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Review Article

Systematic review and meta-analysis of the effect of iron-fortified flour on iron status of populations worldwide

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Abstract

Objective: Assess the effectiveness of iron-fortified flour on iron status.
Design: Systematic review and meta-analysis.
Setting: Argentina, Australia, Azerbaijan, Bangladesh, Brazil, Cameroon, Chile, China, Costa Rica, Côte d'Ivoire, Denmark, India, Iran, Jordan, Kazakhstan, Kenya, Kuwait, Mongolia, Morocco, Norway, South Africa, Sri Lanka, Tajikistan, Thailand, UK, USA, Uzbekistan, Venezuela, Vietnam, and Zambia.
Participants: Fifty-two articles (ninety-four trials) were examined. The main target groups were women, children, and infants/toddlers. The effects of different types of iron-fortified flour (wheat, maize, rice, soy, and beans) on iron status were examined.
Results: A random effects analysis of before–after studies showed that iron-fortified flour led to significant increases of mean haemoglobin level (3·360 g/l; 95 % CI: 0·980, 5·730) and mean serum ferritin level (4·518 μg/l; 95 % CI: 2·367, 6·669); significant decreases of anaemia (−6·7 %; 95 % CI: −9·8 %, −3·6 %) and iron deficiency (ID) (−10·4 %; 95 % CI: −14·3 %, −6·5 %); but had no significant effect on iron deficiency anaemia (IDA). A random effects analysis of controlled trials indicated that iron-fortified flour led to significant increases of mean haemoglobin level (2·630 g/l; 95 % CI: 1·310, 3·950) and mean ferritin level (8·544 μg/l; 95 % CI: 6·767, 10·320); and significant decreases of anaemia (−8·1 %; 95 % CI: −11·7 %, −4·4 %), ID (−12·0 %; 95 % CI: −18·9 %, −5·1 %), and IDA (−20·9 %; 95 % CI: −38·4 %, −3·4 %).
Conclusions: Flour fortification with iron is an effective public health strategy that improves iron status of populations worldwide.

Keywords
Meta-analysis
Systematic review
Iron status
Fortified flour

Anaemia is one of the most common conditions globally, and the highest prevalences are in South-East Asia, the Eastern Mediterranean, and Africa. In 2011, the worldwide prevalence of anaemia was 43 % (273 million) in children, 29 % (496 million) in non-pregnant women, 38 % (32 million) in pregnant women, and 29 % (529 million) in reproductive-age women. The most clinically significant effects of anaemia are adverse outcomes of pregnancy, physical and cognitive impairment, increased risk of disease in children, and reduced productivity in adults. Anaemia is responsible for about 20 % of all deaths in pregnant women[1].

About 42 % of anaemia in children and 50 % of anaemia in women are due to iron deficiency (ID)[1], and ID is the most common cause of anaemia worldwide[2]. In 2015, anaemia was an important condition affecting people worldwide[3]. The Global Burden of Diseases, Injuries, and Risk Factors Study 2016 (GBD 2016) showed that iron deficiency anaemia (IDA) was a major cause of years lived with disabilities (YLDs), contributing 34·7 million cases (95 % uncertainty interval (UI) 23·0 – 49·6 million) of total YLDs[4].

In 2012, the WHO identified six global nutrition targets to be achieved by 2025, one of which is a 50 % reduction in the prevalence of anaemia for women of reproductive age[5]. This corresponds to a reduction of about 6 % per year for this population. The strategies proposed to achieve this goal include increasing dietary diversity, distributing

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iron supplements, controlling infectious diseases and malaria, and fortifying foods with iron, folic acid, and other micronutrients. Food fortification can be implemented on a large-scale (mass fortification). For example, iron can be added to staple foods consumed by the general population (e.g. wheat flour, maize flour, corn meals, rice, and condiments) or to foods consumed by people with the greatest risk of anaemia, such as biscuits for students and women[6]. Bread consumption is high in Eastern Mediterranean countries; therefore, iron-fortified flour may effectively reduce the prevalence of iron deficiency anaemia in this region[7].

Researchers must evaluate programmes that provide iron fortification of staple foods, such as flour, to confirm the effect of these interventions[8]. The results of recent systematic reviews were equivocal regarding the effect of iron-fortified flour on iron status, especially in regard to the prevalence of IDA. Therefore, policymakers need more definitive evaluations of the effectiveness of iron-fortified flour.

The present meta-analysis evaluated the effectiveness of iron-fortified flour on the levels of haemoglobin and ferritin, and on the risks of anaemia, ID, and IDA with stratification by study design. All types of flour and all ages and gender groups were included in the analysis.

Methods

Search strategy

Database searches were performed during February and March of 2019 for literature published up to December 2018 in the English and Persian languages. Some authors were also contacted to identify additional studies. The reference lists of all identified articles were also screened. Electronic databases, including Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), International Clinical Trials Registry Platform (ICTRP), PubMed, Clinicaltrials.gov, World Health Organization Library Information System (WHOLIS), and Scientific Information Database (SID) were searched using the following keywords and queries: (fortif*[Title]) AND iron [Title], (fortif*[Title]) AND hemoglobin/haemoglobin [Title], (fortif*[Title]) AND ferritin [Title], (fortif*[Title]) AND anemia/anaemia [Title], (fortif*[Title]) AND iron deficiency [Title], (fortif*[Title]) AND iron deficiency anemia/anaemia [Title], (iron [Title]) AND flour [Title], (fortif*[Title]) AND flour [Title], and (enrich*[Title]) AND flour [Title]. No review protocol was registered.

Inclusion criteria

Published controlled trials and before–after studies of males or females of all ages were eligible. Controlled trials with the following designs were eligible: clinical trials, double-blind randomized trials, double-blind controlled trials, double-blind randomized placebo-controlled trials, double-blind cluster randomized controlled trials, randomized controlled trials, randomized double-blind trials, randomized double-blind controlled trials, randomized placebo-controlled studies, and randomized double-blind placebo-controlled trials. Before–after studies with the following designs were eligible: comparisons of two surveys, longitudinal studies, pre-and-post intervention studies, prospective non-experimental studies, and prospective non-experimental cross-sectional studies. The intervention of each included study was dietary fortification of flour (e.g. wheat, maize, or rice), either in a raw form or in a cooking process, with iron or with iron and other micronutrients. Studies that used iron as a separate additive (e.g. micronutrient powders) were excluded. The outcome measures were haemoglobin level (g/l), serum ferritin level (μg/l), anaemia, iron deficiency (ID), and iron deficiency anaemia (IDA). These outcomes were adjusted for confounding variables in some of the publications (such as serum ferritin level for inflammation).

Data extraction and data collection

Data were extracted from the different studies and entered into a data worksheet. The data included: first author, year of publication, country, target group (children, infants/toddlers, women, all groups), study design (controlled trials, before-after studies), duration of intervention, fortification vehicle (type of flour used for fortification), intervention type (use of iron alone or iron with other micronutrients), type of iron compound(s), and outcomes.

Publications with multiple intervention arms (e.g. use of different iron compounds, enrolment of individuals from different geographic or demographic groups) were converted to multiple trials, so that each intervention arm was considered a trial. Only the relevant intervention arms (those using iron-fortified flour) were eligible for inclusion. If a publication had multiple intervention arms and a single control group, each intervention arm with that control group was considered to be a trail with a controlled trial design; if a publication did not have a control group, each intervention arm was considered to be a study with a before–after design. In addition, each intervention arm in all controlled trials was also included in the meta-analysis of other studies that had before–after designs. Thus, the meta-analysis of before–after studies also included all intervention arms of the controlled trials.

