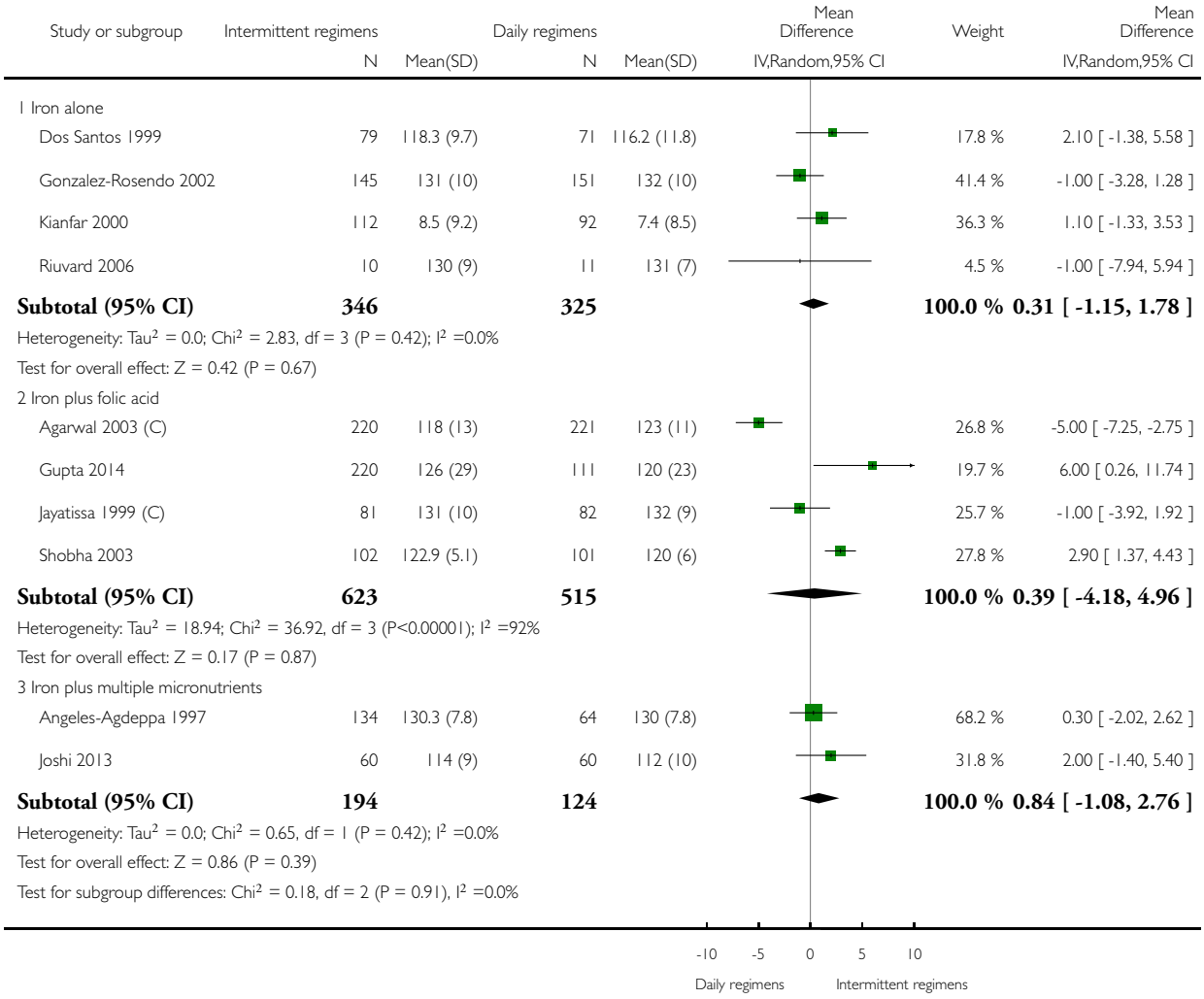
Test for subgroup differences: Not applicable

Analysis 2.9. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 9 Haemoglobin in g/L (by supplement composition).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 9 Haemoglobin in g/L (by supplement composition)



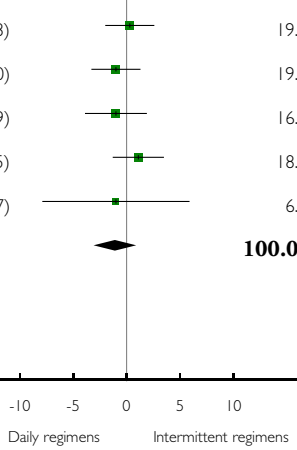
Analysis 2.10. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 10 Haemoglobin in g/L (by anaemia status at baseline).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 10 Haemoglobin in g/L (by anaemia status at baseline)

Study or subgroup	Intermittent regimens N	Mean(SD)	Daily regimens N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Anaemic							
Dos Santos 1999	79	118.3 (9.7)	71	116.2 (11.8)		13.2 %	2.10 [-1.38, 5.58]
Gupta 2014	220	126 (29)	111	120 (23)		4.9 %	6.00 [0.26, 11.74]
Joshi 2013	60	114 (9)	60	112 (10)		13.8 %	2.00 [-1.40, 5.40]
Shobha 2003	102	122.9 (5.1)	101	120 (6)		68.1 %	2.90 [1.37, 4.43]
Subtotal (95% CI)	**461**		**343**			**100.0 %**	**2.82 [1.56, 4.09]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.58$, df = 3 (P = 0.67); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.37 (P = 0.000012)							
2 Mixed/Unknown							
Agarwal 2003 (C)	220	118 (13)	221	123 (11)		19.5 %	-5.00 [-7.25, -2.75]
Angeles-Agdeppa 1997	134	130.3 (7.8)	64	130 (7.8)		19.2 %	0.30 [-2.02, 2.62]
Gonzalez-Rosendo 2002	145	131 (10)	151	132 (10)		19.4 %	-1.00 [-3.28, 1.28]
Jayatissa 1999 (C)	81	131 (10)	82	132 (9)		16.7 %	-1.00 [-3.92, 1.92]
Kianfar 2000	112	8.5 (9.2)	92	7.4 (8.5)		18.8 %	1.10 [-1.33, 3.53]
Riuvard 2006	10	130 (9)	11	131 (7)		6.3 %	-1.00 [-7.94, 5.94]
Subtotal (95% CI)	**702**		**621**			**100.0 %**	**-1.14 [-3.15, 0.87]**
Heterogeneity: $Tau^2 = 4.06$; $Chi^2 = 16.06$, df = 5 (P = 0.01); $I^2 = 69\%$							
Test for overall effect: Z = 1.11 (P = 0.27)							
Test for subgroup differences: $Chi^2 = 10.68$, df = 1 (P = 0.00), $I^2 = 91\%$							

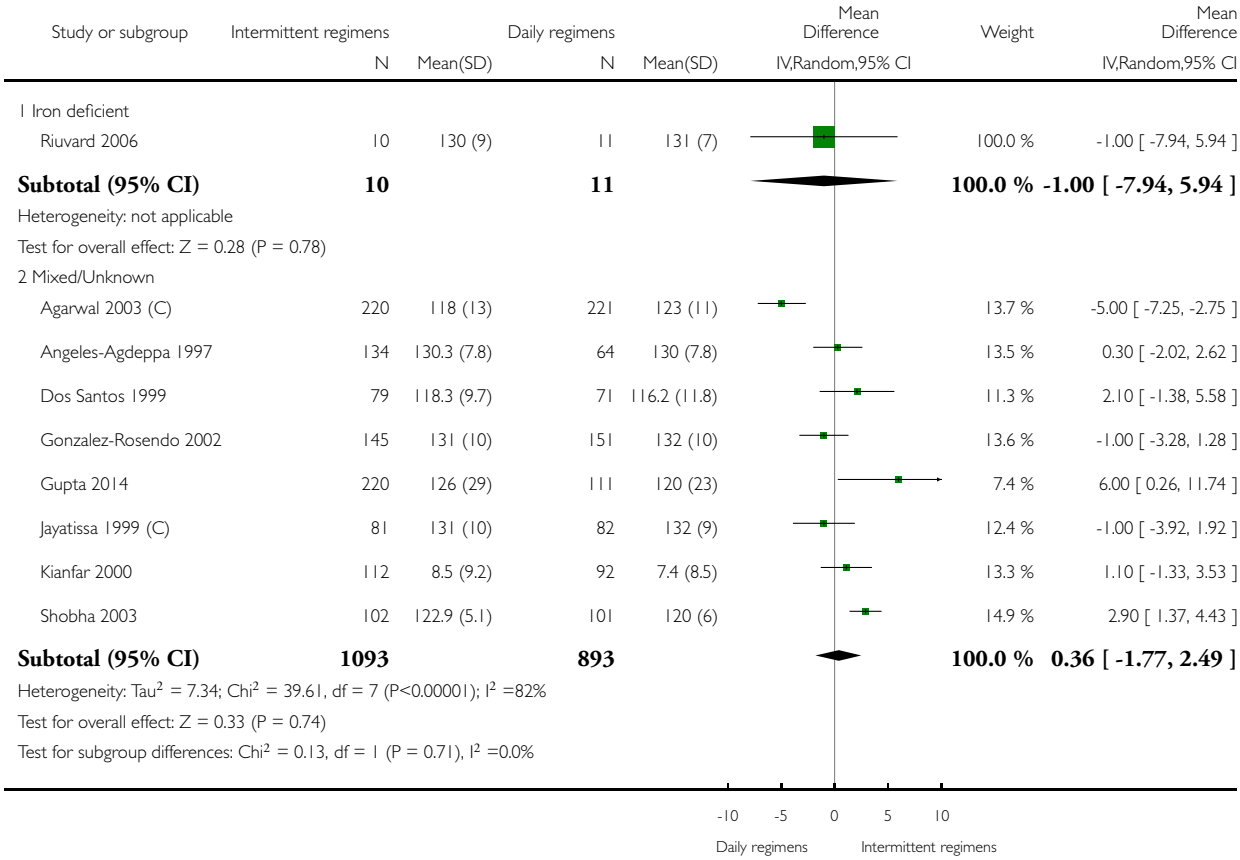


Analysis 2.11. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 11 Haemoglobin in g/L (by iron status at baseline).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 11 Haemoglobin in g/L (by iron status at baseline)