For trials with before–after design, the change of each outcome variable from before to after the intervention (mean difference and risk difference) was recorded. For controlled trials, the differences between the intervention and control groups in 'change of each outcome variable from before to after the intervention' were recorded. The standard error of each cluster trial was adjusted for cluster assignment. For publications that reported median haemoglobin and ferritin levels, these values were converted to means before analysis. Publications that reported the geometric mean haemoglobin and ferritin levels were analysed separately because these values could not be converted into arithmetic means[9].

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Assessment of quality and risk of bias

The criteria for evaluating the quality of publications were from the Cochrane Effective Practice and Organization of Care (EPOC) statement[10]. In particular, the quality of each publication was classified as having low risk (LR) of bias, high risk (HR) of bias, or unclear risk (?) of bias[11]. The risk of bias in each study was determined by its use of the following procedures: random sequence generation, allocation concealment, blinding, similar baseline outcome measurements, similar baseline characteristics, incomplete outcome reported, study protected against contamination, selective reporting, and other risks of bias. To determine the overall quality of each article, we examined the degrees of bias for the various sources of bias listed above and estimated their impact on the accuracy of the results of the study[12].

Statistical analysis

Meta-analysis was performed using Comprehensive Meta-Analysis (CMA) version-2 software. The results are presented as forest plots and effect sizes. Effect size, due to the high heterogeneity among trials, was determined using random effects models[13] and a *P*-value less than 0·05 was considered statistically significant. The heterogeneity of trials was assessed using the *Q*-value and I^2 value. I^2 indicates the amount of variation (0 to 100 %) among trials that is attributable to study heterogeneity rather than chance. Analysis was also performed for the following subgroups: quality of trial (high risk or low risk of bias); target group (children, infants/toddlers, women, or all groups); intervention type (fortified with iron alone or iron with other micronutrients); and type of iron compound(s). Begg and Mazumdar's rank correlation test and Egger's linear regression were used to determine publication bias, and a P-value below 0·05 was considered significant evidence of the presence of publication bias.

Results

Study selection and study characteristics

We selected articles based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1). We initially identified 2641 articles, and identified 1235 after removal of duplicates. An additional 929 articles were deemed irrelevant after screening of the titles. We then screened 306 abstracts, and excluded an additional 219 articles. The remaining eighty-seven articles were eligible for full-text screening, thirty-one of which were excluded for various reasons (e.g. iron was not added to flour, study method was not relevant, complete data were not present). A total of fifty-six articles were included in the systematic review, and these were converted to 101 trials or intervention arms. The characteristics of the included trials in the systematic review are presented in Table 1. Seven trials were excluded either because it was

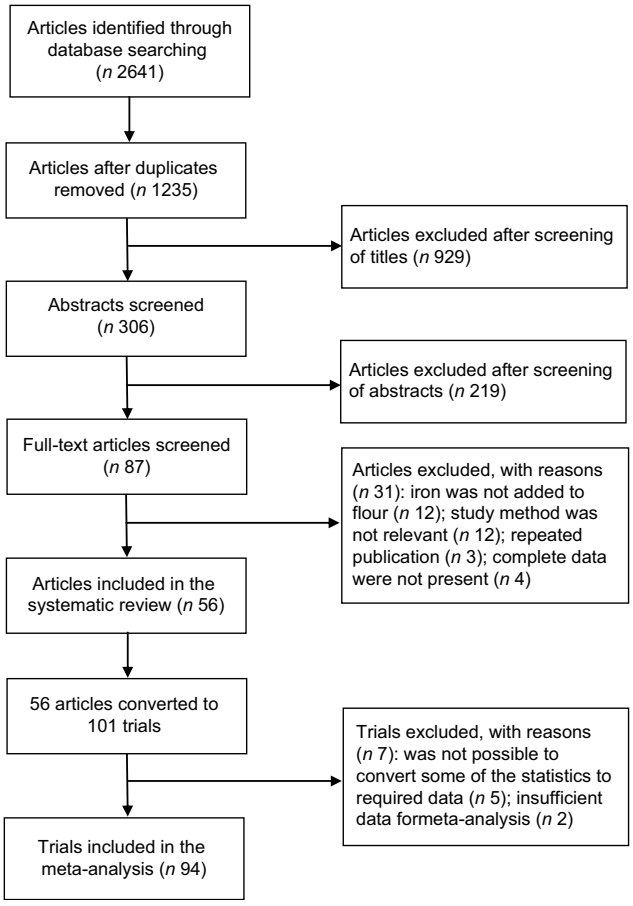

Fig. 1 Flow diagram of article selection process

impossible to convert some of the statistics to the required form or because they contained insufficient data for the meta-analysis. We ultimately included ninety-four trials (fifty-two articles) in the meta-analysis.

The included studies were conducted in Argentina, Australia, Azerbaijan, Bangladesh, Brazil, Cameroon, Chile, China, Costa Rica, Côte d'Ivoire, Denmark, India, Iran, Jordan, Kazakhstan, Kenya, Kuwait, Mongolia, Morocco, Norway, South Africa, Sri Lanka, Tajikistan, Thailand, UK, USA, Uzbekistan, Venezuela, Vietnam, and Zambia. The study design was a controlled trial in forty-nine trials (52·1 %) and a before–after design in forty-five trials (47·9 %). There were nineteen trials (20·2 %) of infants/toddlers, forty-two (44·7 %) of children, thirty-one (33 %) of women, and two (2·1 %) of people of all ages. The mean duration of intervention was 20·6 months (SD: 25·5, range: 2–144). Fortification vehicles were wheat flour in sixty-one trials (64·8 %), maize flour in seven trials (7·4 %), wheat and maize flours in seven trials (7·4 %), rice flour in four trials (4·3 %), wheat and corn flours in four trials (4·3 %), maize and soy flours in two trials (2·1 %), corn flour in one trial (1·.1 %), maize, beans, bambara nuts, and groundnuts flours in one trial (1·1 %), rice and soybeans flours in one trial (1·1 %), rye flour in one trial (1·1 %), wheat and

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Table 1 Characteristics of the trials included in the systematic review and meta-analysis

n.	First Author, Year (Ref.)	Country	Target group	Study design	Duration	Fortification vehicle	Intervention type	Iron compounds
1	Andang'o, 2007[14] 1	Kenya	Children (3–8 years)	Randomized controlled trial	5 months	Maize flour (porridge)	Iron+vitamins/minerals	high-dose NaFeEDTA
2	Andang'o, 2007[14] 2	Kenya	Children (3–8 years)	Randomized controlled trial	5 months	Maize flour (porridge)	Iron+vitamins/minerals	low-dose NaFeEDTA
3	Andang'o, 2007[14] 3	Kenya	Children (3–8 years)	Randomized controlled trial	5 months	Maize flour (porridge)	Iron+vitamins/minerals	Electrolytic iron
4	Araújo, 2013[15]	Brazil	Pregnant women	Before-after study	2 years	Wheat and corn flours	Iron+vitamins/minerals	Unknown
5	Assunção, 2012[16]	Brazil	Children (under 6 years)	Before-after study	4 years	Wheat flour	Iron	Ferrousfumarate and ferrous sulphate
6	Barbosa, 2012[17]	Brazil	Children (2–6 years)	Randomized, double-blind controlled trial	24 weeks	Wheat flour (rolls)	Iron	Ferrous sulphate
7	Biebinger, 2009[18] 1	Kuwait	Women (18–35 years)	Randomized, double-blind controlled trial	22 weeks	Wheat flour (biscuits)	Iron	H-reduced Fe (Nutra-Fine®RS)
8	Biebinger, 2009[18] 2	Kuwait	Women (18–35 years)	Randomized, double-blind controlled trial	22 weeks	Wheat flour (biscuits)	Iron+vitamins/minerals	Ferrous sulphate
9	Bouhouch, 2016[19] 1	Morocco	Preschool Children	Double-blind placebo-controlled trial	28 weeks	Wheat flour (biscuits)	Iron	Ferrous sulphate
10	Bouhouch, 2016[19] 2	Morocco	Preschool Children	Double-blind placebo-controlled trial	28 weeks	Wheat flour (biscuits)	Iron	NaFeEDTA
11	Cabalda, 2009[20] 1*	Philippines	Children (6–12 years)	Randomized, double-blind, placebo-controlled trial	8 months	Wheat flour	Iron	H-reduced iron, electrolytic iron, and ferrous fumarate
12	Cabalda, 2009[20] 2*	Philippines	Children (6–12 years)	Randomized, double-blind, placebo-controlled trial	8 months	Wheat flour	Iron+vitamins/minerals	H-reduced iron, electrolytic iron, and ferrous fumarate
13	da Silva, 2012[21]	Brazil	Pregnant women	Before-after study	3 years	Wheat and corn flours	Iron	Ferrous sulphate, ferrous fumarate, H-reduced Fe, ...
14	Davidsson, 2009[22] 1	Bangladesh	Children (7–24 months)	Double-blind study	9 months	Wheat flour (cereal)	Iron+vitamins/minerals	Ferrous fumarate
15	Davidsson, 2009[22] 2	Bangladesh	Children (7–24 months)	Double-blind study	9 months	Wheat flour (cereal)	Iron+vitamins/minerals	Ferric pyrophosphate
16	Davidsson, 2009[22] 3	Bangladesh	Children (7–24 months)	Double-blind study	9 months	Wheat flour (cereal)	Iron+vitamins/minerals	Ferrous sulphate
17	Elwood,1963[23] 1	United Kingdom	Women	Clinical trial	6 months	Unknown flour (bread)	Iron+vitamins/minerals	Ferrous gluconate (Ferrum redactum)
18	Elwood,1963[23] 2	United Kingdom	Women	Clinical trial	6 months	Unknown flour (bread)	Iron+vitamins/minerals (different type of vitamins)	Ferrous gluconate (Ferrum redactum)
19	Engle-Stone, 2017[24] 1	Cameroon	Woman of reproductive age (15–49 years)	Comparison of two cross-sectional surveys	1 year	Wheat flour	Iron+vitamin/minerals	Ferrous fumarate
20	Engle-Stone, 2017[24] 2	Cameroon	Children (12–59 months)	Comparison of two cross-sectional surveys	1 year	Wheat flour	Iron+vitamin/minerals	Ferrous fumarate
21	Faber, 2005[25]	South Africa	Infants (6–12 months)	Randomized controlled trial	6 months	Milled maize (porridge)	Iron+vitamins/minerals	Ferrous fumarate
22	Fujimori, 2011[26]	Brazil	Pregnant women	Before-after study	1 year	Wheat and corn flour	Iron+vitamins/minerals	Unknown

Table 1 *Continued*

n.	First Author, Year (Ref.)	Country	Target group	Study design	Duration	Fortification vehicle	Intervention type	Iron compounds
23	Gibson, 2011[27]	Zambia	Infants (6 months)	Double-blind randomized trial	12 months	Maize, beans, and bambara groundnut flours	Iron+vitamins/minerals	Ferrous fumarate
24	Giorgini, 2001[28]	Brazil	Preschool children (12–72 months)	Before-after study	6 months	Wheat flour (sweet roll)	Iron	Iron bisglycinate chelate
25	Glinz, 2017[29] 1	Côte d'Ivoire	Children (12–36 months)	Cluster-randomized controlled trial	9 months	Maize and soy flours (porridge)	Iron+vitamins/minerals	NaFeEDTA and ferrous fumarate
26	Glinz, 2017[29] 2	Côte d'Ivoire	Children (12–36 months)	Cluster-randomized controlled trial	9 months	Maize and soy flours (porridge)	Iron+vitamins/minerals	NaFeEDTA and ferric pyrophosphate
27	Hamdouchi, 2013[30] 1	Morocco	Women (15–49 years)	Comparison of two surveys	20 months	Wheat flour	Iron+vitamins/minerals	Electrolytic elemental iron
28	Hamdouchi, 2013[30] 2	Morocco	Preschool children (2–5 years)	Comparison of two surveys	20 months	Wheat flour	Iron+vitamins/minerals	Electrolytic elemental iron
29	Hansen, 2005[31]	Denmark	Women (20–38 years)	Single-blind intervention	5 months	Rye flour (bread)	Iron	Ferrous fumarate
30	Hieu, 2012[32]	Vietnam	Children (6–9 years)	Randomized placebo-controlled study	6 months	Wheat flour (biscuits)	Iron+vitamins/minerals	Ferrous fumarate
31	Huang, 2009[33] 1	China	Students (11–18 years)	Controlled trial	6 months	Wheat flour	Iron	Electrolytic iron
32	Huang, 2009[33] 2	China	Students (11–18 years)	Controlled trial	6 months	Wheat flour	Iron	Ferrous sulphate
33	Huang, 2009[33] 3	China	Students (11–18 years)	Controlled trial	6 months	Wheat flour	Iron	NaFeEDTA
34	Hund, 2013[34]**	Uzbekistan	Women (reproductive age)	Before-after study	3 years	Wheat flour	Iron+vitamins/minerals	Ferrous sulphate
35	Huo, 2012[35]	China	Non-pregnant women (20- 60 years)	Controlled Trial	3 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
36	Huo, 2011[36]	China	Women (20–60 years)	Controlled trial	3 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
37	Kamien, 1975[37]	Australia	Australian aborigines (all age groups)	Before-after study	6·5 months	Wheat flour (bread)	Iron+vitamins/minerals	Ferrous sulphate
38	Landim, 2016[38] 1	Brazil	Preschool children (2–5 years)	Before-after study (one arm of a controlled trial)	2 months	Wheat flour (cookies)	Iron+vitamins/minerals	Unknown
39	Landim, 2016[38] 2	Brazil	Preschool children (2–5 years)	Before-after study (one arm of a controlled trial)	2 months	Wheat and cowpea flours (cookies)	Iron+vitamin/minerals	Unknown
40	Layrisse, 2002[39]	Venezuela	Children (7, 11, 15 years)	Comparison of two surveys	7 years	Corn and wheat flours	Iron+vitamins/minerals	Ferrous fumarate and electrolytic iron
41	Layrisse, 1996[40]	Venezuela	Children (7, 11, 15 years)	Comparison of two surveys	1 year	Wheat and maize flours	Iron+vitamins/minerals	Ferrous fumarate
42	Ma, 2016[41]**	China	Infants and young children (6–18 months)	Cluster-randomized, non-masked, controlled trial	1 year	Rice flour (cereal)	Iron+vitamins/minerals	Ferrous fumarate
43	Malpeli, 2013[42]	Argentina	Pregnant women	Cross-sectional study (before-after study)	1 year	Wheat and maize flours (food aid)	Iron+vitamins/minerals	Unknown
44	Martorell, 2015[43] 1	Costa Rica	Children (1–7 years)	Pretest-posttest design	12 years	Wheat and maize flours	Iron+vitamins/minerals	Ferrous fumarate and ferrous bisglycinate
45	Martorell, 2015[43] 2	Costa Rica	Women (15–45 years)	Pretest-posttest design	12 years	Wheat and maize flours	Iron+vitamins/minerals	Ferrous fumarate and ferrous bisglycinate