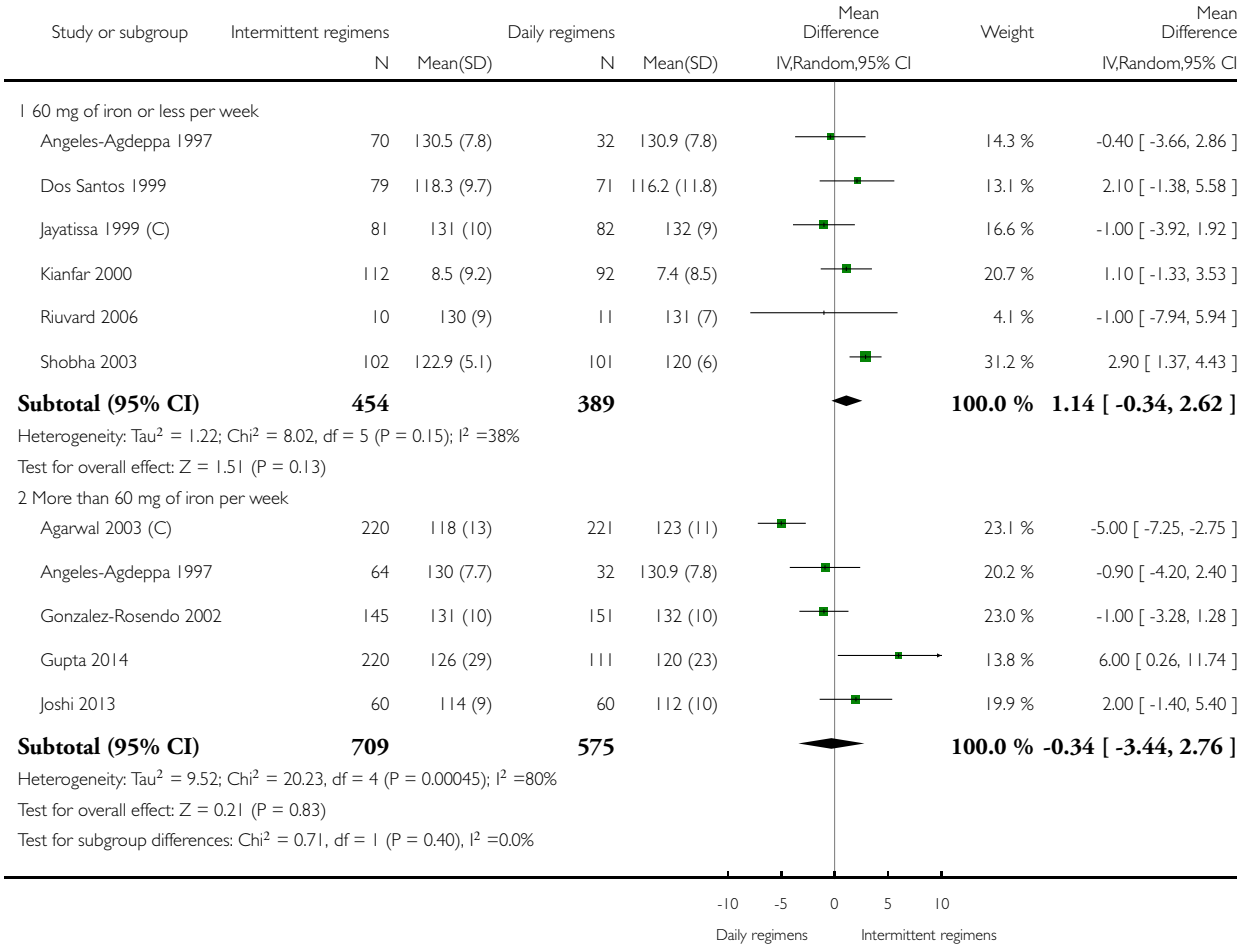


Analysis 2.12. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 12 Haemoglobin in g/L (by dose of elemental iron per week in the intermittent group).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 12 Haemoglobin in g/L (by dose of elemental iron per week in the intermittent group)

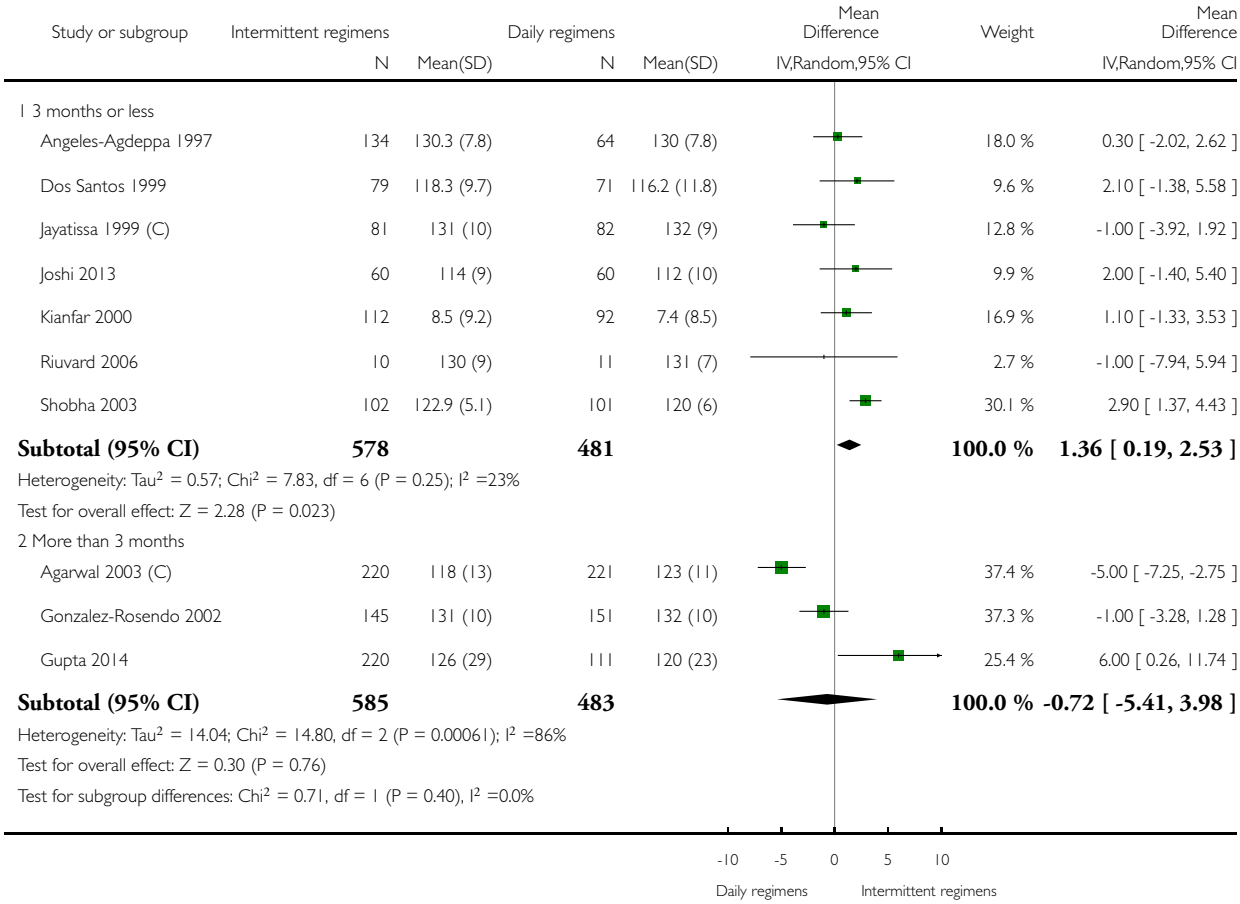


Analysis 2.13. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 13 Haemoglobin in g/L (by duration of supplementation).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 13 Haemoglobin in g/L (by duration of supplementation)

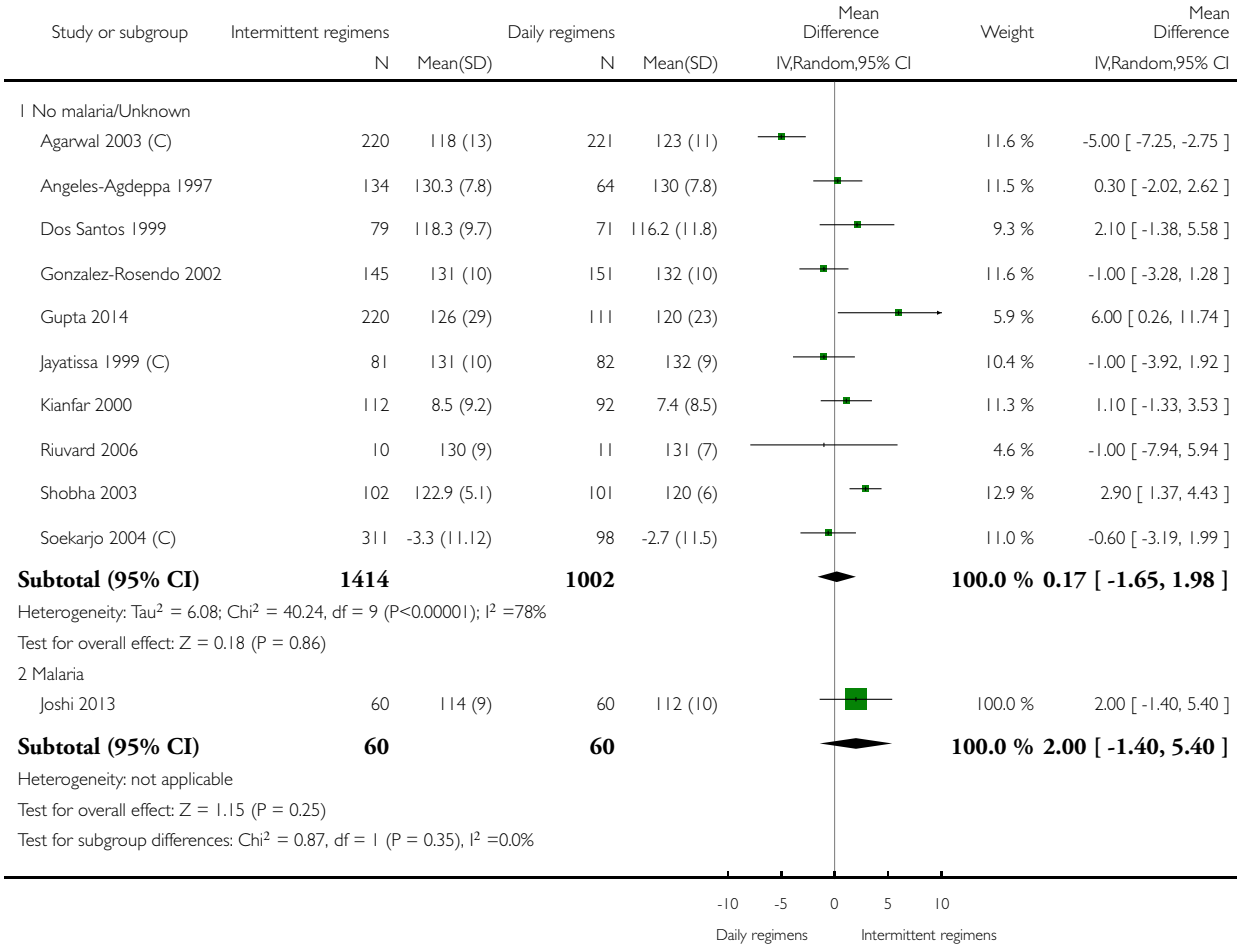


Analysis 2.14. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 14 Haemoglobin in g/L (by malaria endemicity).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 14 Haemoglobin in g/L (by malaria endemicity)



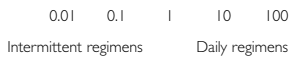
Analysis 2.15. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 15 Iron deficiency (All).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 15 Iron deficiency (All)

Study or subgroup	Intermittent regimens n/N	Daily regimens n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Angeles-Agdeppa 1997	9/134	1/64		4.30 [0.56, 33.20]



Analysis 2.16. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 16 Ferritin in µg/L (All).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 16 Ferritin in g/L (All)

Study or subgroup	Intermittent regimens N	Mean(SD)	Daily regimens N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Agarwal 2003 (C)	220	14.2 (9.7)	218	16.7 (10.5)		33.3 %	-2.50 [-4.39, -0.61]
Angeles-Agdeppa 1997	134	43.5 (24.5)	64	62 (32)		15.2 %	-18.50 [-27.37, -9.63]
Gupta 2014	220	34.9 (3)	111	34.8 (3.9)		34.9 %	0.10 [-0.73, 0.93]
Riuvard 2006	10	8 (5.3)	11	22.8 (12.7)		16.6 %	-14.80 [-22.99, -6.61]
Total (95% CI)	**584**		**404**			**100.0 %**	**-6.07 [-10.66, -1.48]**

Heterogeneity: Tau² = 15.55; Chi² = 33.80, df = 3 (P<0.00001); I² =91%

Test for overall effect: Z = 2.59 (P = 0.0095)

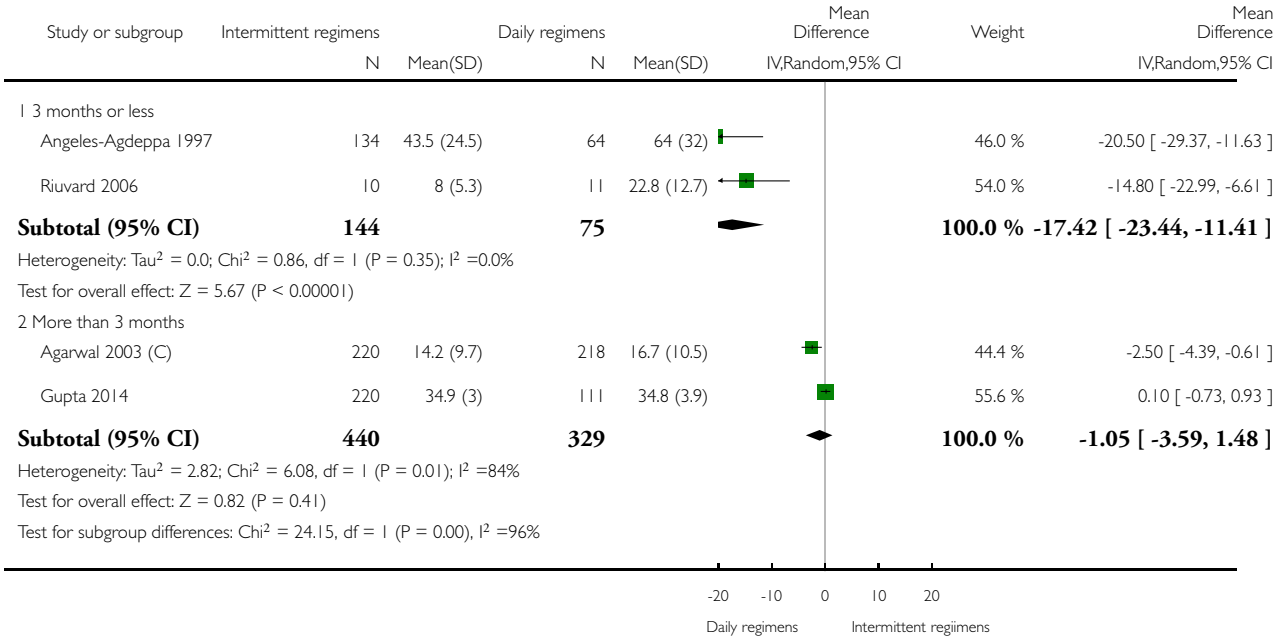
Test for subgroup differences: Not applicable

Analysis 2.17. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 17 Ferritin in µg/L (by duration of supplementation).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 17 Ferritin in g/L (by duration of supplementation)



Analysis 2.18. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 18 Ferritin in µg/L (by anaemia status at baseline).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 18 Ferritin in g/L (by anaemia status at baseline)

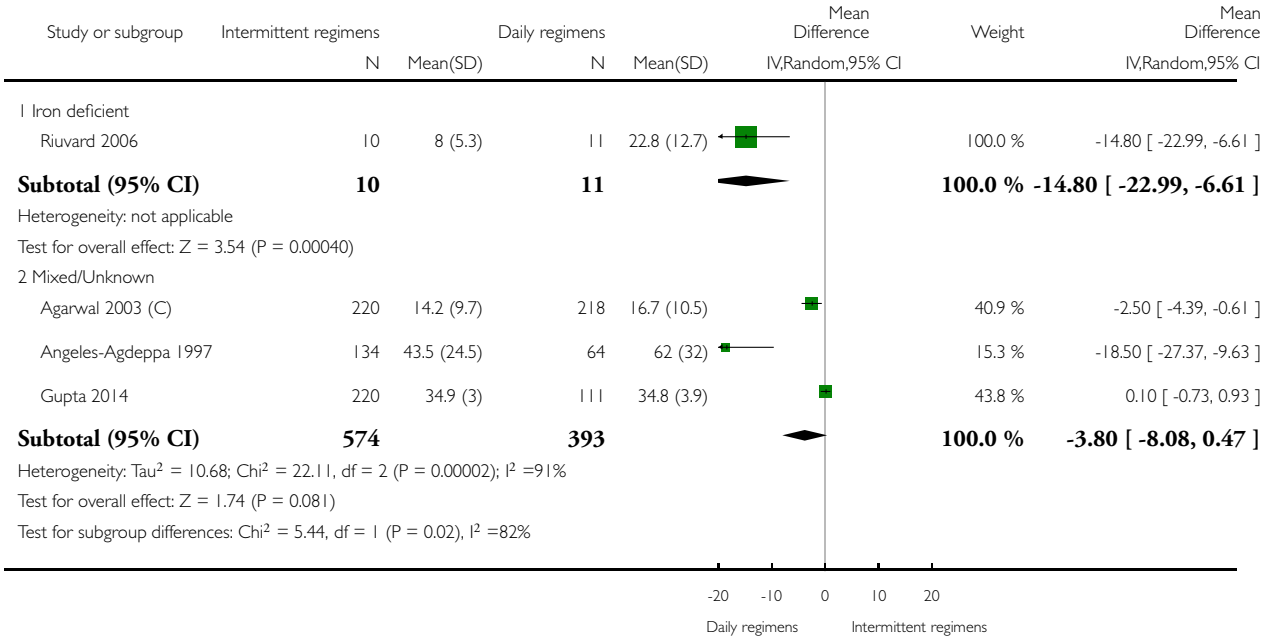
Study or subgroup	Intermittent regimens N	Mean(SD)	Daily regimens N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Anaemic							
Gupta 2014	220	34.9 (3)	111	34.8 (3.9)		100.0 %	0.10 [-0.73, 0.93]
Subtotal (95% CI)	**220**		**111**			**100.0 %**	**0.10 [-0.73, 0.93]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.24 (P = 0.81)							
2 Mixed/Unknown							
Agarwal 2003 (C)	220	14.2 (9.7)	218	16.7 (10.5)		37.6 %	-2.50 [-4.39, -0.61]
Angeles-Agdeppa 1997	134	43.5 (24.5)	64	62 (32)		30.8 %	-18.50 [-27.37, -9.63]
Riuvard 2006	10	8 (5.3)	11	22.8 (12.7)		31.7 %	-14.80 [-22.99, -6.61]
Subtotal (95% CI)	**364**		**293**			**100.0 %**	**-11.32 [-22.61, -0.02]**
Heterogeneity: Tau^2 = 87.40; Chi^2 = 19.29, df = 2 (P = 0.00006); I^2 =90%							
Test for overall effect: Z = 1.96 (P = 0.050)							
Test for subgroup differences: Chi^2 = 3.91, df = 1 (P = 0.05), I^2 =74%							

Analysis 2.19. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 19 Ferritin in µg/L (by iron status at baseline).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 19 Ferritin in g/L (by iron status at baseline)