Table 1 *Continued*

n.	First Author, Year (Ref.)	Country	Target group	Study design	Duration	Fortification vehicle	Intervention type	Iron compounds
46	Miglioranza, 2009[44]	Brazil	Children and adolescents (7–14 years)	Before-after study	6 months	Corn flour	Iron+vitamins/minerals	Elemental Fe (H2-reduced Fe)
47	Muthayya, 2012[45]	India	School-aged children (6- 15 years)	Randomized, double-blind, controlled trial	7 months	Wheat flour (lunch meal)	Iron	NaFeEDTA
48	Natvig,1973[46]	Norway	Women (25–40 years)	Community-based experiment (Before-after study)	20 months	Wheat flour (bread)	Iron	Ferrous sulphate
49	Nestel, 2004[47] 1	Sri Lanka	Children (9–71 months)	Double-blind controlled trial	2 years	Wheat flour	Iron	Electrolytic iron
50	Nestel, 2004[47] 2	Sri Lanka	Children (6–11 years)	Double-blind controlled trial	2 years	Wheat flour	Iron	Electrolytic iron
51	Nestel, 2004[47] 3	Sri Lanka	Non-pregnant women	Double-blind controlled trial	2 years	Wheat flour	Iron	Electrolytic iron
52	Nestel, 2004[47] 4	Sri Lanka	Children (9–71 months)	Double-blind controlled trial	2 years	Wheat flour	Iron	Reduced iron
53	Nestel, 2004[47] 5	Sri Lanka	Children (6–11 years)	Double-blind controlled trial	2 years	Wheat flour	Iron	Reduced iron
54	Nestel, 2004[47] 6	Sri Lanka	Non-pregnant women	Double-blind controlled trial	2 years	Wheat flour	Iron	Reduced iron
55	Nga, 2009[48]	Vietnam	School children (6–8 years)	Randomized, double-blind, placebo-controlled trial	4 months	Wheat flour (biscuits)	Iron+vitamins/minerals	Ferrous fumarate
56	Olivares, 1990[49]	Chile	School children	Controlled trial	15 months	Wheat flour (biscuits)	Iron	Bovine haem iron concentrate
57	Phu, 2010[50]	Vietnam	Infants (5 months)	Controlled Trial	23 months	Rice and soybeans flours	Iron+vitamins/minerals	Iron fumarate
58	Rahman, 2015[51]	Bangladesh	School children (6–15 years)	Double-blind cluster randomized controlled trial	6 months	Wheat flour (Chapatti)	Iron+vitamins/minerals	H-reduced elementaliron
59	Rifai, 2016[52]	Jordan	Children (6–59 months)	Two repeated cross-sectional study	25 months	Wheat flour	Iron+vitamins/minerals	Ferrous sulphate
60	Rohner, 2010[53] 1	Côte d'Ivoire	School children (6–14 years)	Double-blind randomized, placebo-controlled trial	6 months	Wheat flour (biscuits)	Iron	Electrolytic iron
61	Rohner, 2010[53] 2	Côte d'Ivoire	School children (6–14 years)	Double-blind, randomized, placebo-controlled trial	6 months	Wheat flour (biscuits)	Iron with anthelmintic treatment	Electrolytic iron
62	Rohner, 2010[53] 3	Côte d'Ivoire	School children (6–14 years)	Double-blind, randomized, placebo-controlled trial	6 months	Wheat flour (biscuits)	Iron with malaria preventive treatment	Electrolytic iron
63	Rohner, 2010[53] 4	Côte d'Ivoire	School children (6–14 years)	Double-blind, randomized, placebo-controlled trial	6 months	Wheat flour (biscuits)	Iron with malaria preventive treatment and anthelmintic treatment	Electrolytic iron
64	Sadighi, 2009[54] 1	Iran	Women (15–49 years), Bushehr province	Before-after study	8 years	Wheat flour (bread)	Iron+vitamins/minerals	Ferrous sulphate

Table 1 *Continued*

n.	First Author, Year (Ref.)	Country	Target group	Study design	Duration	Fortification vehicle	Intervention type	Iron compounds
65	Sadighi, 2009[54] 2	Iran	Women (15–49 years), Golestan province	Before-after study	2 years	Wheat flour (bread)	Iron+vitamins/minerals	Ferrous sulphate
66	Sadighi, 2008[55]	Iran	Women (15–49 years)	Controlled trial	3 years	Wheat flour (bread)	Iron+vitamins/minerals	Ferrous sulphate
67	Safavi, 2001[56]	Iran	Households	Before-after study	6 months	Wheat flour (bread)	Iron	Ferrous sulphate
68	Seal, 2008[57] 1	Zambia	Adolescents (10–19 years)	Pre-post-intervention study	7 months	Maize meal (coarse flour)	Iron+vitamins/minerals	Elemental iron
69	Seal, 2008[57] 2	Zambia	Children (6–59 months)	Pre-post-intervention study	7 months	Maize meal (coarse flour)	Iron+vitamins/minerals	Elemental iron
70	Seal, 2008[57] 3	Zambia	Women (20–49 years)	Pre-post-intervention study	7 months	Maize meal (coarse flour)	Iron+vitamins/minerals	Elemental iron
71	Stuetz, 2012[58]	Thailand	Women (16–46 years)	Before-after study	4–5 months	Wheat and soybean flours	Iron+vitamins/minerals	Unknown
72	Sun, 2007[59] 1	China	Students (11–8 years)	Controlled trial	6 months	Wheat flour	Iron	NaFeEDTA
73	Sun, 2007[59] 2	China	Students (11–18 years)	Controlled trial	6 months	Wheat flour	Iron	Ferrous sulphate
74	Sun, 2007[59] 3	China	Students (11–18 years)	Controlled trial	6 months	Wheat flour	Iron	Electrolytic iron
75	Tazhibayev, 2008[60] 1	Azerbaijan	Woman (reproductive age)	Before-after study	4 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
76	Tazhibayev, 2008[60] 2	Azerbaijan	Children (2–15 years)	Before-after study	4 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
77	Tazhibayev, 2008[60] 3	Kazakhstan	Woman (reproductive age)	Before-after study	4 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
78	Tazhibayev, 2008[60] 4	Kazakhstan	Children (2–15 years)	Before-after study	4 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
79	Tazhibayev, 2008[60] 5	Mongolia	Woman (reproductive age)	Before-after study	4 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
80	Tazhibayev, 2008[60] 6	Mongolia	Children (2–15 years)	Before-after study	4 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
81	Tazhibayev, 2008[60] 7	Tajikistan	Woman (reproductive age)	Before-after study	4 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
82	Tazhibayev, 2008[60] 8	Tajikistan	Children (2–15 years)	Before-after study	4 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
83	Tazhibayev, 2008[60] 9	Uzbekistan	Woman (reproductive age)	Before-after study	4 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
84	Tazhibayev, 2008[60] 10	Uzbekistan	Children (2–15 years)	Before-after study	4 years	Wheat flour	Iron+vitamins/minerals	Electrolytic iron
85	van Stuijvenberg, 1999[61]	South Africa	Children (6–11 years)	Randomized controlled trial	12 months	Unknown flour (biscuits)	Iron+vitamins/minerals	Ferrous fumarate
86	van Stuijvenberg, 2001[62]	South Africa	Children (6–11 years)	Longitudinal study (before-after study)	2·5 years	Unknown flour (biscuits)	Iron+vitamins/minerals	Ferrous fumarate
87	van Stuijvenberg, 2006[63] 1	South Africa	Children (6–11 years)	Randomized controlled trial	7·5 months	Wheat flour (brown bread)	Iron+vitamins/minerals	Ferrousbisglycinate
88	van Stuijvenberg, 2006[63] 2	South Africa	Children (6–11 years)	Randomized controlled trial	7·5 months	Wheat flour (brown bread)	Iron+vitamins/minerals	ElectrolyticFe
89	van Stuijvenberg, 2008[64] 1*	South Africa	Children (6–11 years)	Randomized controlled trial	34 weeks	Wheat flour (brown bread)	Iron+vitamins/minerals	NaFeEDTA
90	van Stuijvenberg, 2008[64] 2*	South Africa	Children (6–11 years)	Randomized controlled trial	34 weeks	Wheat flour (brown bread)	Iron+vitamins/minerals	Ferrous fumarate
91	van Stuijvenberg, 2008[64] 3*	South Africa	Children (6–11 years)	Randomized controlled trial	34 weeks	Wheat flour (brown bread)	Iron+vitamins/minerals	Electrolytic Fe
92	Varea, 2012[65]	Argentina	Lactating mothers (15–47 years)	Prospective, non-experimental study	1 year	Wheat and maize flour	Iron+vitamins/minerals	Ferrous sulphate