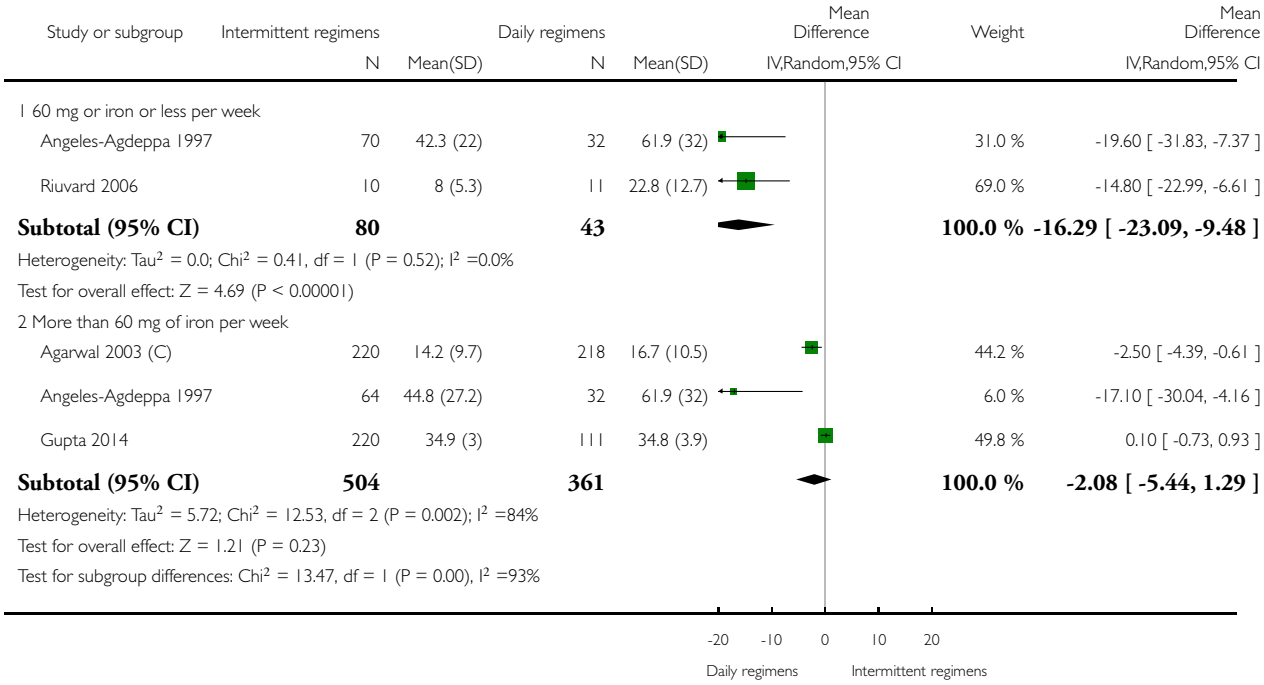


Analysis 2.20. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 20 Ferritin in µg/L (by dose of elemental iron per week in the intermittent group).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 20 Ferritin in g/L (by dose of elemental iron per week in the intermittent group)

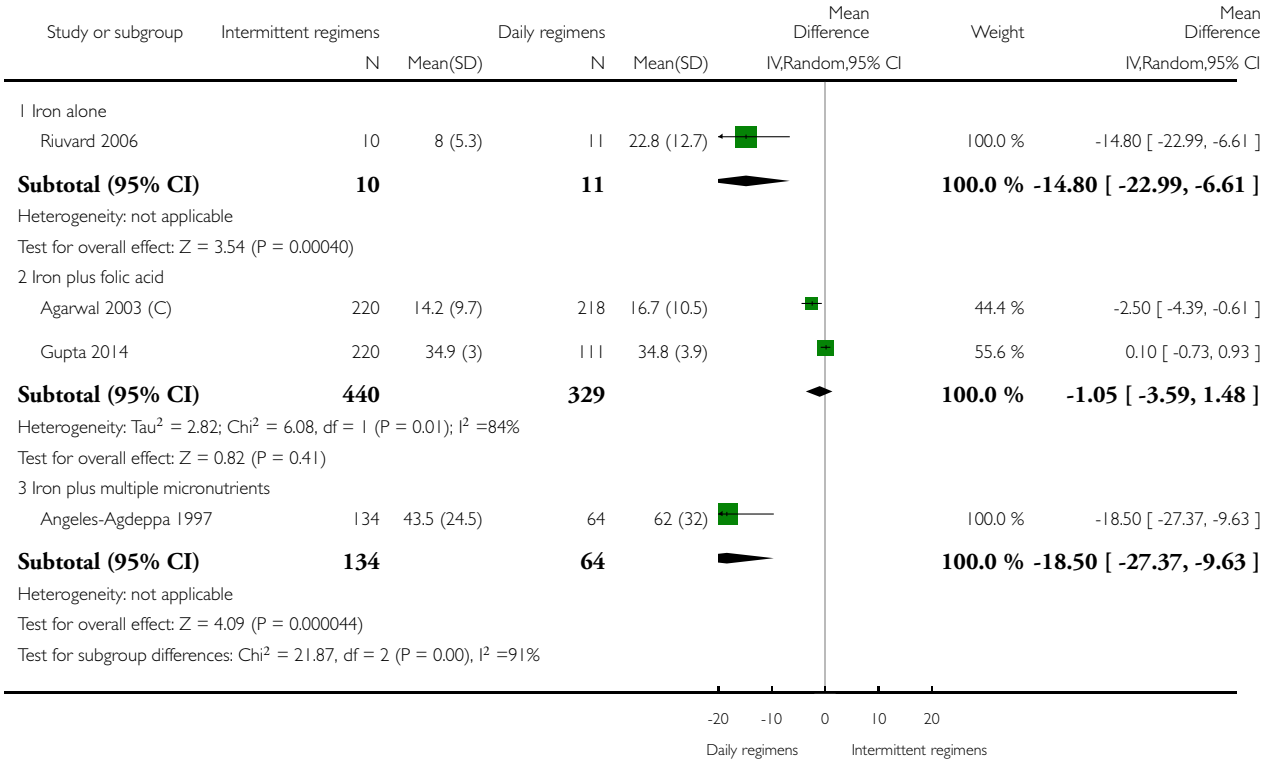


Analysis 2.21. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 21 Ferritin in µg/L (by supplement composition).

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 21 Ferritin in g/L (by supplement composition)

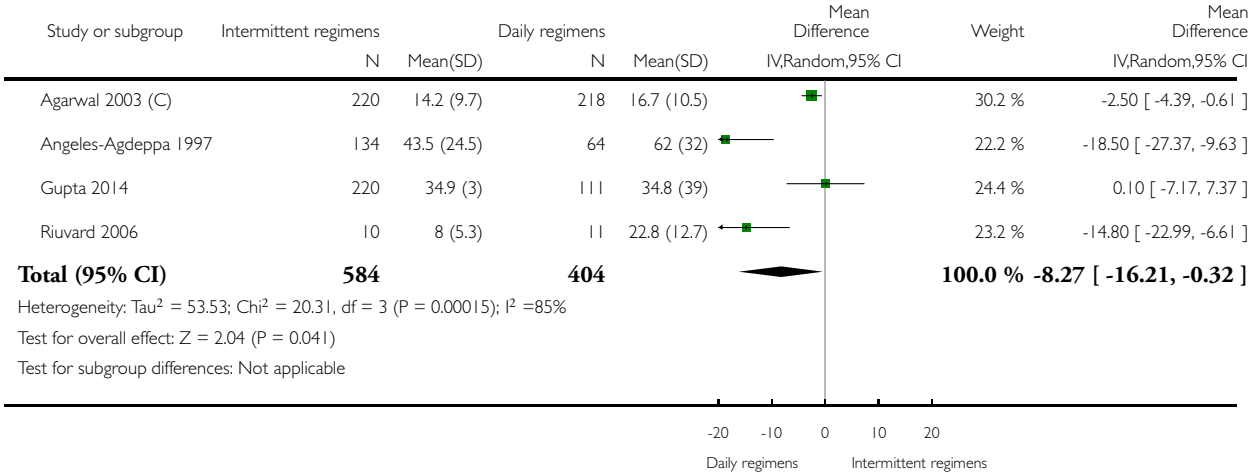


Analysis 2.22. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 22 Ferritin in µg/L (by malaria endemicity): No malaria/Unknown.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 22 Ferritin in g/L (by malaria endemicity): No malaria/Unknown

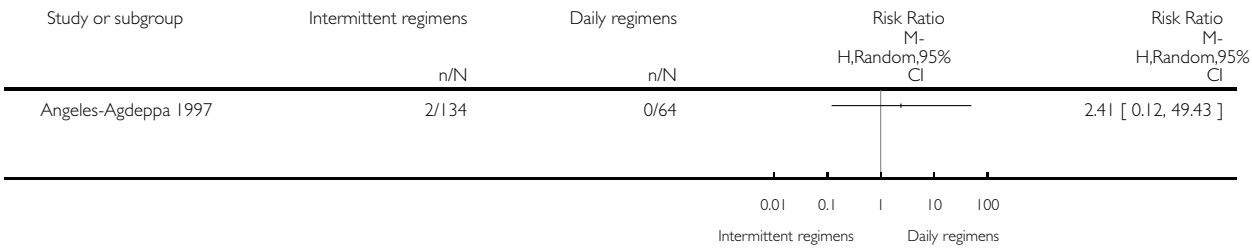


Analysis 2.23. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 23 Diarrhoea.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 23 Diarrhoea

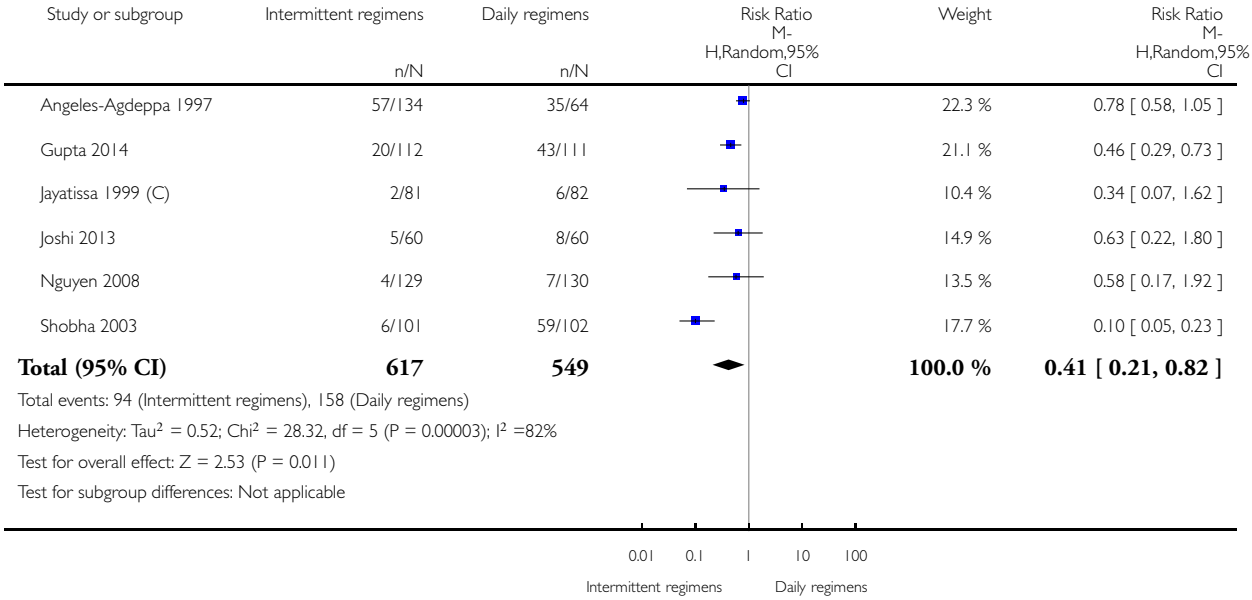


Analysis 2.24. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 24 Any adverse side effects.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 24 Any adverse side effects

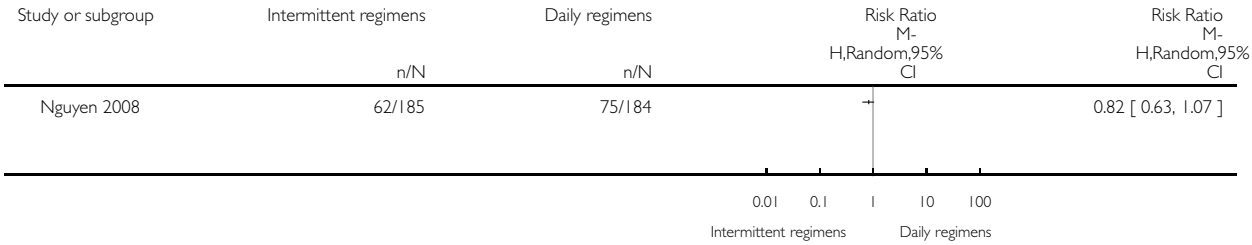


Analysis 2.25. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 25 Depression.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 25 Depression

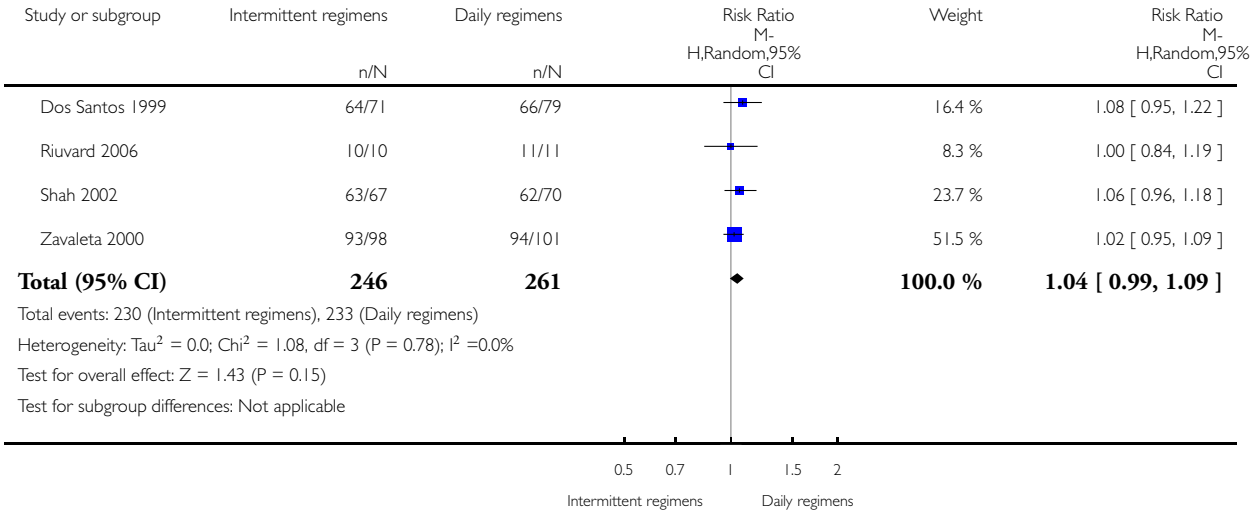


Analysis 2.26. Comparison 2 Intermittent iron supplementation versus daily iron supplementation, Outcome 26 Adherence.

Review: Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women

Comparison: 2 Intermittent iron supplementation versus daily iron supplementation

Outcome: 26 Adherence



ADDITIONAL TABLES

Table 1. Unused methods

Method	Approach	Reason for non-use
Measures of treatment effects	**Continuous data** We had planned to use the SMD to combine trials that measured the same outcome but used different methods	There was no need to use the SMD to combine trials as outcomes were measured with the same methods
Sensitivity analysis	We had planned to conduct a sensitivity analysis to examine the effects of removing studies at high risk of bias (studies with unclear or high risk of bias for sequence generation and allocation concealment, and either high levels of attrition or no blinding) from the analyses and comparing the effect	It was not possible to conduct this analysis because only two studies were considered at low risk of bias according to our predefined criteria (Hall 2002 (C) and Nguyen 2008).
	We had planned to conduct a sensitivity analysis to explore the effect of missing data	We were not able to conduct this analysis given that 13 out of 25 studies had attrition, and 22 out of 25 studies had unclear risk of reporting bias

SMD:standardisedmeandifference

APPENDICES

Appendix 1. Search strategies 2011 onwards

Cochrane Central Register of Controlled Trials (CENTRAL)

#1MeSH descriptor Iron, this term only
#2MeSH descriptor Iron, Dietary, this term only
#3MeSH descriptor Anemia, Iron-Deficiency, this term only
#4MeSH descriptor Folic Acid, this term only
#5iron* or folic* or folate* or folvite* or folacin* or pteroylglutamic*
#6MeSH descriptor Ferric Compounds, this term only
#7MeSH descriptor Ferrous Compounds, this term only
#8ferrous* or ferric* or fe
#9{or #1-#8}
#10MeSH descriptor Drug Administration Schedule, this term only
#11MeSH descriptor Dose-Response Relationship, Drug explode all trees
#12MeSH descriptor Time Factors, this term only
#13week* or biweek* or bi next week* or intermittent* or alternat*
#14{or #10-#13}
#15#9 and #14

#16(iron near/3 (dose* or dosage or administer* or administration or frequency or schedule))
#17#15 or #16
#18MeSH descriptor Adolescent, this term only
#19MeSH descriptor Adult, this term only
#20MeSH descriptor Middle Aged, this term only
#21(adult* or teen* or adoles* or pubert* or pubescen*)
#22{or #18-#21}
#23MeSH descriptor: [Female] explode all trees
#24girl* or female*
#25#23 or #24
#26#22 and #25
#27wom*n*
#28#26 or #27
#29#17 and #28 Publication Year from 2011 to 2017, in Trials
#30#17 and #28 Publication Year from 2016 to 2018, in Trials

MEDLINE

1 Iron/
2 Anemia, Iron-Deficiency/
3 Iron, Dietary/
4 Folic Acid/
5 iron$.tw.
6 (folic$ or folate$ or folvite$ or folacin$ or pteroylglutamic$).tw.
7 Ferric Compounds/
8 Ferrous Compounds/
9 (ferrous$ or ferric$ or fe).tw.
10 or/1-9
11 Drug Administration Schedule/
12 Time Factors/)
13 (week$ or biweek$ or bi-week$ or intermittent$ or alternat$).tw.
14 or/11-13
15 10 and 14
16 (iron adj3 (dose$ or dosage or administer$ or administration or frequency or regimen$ or supplement$)).tw.
17 15 or 16
18 adolescent/ or adult/ or middle aged/
19 (adult$ or teen$ or adoles$ or pubert$ or pubescen$).tw.
20 18 or 19
21 Female/
22 (girl$ or female$).tw.
23 or/21-22
24 20 and 23
25 wom#n.tw.
26 24 or 25
27 randomized controlled trial.pt.
28 controlled clinical trial.pt.
29 randomi#ed.ab.
30 placebo$.ab.
31 drug therapy.fs.
32 randomly.ab.
33 trial.ab.
34 groups.ab.
35 or/27-34

36 exp animals/ not humans.sh.
37 35 not 36
38 17 and 26 and 37
39 limit 38 to ed=20110502-20180208

MEDLINE In-Process & Other Non-Indexed Citations

1 iron$.tw.
2 (folic acid or folate$ or folvite$ or folacin$ or pteroylglutamic$).tw.
3 (ferric or ferrous or ferritin$).tw.
4 or/1-3
5 (week$ or biweek$ or bi-week$ or intermittent$ or alternat$).tw.
6 4 and 5
7 (iron adj3 (dose$ or dosage or administer$ or administration or frequency or regimen$ or schedule or supplement$)).tw.
8 6 or 7
9 (adult$ or teen$ or adoles$ or pubert$ or pubescen$).tw.
10 (girl$ or female$).tw.
11 9 and 10
12 wom#n$.tw.
13 11 or 12
14 8 and 13
15 (random$ or trial$ or control$ or group$ or placebo$ or blind$ or prospectiv$ or longitudinal$ or meta-analys$ or systematic review$).tw.
16 14 and 15

MEDLINE Epub Ahead of Print

1 iron$.tw.
2 (folic acid or folate$ or folvite$ or folacin$ or pteroylglutamic$).tw.
3 (ferric or ferrous or ferritin$).tw.
4 or/1-3
5 (week$ or biweek$ or bi-week$ or intermittent$ or alternat$).tw.
6 4 and 5
7 (iron adj3 (dose$ or dosage or administer$ or administration or frequency or regimen$ or schedule or supplement$)).tw.
8 6 or 7
9 (adult$ or teen$ or adoles$ or pubert$ or pubescen$).tw.
10 (girl$ or female$).tw.
11 9 and 10
12 wom#n$.tw.
13 11 or 12
14 8 and 13