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Table 1 *Continued*

n.	First Author, Year (Ref.)	Country	Target group	Study design	Duration	Fortification vehicle	Intervention type	Iron compounds
93	Varea, 2011[66] 1	Argentina	Children (1–2 years)	Prospective, non-experimental study	1 year	Wheat and maize flours (cereals and pudding)	Iron+vitamins/minerals	Unknown
94	Varea, 2011[66] 2	Argentina	Children (2–6 years)	Prospective, non-experimental study	1 year	Wheat and maize flours	Iron+vitamins/minerals	Unknown
95	Walter,1993[67] 1	Chile	Formula-fed infants (4 months)	Double–blind trial	11 months	Rice flour (cereal)	Iron	Electrolytic iron
96	Walter,1993[67] 2	Chile	Breastfed infants (4 months)	Double-blind trial	11 months	Rice flour (cereal)	Iron	Electrolytic iron
97	Ziegler, 2011[68] 1	USA	Breastfed infants (4 months)	Randomized double-blind trial	8 months	Rice flour (cereal)	Iron+vitamins/minerals	Electrolytic iron
98	Ziegler, 2011[68] 2	USA	Breastfed infants (4 months)	Randomized double-blind	8 months	Rice flour (cereal)	Iron+vitamins/minerals	Ferrous fumarate
99	Zimmermann, 2005[69] 1	Thailand	Women (18–50 years)	Controlled Trial	35 weeks	Wheat flour (snack)	Iron	Ferrous sulphate
100	Zimmermann, 2005[69] 2	Thailand	Women (18–50 years)	Controlled Trial	35 weeks	Wheat flour (snack)	Iron	Electrolytic iron
101	Zimmermann, 2005[69] 3	Thailand	Women (18–50 years)	Controlled Trial	35 weeks	Wheat flour (snack)	Iron	H-reduced iron

*This trial was excluded because some of the statistics could not be converted to appropriate values.
**This trial was excluded due to a lack of pre-intervention data.

soybean flours in one trial (1·1 %), and unknown flour in four trials (4·3 %). Iron alone was added to flour in thirty-one trials (33 %) and iron with other micronutrients was added in sixty-three trials (67 %). In regard to the quality criteria, sixty-four trials (68 %) had an overall low risk of bias, and thirty trials (32 %) had an overall high risk of bias.

Assessment of quality and risk of bias

Table 2 shows the different possible sources of bias in which each criterion is rated as LR, HR, or unclear risk (?).

Meta-analysis

1. Effect of iron-fortified flour on mean haemoglobin level: before–after studies

Seventy-seven trials with before–after design reported mean haemoglobin levels. These trials had 19 083 subjects after the interventions (although sample size was not reported in two trials). Begg's funnel plot was asymmetrical, suggesting publication bias ($P < 0·001$), consistent with the results of Egger's linear regression test ($P = 0·001$). There was also significant heterogeneity among these trials ($I^2 = 99·9$ %, $P < 0·001$). The results of the random-effects model show that flour fortification significantly increased mean haemoglobin level. The overall effect size was 3·360 g/l (95 % CI: 0·980, 5·730; $P = 0·006$) (Table 3, Figure S1). Subgroup analysis indicated there was a significant difference in the results of trials with high and low risk of bias ($P = 0·025$), in that fortification significantly increased the mean haemoglobin in high-risk trials. The target group ($P = 0·347$), intervention type ($P = 0·697$), and type of iron compounds ($P = 0·931$) had no effects on the results (Table 3).

2. Effect of iron-fortified flour on geometric mean haemoglobin level: before–after studies (data not shown)

Seven trials with before–after design reported geometric mean haemoglobin levels and there were 1840 subjects after the interventions. Begg's funnel plot was symmetrical, suggesting no evidence of publication bias ($P = 0·293$), consistent with the results of Egger's linear regression test ($P = 0·140$). The results of the random effects model showed that flour fortification significantly increased the geometric mean haemoglobin level. The overall effect size was 3·700 g/l (95 % CI: 1·430, 5·890; $P = 0·001$). There was significant heterogeneity among the trials ($I^2 = 89·1$ %, $P < 0·001$). Subgroup analysis showed that trial quality ($P = 1·0$), target group ($P = 0·122$), intervention type ($P = 0·708$), and type of iron compounds ($P = 0·794$) had no effects on the results.

3. Effect of iron-fortified flour on mean ferritin level: before-after studies

Forty-four trials with before–after design reported mean serum ferritin level and there were 6790 subjects after interventions. Begg's funnel plot was symmetrical, suggesting no publication bias ($P = 0·124$), consistent with the results of

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Table 2 Risk of bias and quality assessment for articles included in the meta-analysis

n.	First Author,Year (Ref.)	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding (performance bias and detection bias)	Similar baseline outcome measurements	Similar baseline characteristics	Incomplete outcome Reported (attrition bias)	Study protected against contamination	Selective reporting (reporting bias)	Other risks of bias	Quality*
1	Andang'o, 2007[14]	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
2	Araújo 2013[15]	HR	HR	LR	LR	LR	LR	LR	LR	LR	LR
3	Assunc¸a˜o, 2012[16]	HR	HR	LR	LR	LR	HR	LR	LR	LR	LR
4	Barbosa, 2012[17]	LR	LR	LR	HR	LR	LR	LR	LR	HR	LR
5	Biebinger, 2009[18]	?	LR	LR	LR	LR	HR	LR	LR	LR	LR
6	Bouhouch, 2016[19]	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
7	da Silva, 2012[21]	HR	HR	LR	LR	LR	LR	LR	LR	LR	LR
8	Davidsson, 2009[22]	LR	LR	LR	LR	HR	HR	LR	HR	LR	LR
9	Elwood, 1963[23]	?	?	?	LR	LR	LR	LR	LR	LR	LR
10	Engle-Stone, 2017[24]	HR	HR	HR	LR	LR	LR	LR	LR	LR	LR
11	Faber, 2005[25]	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
12	Fujimori, 2011[26]	HR	HR	LR	LR	HR	LR	LR	HR	LR	HR
13	Gibson, 2011[27]	?	LR	LR	LR	LR	HR	LR	LR	LR	LR
14	Giorgini, 2001[28]	HR	HR	LR	LR	HR	HR	LR	LR	HR	HR
15	Glinz, 2017[29]	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
16	Hamdouchi, 2013[30]	HR	HR	LR	LR	HR	LR	LR	LR	LR	LR
17	Hansen, 2005[31]	LR	LR	LR	HR	HR	HR	LR	LR	HR	HR
18	Hieu, 2012[32]	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
19	Huang, 2009[33]	HR	LR	?	LR	HR	LR	LR	HR	LR	HR
20	Huo, 2012[35]	HR	HR	LR	LR	LR	HR	LR	LR	LR	LR
21	Huo, 2011[36]	HR	HR	LR	HR	LR	HR	LR	LR	HR	HR
22	Kamien, 1975[37]	HR	HR	LR	LR	HR	HR	LR	LR	HR	HR
23	Landim, 2016[38]	HR	HR	?	LR	LR	HR	LR	LR	HR	HR
24	Layrisse, 2002[39]	HR	HR	HR	LR	HR	HR	LR	LR	HR	HR
25	Layrisse, 1996[40]	HR	HR	LR	LR	HR	LR	LR	LR	LR	LR
26	Malpeli, 2013[42]	HR	HR	LR	LR	LR	HR	LR	LR	LR	LR
27	Martorell, 2015[43]	HR	HR	HR	LR	LR	LR	LR	LR	LR	LR
28	Miglioranza, 2009[44]	HR	HR	LR	LR	HR	HR	LR	LR	LR	HR
29	Muthayya, 2012[45]	LR	LR	LR	LR	LR	HR	LR	LR	HR	LR
30	Natvig, 1973[46]	HR	LR	LR	HR	HR	HR	LR	LR	HR	HR
31	Nestel, 2004[47]	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
32	Nga, 2009[48]	LR	LR	LR	LR	LR	HR	LR	LR	HR	LR
33	Olivares, 1990[49]	LR	HR	?	LR	LR	LR	LR	LR	LR	LR
34	Phu, 2010[50]	LR	HR	HR	LR	LR	LR	LR	LR	LR	LR
35	Rahman, 2015[51]	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
36	Rifai, 2016[52]	HR	HR	HR	LR	LR	LR	LR	LR	LR	LR
37	Rohner, 2010[53]	?	LR	LR	LR	LR	LR	LR	LR	LR	LR
38	Sadighi, 2009[54]	HR	HR	LR	LR	LR	LR	LR	LR	LR	LR
39	Sadighi, 2008[55]	HR	HR	LR	LR	LR	LR	LR	LR	LR	LR
40	Safavi, 2001[56]	HR	HR	LR	LR	HR	HR	LR	LR	HR	HR
41	Seal, 2008[57]	HR	HR	LR	LR	HR	LR	LR	LR	LR	LR
42	Stuetz, 2012[58]	HR	HR	LR	LR	LR	LR	LR	HR	LR	LR