Embase Ovid

1 iron/
2 iron intake/
3 iron deficiency anemia/
4 folic acid/
5 iron$.tw.
6 (folic$ or folate$ or folvite$ or folacin$ or pteroylglutamic$).tw.
7 ferric ion/
8 ferrous ion/
9 or/1-8

10 drug administration/
11 drug dose regimen/
12 (week$ or biweek$ or bi-week$ or intermittent$ or alternat$).tw.
13 or/10-12
14 9 and 13
15 (iron adj3 (dose$ or dosage or administer$ or administration or frequency or shedule)).tw.
16 14 or 15
17 adult/ or middle aged/ or adolescent/
18 (teen$ or adoles$ or pubert$ or pubescen$).tw.
19 17 or 18
20 female/
21 (girl$ or female$).tw.
22 20 or 21
23 wom#n.tw.
24 (19 and 22) or 23
25 16 and 24
26 Randomized controlled trial/
27 controlled clinical trial/
28 Single blind procedure/
29 Double blind procedure/
30 triple blind procedure/
31 Crossover procedure/
32 (crossover or cross-over).tw.
33 ((singl$ or doubl$ or tripl$ or trebl$) adj1 (blind$ or mask$)).tw.
34 Placebo/
35 placebo.tw.
36 prospective.tw.
37 factorial$.tw.
38 random$.tw.
39 assign$.ab.
40 allocat$.tw.
41 volunteer$.ab.
42 or/26-41
43 25 and 42
44 limit 43 to yr="2011 -Current"

CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature)

S1(MH "Iron")
S2(MH "Iron Compounds")
S3(MH "Ferric Compounds")
S4(MH "Ferrous Compounds")
S5(MH "Folic Acid")
S6(MH "Anemia, Iron Deficiency")
S7(MH "Anemia, Iron Deficiency")
S8TI(iron*) OR AB(iron*)
S9TI(folic* or folate* or folvite* or folacin* or pteroylglutamic*) OR AB(folic* or folate* or folvite* or folacin* or pteroylglutamic*)
S10S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S11(MH "Drug Administration Schedule")
S12(MH "Time Factors")
S13(week* or biweek* or bi-week*or bi week* or intermittent* or alternat* or regimen*)
S14S11 OR S12 OR S13
S15S10 AND S14

S16(iron N3 dose*) or (iron N3 dosage) or (iron N3 administer*) or (iron N3 administration) or (iron N3 frequency) or (iron N3 supplement*) or (iron* N3 schedule)
S17S15 OR S16
S18(AG adolescent or AG adult or AG middle aged) OR (adolescen* or pubert* or pubescen* or adult*)
S19CT female or TI(female* or girl*) OR AB(female* or girl*)
S20S18 AND S19
S21(MH "Women") or TI(women or woman) OR AB(women or woman)
S22S20 OR S21
S23S17 AND S22
S24(MH "Clinical Trials+")
S25MH random assignment
S26(MH "Meta Analysis")
S27(MH "Crossover Design")
S28(MH "Quantitative Studies")
S29PT randomized controlled trial
S30PT Clinical trial
S31(clinical trial*) or (control* N2 trial*)
S32("follow-up study" or "follow-up research")
S33(prospectiv* study or prospectiv* research)
S34(evaluat* N2 study or evaluat* N2 research)
S35(MH "Program Evaluation")
S36(MH "Treatment Outcomes")
S37TI(single N2 mask* or single N2 blind*) OR AB(single N2 mask* or single N2 blind*)
S38TI((doubl* N2 mask*) or (doubl* N2 blind*)) OR AB((doubl* N2 mask*) or (doubl* N2 blind*))
S39TI ((tripl* N2 mask*) or (tripl* N2 blind*)) or ((trebl* N2 mask*) or (trebl* N2 blind*)) OR AB((tripl* N2 mask*) or (tripl* N2 blind*)) or ((trebl* N2 mask*) or (trebl* N2 blind*)
S40random*
S41S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40
S42S23 AND S41
S43EM 20110501-
S44S42 AND S43

Science Citation Index (SCI)

#7 #6 AND #5
Indexes=SCI-EXPANDED Timespan=2011-2018
# 6 TS=(random* or RCT or trial* or allocat* or assign* or placebo* or cross-over or crossover or "cross over" or factorial* or "double blind*" or "single blind")
Indexes=SCI-EXPANDED Timespan=2011-2018
# 5 #4 AND #1
Indexes=SCI-EXPANDED Timespan=2011-2018
# 4 #3 OR #2
Indexes=SCI-EXPANDED Timespan=2011-2018
# 3 TS=(women* or woman*)
Indexes=SCI-EXPANDED Timespan=2011-2018
# 2 TS=((female* or girl*) and (adult* or adolescen* or teen* or pubert* or pubescen*))
Indexes=SCI-EXPANDED Timespan=2011-2018
# 1 TS=((iron* or "folic acid" or ferrous or ferric) near/10 (alternate* or dose* or week* or intermittent or biweek* or bi-week* or schedule or supplement*))
Indexes=SCI-EXPANDED Timespan=2011-2018

Conference Proceedings Citation Index- Science (CPCI-S)

#7 #6 AND #5
Indexes=CPCI-S Timespan=2011-2018
# 6 TS=(random* or RCT or trial* or allocat* or assign* or placebo* or cross-over or crossover or "cross over" or factorial* or "double blind*" or "single blind")
Indexes=CPCI-S Timespan=2011-2018
# 5 #4 AND #1
Indexes=CPCI-S Timespan=2011-2018
# 4 #3 OR #2
Indexes=CPCI-S Timespan=2011-2018
# 3 TS=(women* or woman*)
Indexes=CPCI-S Timespan=2011-2018
# 2 TS=((female* or girl*) and (adult* or adolescen* or teen* or pubert* or pubescen*))
Indexes=CPCI-S Timespan=2011-2018
# 1 TS=((iron* or "folic acid" or ferrous or ferric) near/10 (alternate* or dose* or week* or intermittent or biweek* or bi-week* or schedule or supplement*))
Indexes=CPCI-S Timespan=2011-2018

Cochrane Database of Systematic Reviews (CDSR)

#1MeSH descriptor Iron, this term only
#2MeSH descriptor Iron, Dietary, this term only
#3MeSH descriptor Anemia, Iron-Deficiency, this term only
#4MeSH descriptor Folic Acid, this term only
#5iron* or folic* or folate* or folvite* or folacin* or pteroylglutamic*
#6MeSH descriptor Ferric Compounds, this term only
#7MeSH descriptor Ferrous Compounds, this term only
#8ferrous* or ferric* or fe:TI,AB
#9{or #1-#8}
#10MeSH descriptor Drug Administration Schedule, this term only
#11MeSH descriptor Dose-Response Relationship, Drug explode all trees
#12MeSH descriptor Time Factors, this term only
#13(week* or biweek* or bi next week* or intermittent* or alternat*):TI,AB
#14{or #10-#13}
#15#9 and #14
#16(iron near/3 (dose* or dosage or administer* or administration or frequency or schedule)):TI,AB
#17#15 or #16
#18MeSH descriptor Adolescent, this term only
#19MeSH descriptor Adult, this term only
#20MeSH descriptor Middle Aged, this term only
#21(adult* or teen* or adoles* or pubert* or pubescen*):TI,AB
#22{or #18-#21}
#23MeSH descriptor: [Female] explode all trees
#24(girl* or female*):TI,AB
#25#23 or #24
#26#22 and #25
#27wom*n*:TI,AB
#28#26 or #27
#29#17 and #28 in Cochrane Reviews (Reviews and Protocols)

Database of Abstracts of Reviews of Effect (DARE)

#1MeSH descriptor Iron, this term only

#2MeSH descriptor Iron, Dietary, this term only
#3MeSH descriptor Anemia, Iron-Deficiency, this term only
#4MeSH descriptor Folic Acid, this term only
#5iron* or folic* or folate* or folvite* or folacin* or pteroylglutamic*
#6MeSH descriptor Ferric Compounds, this term only
#7MeSH descriptor Ferrous Compounds, this term only
#8ferrous* or ferric* or fe:TI,AB
#9{or #1-#8}
#10MeSH descriptor Drug Administration Schedule, this term only
#11MeSH descriptor Dose-Response Relationship, Drug explode all trees
#12MeSH descriptor Time Factors, this term only
#13(week* or biweek* or bi next week* or intermittent* or alternat*):TI,AB
#14{or #10-#13}
#15#9 and #14
#16(iron near/3 (dose* or dosage or administer* or administration or frequency or schedule)):TI,AB
#17#15 or #16
#18MeSH descriptor Adolescent, this term only
#19MeSH descriptor Adult, this term only
#20MeSH descriptor Middle Aged, this term only
#21(adult* or teen* or adoles* or pubert* or pubescen*):TI,AB
#22{or #18-#21}
#23MeSH descriptor: [Female] explode all trees
#24(girl* or female*):TI,AB
#25#23 or #24
#26#22 and #25
#27wom*n*:TI,AB
#28#26 or #27
#29#17 and #28 in Other Reviews

POPLINE

((((iron*) OR (folic*) OR (folate*) OR (supplement*))) AND (((week*) OR ('bi\-weekly') OR ('bi weekly') OR (biweekly) OR (alternat*) OR (intermittent*))) AND (((women*) OR (girl*) OR (female*) OR (women*))) AND (((random*) OR (placebo*) OR (group*) OR (trial*) OR (control*) OR (blind*))))

Scientific Electronic Library Online (SciElo)

iron AND supplementation AND women

LILACS (Latin American and Caribbean Health Science Information database)

iron AND supplementation AND women

IBECS

iron AND supplementation AND women

IMBIOMED

iron AND supplementation AND women

ClinicalTrials.gov

Interventional Studies | iron OR folic OR ferrous OR ferric | (female* OR women OR girl*) NOT pregnant | Studies received from 05/01/2011 to 02/20/2018

World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)

Advanced search. TITLE: women NOT pregnant OR girl NOT pregnant OR female NOT pregnant AND Intervention :ferrous OR ferric OR iron OR folic Date of registration 01/05/2011 to 22/02/2018

Appendix 2. Search strategies up to 2011

CENTRAL

#1MeSH descriptor Iron, this term only
#2MeSH descriptor Iron, Dietary, this term only
#3MeSH descriptor Anemia, Iron-Deficiency, this term only
#4MeSH descriptor Folic Acid, this term only
#5MeSH descriptor Dietary Supplements, this term only
#6MeSH descriptor Trace Elements, this term only
#7folic* or folate* or folvite* or folacin* or pteroylglutamic*
#8diet* NEAR/3 supplement*
#9micro-nutrient* or micronutrient* or multi-nutrient* or multinutrient*
#10MeSH descriptor Ferric Compounds, this term only
#11MeSH descriptor Ferrous Compounds, this term only
#12ferrous* or ferric* or fe
#13MeSH descriptor Micronutrients, this term only
#14(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15MeSH descriptor Drug Administration Schedule, this term only
#16MeSH descriptor Dose-Response Relationship, Drug explode all trees
#17MeSH descriptor Time Factors, this term only
#18week* or biweek* or bi NEXT week* or intermittent* or alternat*
#19(#15 OR #16 OR #17 OR #18)
#20(#14 AND #19)
#21(iron NEAR/3 (dose* or dosage or administer* or administration or frequency))
#22(#20 OR #21)
#23MeSH descriptor Adolescent, this term only
#24MeSH descriptor Adult, this term only
#25MeSH descriptor Middle Aged, this term only
#26(teen* or adoles* or pubert* or pubescen*)
#27(#23 OR #24 OR #25 OR #26)
#28(girl* or female* or woman* or women*)
#29(#27 AND #28)
#30(#22 AND #29)
#31(#30), from 1980 to 2011

MEDLINE

1 Iron/
2 Anemia, Iron-Deficiency/
3 Iron, Dietary/
4 Folic Acid/

5 iron$.tw.
6 (folic$ or folate$ or folvite$ or folacin$ or pteroylglutamic$).tw.
7 Ferric Compounds/
8 Ferrous Compounds/
9 (ferrous$ or ferric$ or fe).tw.
10 micronutrients/
11 (micro-nutrient$ or micronutrient$ or multi-nutrient$ or multinutrient$).tw.
12 Dietary Supplements/
13 (diet$ adj3 supplement$).tw.
14 or/1-13
15 Drug Administration Schedule/
16 Time Factors/
17 (week$ or biweek$ or bi-week$ or intermittent$ or alternat$).tw.
18 or/15-17
19 14 and 18
20 (iron adj3 (dose$ or dosage or administer$ or administration or frequency or regimen$ or supplement$)).tw.
21 19 or 20
22 adolescent/ or adult/ or middle aged/
23 (teen$ or adoles$ or pubert$ or pubescen$).tw.
24 22 or 23
25 Female/
26 (girl$ or female$ or wom#n).tw.
27 or/25-26
28 24 and 27
29 randomized controlled trial.pt.
30 controlled clinical trial.pt.
31 randomi#ed.ab.
32 placebo$.ab.
33 randomly.ab.
34 trial.ab.
35 clinical trials as topic.sh.
36 or/29-35
37 exp animals/ not humans.sh.
38 36 not 37
39 21 and 28 and 38
40 limit 39 to yr="1980 -Current"

Embase

1 iron/
2 iron intake/
3 iron deficiency anemia/
4 folic acid/ (32481)
5 diet supplementation/
6 trace element/
7 iron$.tw.
8 (folic$ or folate$ or folvite$ or folacin$ or pteroylglutamic$).tw.
9 (diet$ adj3 supplement$).tw.
10 (micro-nutrient$ or micronutrient$ or multi-nutrient$ or multinutrient$).tw.
11 ferric ion/
12 ferrous ion/
13 or/1-12
14 drug administration/

15 drug dose regimen/
16 (week$ or biweek$ or bi-week$ or intermittent$ or alternat$).tw.
17 or/14-16
18 13 and 17
19 (iron adj3 (dose$ or dosage or administer$ or administration or frequency)).tw.
20 18 or 19
21 adult/ or middle aged/ or adolescent/
22 (teen$ or adoles$ or pubert$ or pubescen$).tw.
23 21 or 22
24 female/
25 (girl$ or female$ or wom#n).tw.
26 24 or 25 (
27 23 and 26
28 20 and 27
29 Randomized controlled trial/
30 Randomization/
31 Single blind procedure/
32 Double blind procedure/
33 Crossover procedure/
34 Placebo/ (178428)
35 Randomi#ed.tw.
36 RCT.tw.
37 (random$ adj3 (allocat$ or assign$)).tw.
38 randomly.ab.
39 groups.ab.
40 trial.ab.
41 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
42 Placebo$.tw.
43 Prospective study/
44 (crossover or cross-over).tw.
45 prospective.tw.
46 or/29-45
47 28 and 46

CINAHL Plus

S42 S23 and S41
S41 S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40
S40 (MH "Evaluation Research") OR (MH "Summative Evaluation Research") OR (MH "Program Evaluation")
S39 (MH "Treatment Outcomes")
S38 (MH "Comparative Studies")
S37 TI (evaluat* study or evaluat* research) or AB (evaluate* study or evaluat* research) or TI (effectiv* study or effectiv* research) or AB (effectiv* study or effectiv* research) OR TI (prospectiv* study or prospectiv* research) or AB(prospectiv* study or prospectiv* research) or TI (follow-up study or follow-up research) or AB (prospectiv* study or prospectiv* research)
S36 "cross over*"
S35 crossover*
S34 (MH "Crossover Design")
S33 (tripl* N3 mask*) or (tripl* N3 blind*)
S32 (trebl* N3 mask*) or (trebl* N3 blind*)
S31 (doubl* N3 mask*) or (doubl* N3 blind*)
S30 (singl* N3 mask*) or (singl* N3 blind*)
S29 (clinic* N3 trial*) or (control* N3 trial*)
S28 (random* N3 allocat*) or (random* N3 assign*)

S27 randomis* or randomiz*
S26 (MH "Meta Analysis")
S25 (MH "Clinical Trials+")
S24 MH random assignment
S23 S17 and S22
S22 S20 or S21
S21 (MH "Women's Health")
S20 18 and 19
S19 CT female or (woman or women or female* or girl*)
S18 (AG adolescent or AG adult or AG middle aged) OR (adolescen* or pubert* or pubescen*)
S17 S15 or S16
S16 (iron N3 dose*) or (iron N3 dosage) or (iron N3 administer*) or (iron N3 administration) or (iron N3 frequency) or (iron N3 supplement*)
S15 S10 and S14
S14 S11 or S12 or S13
S13 (week* or biweek* or bi-week*or bi week* or intermittent* or alternat* or regimen*)
S12 (MH "Time Factors")
S11 (MH "Drug Administration Schedule")
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9 micro-nutrient* or micronutrient* or micro nutrient* multi-nutrient* or multinutrient* or multi nutrient*
S8 ferrous* or ferric* or "fe"
S7 diet* N3 supplement*
S6 folic* or folate* or folvite* or folacin* or pteroylglutamic*
S5 iron* 5
S4 (MH "Micronutrients")
S3 (MH "Dietary Supplements")
S2 (MH "Folic Acid")
S1 (MH "Iron") OR (MH "Anemia, Iron Deficiency") OR (MH "Iron Compounds") OR (MH "Ferric Compounds") OR (MH "Ferrous Compounds")

SCI

#7 #6 AND #5
#6 TS=(random* or RCT or trial* or allocat* or assign* or placebo* or cross-over or crossover or "cross over" or factorial* or "double blind*" or "single blind")
#5 #4 AND #3
#4 TS=(women or woman or female* or girl*)
#3 #1 same #2
#2 TS=(iron or "folic acid" or ferrous or ferric or micronutrient* or multiutrient* or micro-nutrient* or multi-nutrient*)
#1 TS= (alternate* or week* or intermittent or biweek* or bi-week* or "bi week*" or supplement*)

CPCI-S

#7 #6 AND #5
#6 TS=(random* or RCT or trial* or allocat* or assign* or placebo* or cross-over or crossover or "cross over" or factorial* or "double blind*" or "single blind")
#5 #4 AND #3
#4 TS=(women or woman or female* or girl*)
#3 #1 same #2
#2 TS=(iron or "folic acid" or ferrous or ferric or micronutrient* or multiutrient* or micro-nutrient* or multi-nutrient*)
#1 TS= (alternate* or week* or intermittent or biweek* or bi-week* or "bi week*" or supplement*)

BIOSIS

#7 #6 AND #5
#6 TS=(random* or RCT or trial* or allocat* or assign* or placebo* or cross-over or crossover or "cross over" or factorial* or "double blind*" or "single blind")
#5 #4 AND #3
#4 TS=(women or woman or female* or girl*)
#3 #1 same #2
#2 TS=(iron or "folic acid" or ferrous or ferric or micronutrient* or multiutrient* or micro-nutrient* or multi-nutrient*)
#1 TS= (alternate* or week* or intermittent or biweek* or bi-week* or "bi week*" or supplement*)

POPLINE

(iron* /folic* / folate* /supplement*/micronutrient*/micro-nutrient*) & (week* /bi-week* / bi week* / biweek* / intermittent / alternat*) & (women / woman /girl* / female*)

SciElo

iron AND supplementation AND women

LILACS

iron AND supplementation AND women

IBECS

iron AND supplementation AND women

IMBIOMED

iron AND supplementation AND women

WHO ICTRP

Iron supplementation AND women
Iron supplementation AND girls

metaRegister

Iron supplementation AND women
Iron supplementation AND girls

Appendix 3. Criteria for assessing risk of bias

Sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence. We assessed the method as follows.

1. Low risk of bias: any truly random process (for example, random number table; computer random number generator)
2. High risk of bias: any non-random process (for example, odd or even date of birth; hospital or clinic record number)
3. Unclear risk of bias: insufficient information to facilitate a judgement of low or high risk of bias

Allocation concealment (checking for possible selection bias)

For each included study we described the method used to conceal the allocation sequence (when applicable) and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the method as follows.