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Table 2 *Continued*

n.	First Author, Year (Ref.)	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding (performance bias and detection bias)	Similar baseline outcome measurements	Similar baseline characteristics	Incomplete outcome Reported (attrition bias)	Study protected against contamination	Selective reporting (reporting bias)	Other risks of bias	Quality*
43	Sun, 2007[59]	?	LR	?	LR	HR	LR	LR	LR	HR	HR
44	Tazhibayev, 2008[60]	HR	HR	?	LR	HR	?	LR	LR	LR	HR
45	van Stuijvenberg, 1999[61]	LR	LR	LR	LR	LR	HR	LR	LR	HR	LR
46	van Stuijvenberg, 2001[62]	HR	HR	LR	LR	HR	LR	LR	HR	LR	HR
47	van Stuijvenberg, 2006[63]	LR	LR	LR	LR	LR	HR	LR	HR	HR	LR
48	Varea, 2012[65]	HR	HR	LR	LR	HR	LR	LR	LR	LR	LR
49	Varea, 2011[66]	HR	HR	LR	LR	HR	LR	LR	LR	LR	LR
50	Walter, 1993[67]	LR	?	LR	LR	HR	HR	LR	LR	HR	HR
51	Ziegler, 2011[68]	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
52	Zimmermann, 2005[69]	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR

*Each article was classified as having low risk (LR) of bias, high risk (HR) of bias, or unclear risk (?) of bias.

Egger's linear regression test ($P = 0{\cdot}452$). There was significant heterogeneity among the trials ($I^2 = 99\,\%$, $P < 0{\cdot}001$). The results of the random effects model showed that flour fortification significantly increased serum ferritin level. The overall effect size was 4·518 μg/l (95 % CI: 2·367, 6·669; $P < 0{\cdot}001$) (Table 4, Figure S2). Subgroup analysis indicated there were no differences between types of interventions ($P = 0{\cdot}244$). However, there were significant differences in the results of studies with high risk and low risk of bias ($P = 0{\cdot}002$), for different target groups ($P = 0{\cdot}002$), and for different types of iron compounds ($P = 0{\cdot}032$). In particular, fortification significantly increased the mean ferritin level in trials with high risk of bias, in all target groups, and in trials that used ferrous sulphate or NaFeEDTA (Table 4).

4. Effect of iron-fortified flour on geometric mean ferritin level: before–after studies (data not shown)

Eighteen trials with before–after design reported geometric mean serum ferritin levels and there were 2142 subjects after interventions. Begg's funnel plot was symmetrical, suggesting no publication bias ($P = 0{\cdot}129$), in agreement with Egger's linear regression test ($P = 0{\cdot}906$). The results of the random effects model showed that flour fortification significantly increased the geometric mean serum ferritin level. The overall effect size was 5·148 μg/l (95 % CI: 0·555, 9·740; $P = 0{\cdot}028$). There was significant heterogeneity among the trials ($I^2 = 93{\cdot}2\,\%$, $P < 0{\cdot}001$). Subgroup analysis showed that trial quality ($P = 0{\cdot}134$), intervention type ($P = 0{\cdot}363$), and type of iron compounds ($P = 0{\cdot}761$) had no effect on the results. However, there was a significant difference between target groups ($P = 0{\cdot}037$), in that flour fortification with iron significantly increased the geometric mean ferritin level in children.

5. Effect of iron-fortified flour on the prevalence of anaemia: before–after studies

Sixty-seven trials with before–after design reported data on anaemia and there were 23 267 subjects after interventions. Begg's funnel plot was asymmetrical, suggesting the presence of publication bias ($P = 0{\cdot}014$), but this result was not confirmed by Egger's linear regression test ($P = 0{\cdot}079$). There was significant heterogeneity among the trials ($I^2 = 99{\cdot}9\,\%$, $P < 0{\cdot}001$). The results of the random effects model showed that flour fortification significantly reduced the prevalence of anaemia. The overall effect size was −0·067 (−6·7 %) (95 % CI: −0·098, −0·036; $P < 0{\cdot}001$) (Table 5, Figure S3). Subgroup analysis showed that trial quality ($P = 0{\cdot}331$), target group ($P = 0{\cdot}401$), intervention type ($P = 0{\cdot}571$), and type of iron compounds ($P = 0{\cdot}399$) had no significant effects on the results (Table 5).

6. Effect of iron-fortified flour on the prevalence of ID: before–after studies

Fifty-two trials with before–after design reported data on ID and there were 7683 subjects after interventions. Begg's funnel plot was symmetrical, suggesting no publication

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Table 3 Meta-analysis of the effect of iron-fortified flour on the mean haemoglobin (g/l) in before-after studies

Changes of mean haemoglobin level	Random effects model and 95 % CI					Test for heterogeneity		P-differences between subgroups
Stratification variable	Number of trials	Point estimate	Lower limit	Upper limit	*P*-value	*Q*-value	*I*-squared	
Overall	77	3·360	0·980	5·730	0·006	18702·253	99·6	
Quality								0·025
High risk of bias	27	6·890	3·070	10·710	<0·001	14245 ·149	99 8	
Low risk of bias	50	1·490	−1·290	4·260	0·294	1028·050	95·2	
Target group								0·347
All groups	1	3·000	−17·440	23·440	0·774	0·000	0·0	
Children	35	5·050	1·680	8·430	0·003	15213·119	99·8	
Infants/toddlers	13	4·750	−0·790	10·300	0·093	69·576	82·8	
Women	28	0·560	−3·240	4·360	0·773	202·815	86·7	
Intervention type								0·697
Iron	28	3·980	0·060	7·900	0·047	1127·904	97·6	
Iron+vitamins/ minerals	49	3·000	0·020	5·980	0·049	16058·486	99·7	
Iron Compounds								0·931
Electrolytic iron	29	3·380	−0·510	7·270	0·088	351·977	92·0	
Ferric pyrophosphate	1	9·000	−11·880	29·880	0·398	0·000	0·0	
Ferrous bisglycinate	2	7·040	−7·640	21·730	0·347	22·897	95·6	
Ferrous fumarate	10	3·800	−2·770	10·370	0·257	296·373	97·0	
Ferrous gluconate	2	−1·300	−15·990	13·380	0·862	1·826	45·2	
Ferrous sulphate	11	1·860	−4·410	8·130	0·561	322·777	96·9	
H-reduced elemental iron	6	0·990	−7·490	9·480	0·818	18·905	73·6	
NaFeEDTA	5	10·040	0·780	19·300	0·034	283·941	98·6	
Others	3	0·390	−11·610	12·400	0·949	21·073	90·5	
Unknown	8	3·010	−4·320	10·340	0·421	13811·654	99·9	

Table 4 Meta-analysis of the effect of iron-fortified flour on the mean serum ferritin (μg/l) in before-after studies

Changes of mean ferritin level	Random effects model and 95 % CI					Test for heterogeneity		P-differences between subgroups
Stratification variable	Number of trials	Point estimate	Lower limit	Upper limit	P-value	*Q*-value	*I*-squared	
Overall	44	4·518	2·367	6·669	<0·001	4291·809	99·0	
Quality								0·002
High risk of bias	19	8·683	5·241	12·124	<0·001	389·925	95·4	
Low risk of bias	25	1·762	−1·036	4·560	0·217	3895·600	99·4	
Target group								0·002
Children	27	5·298	2·542	8·055	<0·001	3100·799	99·2	
Infants/toddlers	4	−10·589	−19·153	−2·025	0·015	105·781	97·2	
Women	13	6·411	2·098	10·724	0·004	274·313	95·6	
Intervention type								0·244
Iron	10	6·493	2·668	10·319	0·001	906·181	99·0	
Iron+vitamins/minerals	34	3·858	1·621	6·095	0·001	1796·185	98·2	
Iron Compounds								0·032
Electrolytic iron	19	2·476	−0·562	5·514	0·110	365·310	95·1	
Ferrous bisglycinate	2	5·303	−2·916	13·521	0·206	18·089	94·5	
Ferrous fumarate	7	2·215	−2·637	7·068	0·371	383·843	98·4	
Ferrous sulphate	6	9·472	4·516	14·428	<0·001	13·628	63·3	
H-reduced elemental iron	2	5·555	−3·006	14·115	0·203	2·201	54·6	
NaFeEDTA	5	8·718	3·491	13·946	0·001	1244·538	99·7	
Others	1	13·630	1·984	25·276	0·022	0·000	0·0	
Unknown	2	−3·700	−11·781	4·381	0·369	0·133	0·0	

bias ($P = 0·180$), and this was confirmed by Egger's linear regression test ($P = 0·211$). There was significant heterogeneity among the trials ($I^2 = 99·9\,\%$, $P < 0·001$). The results of the random effects model showed that flour fortification significantly reduced the prevalence of ID. The overall effect size was −0·104 (−10·4 %) (95 % CI: −0·143, −0·065; $P < 0·001$) (Table 6, Figure S4). Subgroup analysis indicated that trial quality ($P = 0·756$) and target group ($P = 0·553$) had no significant effects on the results. However, there was a significant difference between

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Table 5 Meta-analysis of the effect of iron-fortified flour on the prevalence of anaemia in before-after studies

Changes of the prevalence of anaemia	Random effects model and 95 % CI					Test for heterogeneity		P-differences between subgroups
Stratification variable	Number of trials	Point estimate	Lower limit	Upper limit	*P*-value	*Q*-value	*I*-squared	
Overall	67	−0·067	−0·098	−0·036	<0·001	56407·401	99·9	
Quality								0·331
High risk of bias	21	−0·091	−0·149	−0·033	0·002	3391·948	99·4	
Low risk of bias	46	−0·057	−0·094	−0·021	0·002	51206·405	99·9	
Target group								0·401
All groups	2	−0·068	−0·237	0·102	0·434	1·436	30·4	
Children	28	−0·083	−0·128	−0·037	<0·001	34215·009	99·9	
Infants/toddlers	15	−0·089	−0·150	−0·027	0·005	12125·565	99·9	
Women	22	−0·028	−0·082	0·027	0·320	650·162	96·8	
Intervention type								0·571
Iron	14	−0·050	−0·116	0·015	0·133	3507·663	99·6	
Iron+vitamins/minerals	53	−0·072	−0·107	−0·037	<0·001	50862·103	99·9	
Iron Compounds								0·399
Electrolytic iron	25	−0·048	−0·101	0·004	0·070	16846·889	99·9	
Ferric pyrophosphate	2	−0·068	−0·241	0·105	0·441	1105·351	99·9	
Ferrous bisglycinate	1	−0·190	−0·434	0·054	0·127	0·000	0·0	
Ferrous fumarate	11	−0·132	−0·206	−0·057	0·001	17612·597	99·9	
Ferrous sulphate	9	−0·022	−0·104	0·060	0·599	1173·278	99·3	
H-reduced elemental iron	2	−0·001	−0·174	0·172	0·991	32·089	96·9	
NaFeEDTA	4	−0·156	−0·278	−0·034	0·012	2789·133	99·9	
Others	5	−0·046	−0·159	0·066	0·421	80·328	95·0	
Unknown	8	−0·049	−0·139	0·041	0·286	209·683	96·7	

Table 6 Meta-analysis of the effect of iron-fortified flour on the prevalence of ID in before-after studies

Changes of the prevalence of ID	Random effects model and 95 % CI					Test for heterogeneity		P-differences between subgroups
Stratification variable	Number of trials	Point estimate	Lower limit	Upper limit	*P*-value	*Q*-value	*I*-squared	
Overall	52	−0·104	−0·143	−0·065	<0·001	57562·028	99·9	
Quality								0·756
High risk of bias	15	−0·093	−0·172	−0·014	0·022	4520·925	99·7	
Low risk of bias	37	−0·107	−0·154	−0·061	<0·001	52604·364	99·9	
Target group								0·553
All groups	1	−0·162	−0·461	0·137	0·289	0·000	0·0	
Children	25	−0·079	−0·135	−0·023	0·006	43741·087	99·9	
Infants/toddlers	9	−0·154	−0·247	−0·062	0·001	9461·527	99·9	
Women	17	−0·111	−0·182	−0·039	0·002	972·376	98·4	
Intervention type								0·001
Iron	10	−0·211	−0·283	−0·139	<0·001	10492·702	99·9	
Iron+vitamins/minerals	42	−0·076	−0·113	−0·039	<0·001	27566·562	99·9	
Iron Compounds								<0·001
Electrolytic iron	16	0·005	−0·058	0·068	0·881	2891·480	99·5	
Ferric pyrophosphate	2	−0·180	−0·340	−0·020	0·028	32·000	96·9	
Ferrous bisglycinate	1	−0·370	−0·597	−0·143	0·001	0·000	0·0	
Ferrous fumarate	10	−0·114	−0·187	−0·040	0·002	13331·122	99·9	
Ferrous sulphate	9	−0·174	−0·251	−0·096	<0·001	346·599	97·7	
H-reduced elemental iron	4	−0·085	−0·198	0·029	0·142	1091·246	99·7	
NaFeEDTA	4	−0·237	−0·350	−0·123	<0·001	10914·232	100·0	
Others	2	−0·209	−0·376	−0·042	0·014	0·121	0·0	
Unknown	4	−0·001	−0·125	0·122	0·984	16·434	81·7	

intervention types ($P = 0·001$), in that flour fortification in trials that added iron to flour, as well as in trials that used iron in combination with other micronutrients, significantly reduced ID prevalence. There was also a significant difference between types of iron compounds ($P < 0·001$), in that all types of iron compounds except electrolytic iron or H-reduced elemental iron led to significantly reduced prevalence of ID (Table 6).