1. Low risk of bias: concealed allocation using, for example, telephone or central randomisation, consecutively numbered sealed opaque envelopes (or equivalent)
2. High risk of bias: allocation based on, for example, open random allocation, unsealed or non-opaque envelopes
3. Unclear risk of bias: insufficient information to facilitate a judgement of low or high risk of bias

Blinding (checking for possible performance and detection bias)

For each included study we described the methods used to blind performance and outcome assessment. For the first one, we described the methods used, if any, for blinding: 1. study participants and 2. personnel, from knowledge of the allocated intervention during the study. For the second one, we described the methods used, if any, for blinding: 3. outcome assessors, from knowledge of which intervention a participant reviewed. Whilst we reported these judgements separately, we combined the results into one judgement of overall risk of bias associated with blinding as follows (Higgins 2011a).

1. Low risk of bias: blinding of participants, key study personnel and outcome assessment ensured, and unlikely that blinding could have been broken; or none or incomplete blinding but the review authors judged that the outcome or outcome measurement was unlikely to be influenced by lack of blinding
2. High risk of bias: blinding of key study participants and personnel or outcome assessment attempted, but likely that blinding could have been broken and the outcome or outcome measurement influenced by the lack of blinding; or no blinding or incomplete blinding, and the outcome or outcome measurement was likely to be influenced by lack of blinding
3. Unclear risk of bias: insufficient information to facilitate a judgement of low or high risk of bias

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

For each included study we described the completeness of data, including attrition and exclusions from the analysis, and noted if attrition levels were higher for one prespecified outcome or group of outcomes. We also noted whether missing data were imbalanced across groups, the reasons for attrition or exclusions where reported, or whether data were imputed (and, if so, the methods used). We assessed the methods as follows.

1. Low risk of bias: fewer than 20% of cases lost to follow-up and balanced in numbers across intervention groups
2. High risk of bias: 20% or cases lost to follow-up or outcome data imbalanced in numbers across intervention groups
3. Unclear risk of bias: insufficient information to facilitate a judgement of low or high risk of bias

Selective reporting bias

For each included study we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as follows.

1. Low risk of bias: it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review were reported
2. High risk of bias: not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; the study failed to include the results of a key outcome that was expected to be reported

3. Unclear risk of bias: insufficient information to facilitate a judgement of low or high risk of bias

Other sources of bias

For each included study we described any important concerns we had about other possible sources of bias and assessed them as follows.

1. Low risk of bias: study appeared to be free of other sources of bias
2. High risk of bias: there was at least one important risk of bias; for example, the study had a potential source of bias related to the specific study design as not being blinded or selective outcome reporting
3. Unclear risk of bias: insufficient information to facilitate a judgement of low or high risk of bias

Appendix 4. Sensitivity analyses for clustering effect

We conducted sensitivity analyses by reanalysing the data for the primary outcomes with cluster-RCTs excluded. Below, we present the results.

Intermittent iron supplementation (alone or plus any other micronutrients) versus no supplementation or placebo

Anaemia

Anaemia with cluster-RCT: RR 0.65, 95% CI 0.49 to 0.87; 3135 participants; Analysis 1.1; T^2 = 0.16, z = 2.90; P < 0.001
Anaemia without cluster-RCT: RR 0.38, 95% CI 0.24 to 0.62; 765 participants; T^2= 0.16, z = 3.93; P = 0.02

Haemoglobin

Haemoglobin with cluster-RCT: MD 5.19 g/L, 95% CI 3.07 to 7.32; 2886 participants; Analysis 1.8; T^2 = 14.01, z = 5.42; P < 0.001
Haemoglobin without cluster-RCT: MD 6.58 g/L, 95% CI 4.20 to 8.96; 1603 participants; T^2 = 10.34, z = 5.42; P < 0.001

Iron deficiency

Iron deficiency with cluster-RCT: RR 0.50, 95% CI 0.24 to 1.04; 624 participants; Analysis 1.15; T^2 = 0.36, z = 1.86; P < 0.001
Iron deficiency without cluster-RCT: RR 0.37, 95% CI 0.07 to 1.91; 431 participants; T^2 = 1.32, z = 1.18; P = 0.24

Ferritin

Ferritin with cluster-RCT: MD 7.46 μg/L, 95% CI 5.02 to 9.90; 1067 participants, Analysis 1.16; T^2 = 4.10, z = 6.00; P < 0.001
Ferritin without cluster-RCT: MD 7.25 μg/L, 95% CI 4.72 to 9.79; 970 participants; T^2 = 4.32, z = 5.61; P < 0.001

Intermittent iron supplementation versus daily iron supplementation

Anaemia

Anaemia with cluster-RCT: RR 1.09, 95% CI 0.93 to 1.29; 1749 participants; Analysis 2.1; T^2 = 0.01, z = 1.04; P = 0.30
Anaemia without cluster-RCT: RR 1.04, 95% CI 0.82 to 1.32; 1145 participants; T^2 = 0.02, z = 0.30; P = 0.08

Haemoglobin

Haemoglobin with cluster-RCT: MD 0.43, 95% CI −1.44 to 2.31; 2127 participants; Analysis 2.8; T^2= 6.45, z = 0.45; P = 0.65
Haemoglobin without cluster-RCT: MD 01.38, 95% CI 0.06 to 2.71; 1523 participants; T^2= 1.38, z = 2.04; P = 0.10

Ferritin

Ferritin with cluster-RCT: MD −6.07 μg/L, 95% CI −10.66 to −1.48; 988 participants; Analysis 2.16; T^2= 15.55, z = 2.59; P = 0.10
Ferritin without cluster-RCT: MD −10.54 μg/L, 95% CI −24.00 to 2.92; 550 participants; T^2= 129.36, z = 1.53; P = 0.12

Footnotes
MD:meandifference

RCT: randomised controlled trial
RR: risk ratio

WHAT'S NEW

Date	Event	Description
3 October 2018	New search has been performed	Review updated. Four new studies included following searches in January 2017 and February 2018
3 October 2018	New citation required and conclusions have changed	Conclusions on the equivalence between daily and intermittent supplementation changed: both interventions produce a similar effect on anaemia and haemoglobin concentrations

HISTORY

Protocol first published: Issue 7, 2011

Review first published: Issue 12, 2011

Date	Event	Description
4 September 2018	New search has been performed	Reviewers comments and suggestions incorporated and updated with another included trial
20 April 2018	Feedback has been incorporated	Editorial suggestions have been incorporated and search has been updated as indicated

CONTRIBUTIONS OF AUTHORS

Both review authors contributed to drafting the text of the review and approved the final manuscript. AG is the main guarantor of the review.

DECLARATIONS OF INTEREST

Ana Cecilia Fernández-Gaxiola (AG) is a Consultant at the Instituto Nacional de Salud Pública, Mexico, and a Professor at the Universidad Iberoamericanca Ciudad de México. AG declares that she received partial payment from the Evidence and Programme Guidance, World Health Organization (WHO), to update the review.

Luz Maria De-Regil (LD-R) is a full-time staff member of Nutrition International (NI) (formerly the Micronutrient Initiative), an international non-for-profit organisation that delivers multiple micronutrient interventions to children, women of reproductive age and pregnant women; LD-R did not assess any study funded by NI that met the inclusion criteria of this review, nor did she extract data, assess risk of bias, or rate the quality of the evidence from those studies. The Canadian Department of Foreign Affairs, Trade and Development provides funds to NI to implement programmes with different micronutrient interventions in different populations.

Disclaimer: The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policies, or views of the WHO, NI, or the Canadian Department of Foreign Affairs, Trade and Development.

SOURCES OF SUPPORT

Internal sources

- Nutrition International, Ottawa, Canada.

Salary support for Luz Maria De-Regil.

External sources

- Evidence and Programme Unit, Department of Nutrition for Health and Development, World Health Organization, Switzerland.

Ana C Fernández-Gaxiola received partial financial support for updating this work.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are a number of differences between this review and our protocol (Fernández-Gaxiola 2011b).

1. General

i) We cited the relevant chapters of the *Cochrane Handbook of Systematic Reviews of Interventions*, instead of the book, when presenting the methods used in the review, in order to direct the reader to the most relevant sections.

2. Types of outcome measures.

i) Given that the population of menstruating women includes premenarcheal girls and adult women, and each group uses a different cutoff for anaemia, we changed our previous definition of anaemia from "'haemoglobin concentration < 120 g/L, adjusted by altitude where appropriate" to "haemoglobin concentration below a cut-off defined by trialists, adjusted by altitude where appropriate".

ii) We also changed the name of the outcome "any other side effects" to "any adverse side effects", to avoid mixing negative effects, such as nausea or vomiting, with positive effects such as improved awareness or activity.

3. Electronic searches

i) We revised the search strategy to improve its precision.

ii) We did not search the following three databases, which are listed in the protocol for this review (Fernández-Gaxiola 2011b):

a) BIOSIS, as it was no longer available to us;

b) *meta*Register of Controlled Trials, as it was under review at the time of this update; and

c) Networked Digital Library of Theses and Dissertations, as it was not available at the time of this update.

iii) We searched two additional Ovid MEDLINE segments, which are updated daily: MEDLINE In-Process & Other Non-Indexed Citations; and MEDLINE Epub Ahead of Print.

iv) We also searched CinicalTrials.gov and IMBIOMED to look for any relevant registered clinical trials.

4. Subgroup analysis and investigation of heterogeneity

i) As very few studies reported data for most of the outcomes, we limited the subgroup analyses to the following three primary outcomes: anaemia, haemoglobin, and ferritin concentrations.

ii) In addition to visually examining the forest plots, we also used the Borenstein 2008 approach, to formally investigate differences between two or more subgroups.

5. Sensitivity analysis

i) We conducted sensitivity analyses ad hoc to examine the potential effect of clustering on the CI of the summary estimates, by removing cluster-RCTs from the analyses and comparing the effects. We reported the results of this analysis in Appendix 4.

ii) We conducted an additional sensitivity analysis ad hoc with two studies (Hall 2002 (C); Roschnik 2003 (C)), in which approximately half of the participants were young females (< 12 years of age), to assess their effect on our analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; *Menstruation; Administration, Oral; Anemia, Iron-Deficiency [*prevention & control]; Drug Administration Schedule; Ferritins [adverse effects; blood]; Ferrous Compounds [administration & dosage]; Iron [deficiency]; Iron, Dietary [*administration & dosage]; Micronutrients [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Female; Humans; Young Adult