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Table 7 Meta-analysis of the effect of iron-fortified flour on the prevalence of IDA in before-after studies

Changes of the prevalence of IDA	Random effects model and 95 % CI					Test for heterogeneity		P-differences between subgroups
Stratification variable	Number of trials	Point estimate	Lower limit	Upper limit	*P*-value	*Q*-value	*I*-squared	
Overall	24	−0·151	−0·323	0·021	0·086	638025·636	100·0	
Quality								0·001
High risk of bias	4	−0·532	−0·771	−0·292	<0·001	153992·203	100·0	
Low risk of bias	20	−0·074	−0·182	0·034	0·177	11179·927	99·8	
Target group								0·755
Children	14	−0·194	−0·423	0·035	0·096	519620·121	100·0	
Infants/toddlers	5	−0·156	−0·538	0·227	0·425	6921·528	99·9	
Women	5	−0·023	−0·407	0·360	0·904	5·843	31·5	
Intervention type								0·030
Iron	6	−0·387	−0·633	−0·141	0·002	255631·862	100·0	
Iron+vitamins/minerals	18	−0·072	−0·214	0·071	0·325	11542·588	99·9	
Iron Compounds								0·997
Electrolytic iron	4	−0·090	−0·511	0·330	0·674	7207·196	100·0	
Ferric pyrophosphate	1	−0·202	−1·040	0·636	0·637	0·000	0·0	
Ferrous fumarate	7	−0·111	−0·429	0·207	0·495	6114·164	99·9	
Ferrous sulphate	5	−0·144	−0·519	0·231	0·451	8074·711	100·0	
H-reduced elemental iron	1	−0·137	−0·975	0·701	0·749	0·000	0·0	
NaFeEDTA	5	−0·271	−0·646	0·104	0·157	381440·575	100·0	
Others	1	−0·062	−0·901	0·777	0·885	0·000	0·0	

7. Effect of iron-fortified flour on the prevalence of IDA: before–after studies

Twenty-four trials with before–after design reported data on IDA and there were 4909 subjects after interventions. Begg's funnel plot was asymmetrical, indicating publication bias ($P < 0·001$), but Egger's linear regression test ($P = 0·317$) did not confirm this result. There was significant heterogeneity among the trials ($I^2 = 100\,\%$, $P < 0·001$). The results of the random effects model showed that flour fortification had no effect on the prevalence of IDA. The overall effect size was −0·151 (−15·1 %) (95 % CI: −0·323, 0·021; $P = 0·086$) (Table 7, Figure S5). Subgroup analysis indicated that target group ($P = 0·755$) and type of iron compounds ($P = 0·997$) had no significant effect on the results. However, there were significant differences between quality of trials ($P = 0·001$) and between intervention types ($P = 0·03$); in particular, flour fortification significantly reduced the prevalence of IDA in high-risk trials and in trials that only added iron to flour (Table 7).

8. Effect of iron-fortified flour on mean haemoglobin level: controlled trials

Forty-six controlled trials reported haemoglobin levels. After interventions, there were 5290 subjects in the intervention groups and 5063 in the control groups. Sample size was not reported in two trials. Begg's funnel plot was symmetrical, indicating no publication bias ($P = 0·272$), and Egger's linear regression test ($P = 0·336$) confirmed this result. There was significant heterogeneity among the trials ($I^2 = 91·8\,\%$, $P < 0·001$). The results of the random effects model showed that fortification significantly increased haemoglobin level. The overall effect size was 2·630 g/l (95 % CI: 1·310, 3·950; $P < 0·001$) (Table 8, Figure S6). Subgroup analysis indicated that target group ($P = 0·497$) and type of intervention ($P = 0·452$) had no significant effect on the results. However, there were significant differences between quality of trials ($P < 0·001$) and between types of iron compounds ($P = 0·003$). In particular, flour fortification significantly increased mean haemoglobin level in trials that had high risk of bias, and in trials that used ferrous fumarate or ferrous sulphate, or NaFeEDTA (Table 8).

9. Effect of iron-fortified flour on geometric mean haemoglobin level: controlled trials (data not shown)

Two controlled trials reported data on geometric mean haemoglobin levels. There were 204 subjects in the intervention and control groups after interventions. We could not estimate publication bias because this calculation requires at least three trials. There was no significant heterogeneity among the trials ($I^2 = 0\,\%$, $P = 0·365$). The results of the random effects model showed that fortification significantly increased the geometric mean haemoglobin level. The overall effect size was 5·000 g/l (95 % CI: 2·840, 7·160; $P < 0·001$). Subgroup analysis showed that trial quality ($P = 1·0$), target group ($P = 1·0$), intervention type ($P = 1·0$), and type of iron compounds ($P = 0·985$) had no effects on the results.

10. Effect of iron-fortified flour on mean ferritin level: controlled trials

Twenty-two controlled trials reported serum ferritin levels. After interventions, there were 2688 subjects in the intervention groups and 2423 in the control groups. Begg's funnel plot was symmetrical, suggesting no publication bias ($P = 0·553$) and the results of Egger's linear regression test ($P = 0·419$) was confirmatory. There was significant heterogeneity among the trials ($I^2 = 96·4\,\%$, $P < 0·001$). The results

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Table 8 Meta-analysis of the effect of iron-fortified flour on the mean haemoglobin (g/l) in controlled trials

Mean differences of changes in haemoglobin level	Random effects model and 95 % CI					Test for heterogeneity		P-differences between subgroups
Stratification variable	Number of trials	Point estimate	Lower limit	Upper limit	*P*-value	*Q*-value	*I*-squared	
Overall	46	2·630	1·310	3·950	<0·001	550·380	91·8	
Quality								<0·001
High risk of bias	11	6·390	4·070	8·710	<0·001	289·418	96·5	
Low risk of bias	35	1·430	0·100	2·760	0·035	112·689	69·8	
Target group								0·497
Children	24	3·360	1·560	5·170	<0·001	471·923	95·1	
Infants/toddlers	8	2·010	−1·240	5·270	0·226	39·983	82·5	
Women	14	1·630	−0·830	4·090	0·193	17·285	24·8	
Intervention type								0·452
Iron	24	3·120	1·280	4·970	0·001	471·597	95·1	
Iron+vitamins/minerals	22	2·100	0·190	4·020	0·031	59·200	64·5	
Iron Compounds								0·003
Electrolytic iron	16	1·270	−0·650	3·180	0·195	36·178	58·5	
Ferric pyrophosphate	1	4·000	−4·480	12·480	0·355	0·000	0·0	
Ferrous bisglycinate	1	2·400	−5·180	9·980	0·535	0·000	0·0	
Ferrous fumarate	6	3·340	0·310	6·370	0·031	22·716	78·0	
Ferrous gluconate	2	−0·810	−6·360	4·740	0·776	0·738	0·0	
Ferrous sulphate	8	3·120	0·420	5·810	0·023	72·629	90·4	
H-reduced elemental iron	6	0·120	−3·120	3·360	0·941	2·812	0·0	
NaFeEDTA	5	9·470	6·180	12·750	<0·001	164·056	97·6	
Others	1	0·600	−6·560	7·760	0·869	0·000	0·0	

Table 9 Meta-analysis of the effect of iron-fortified flour on the mean serum ferritin (μg/l) in controlled trials

Mean differences of changes in ferritin level	Random effects model and 95 % CI					Test for heterogeneity		P-differences between subgroups
Stratification variable	Number of trials	Point estimate	Lower limit	Upper limit	*P*-value	*Q*-value	*I*-squared	
Overall	22	8·544	6·767	10·320	<0·001	579·179	96·4	
Quality								0·258
High risk of bias	6	10·491	6·673	14·309	<0·001	18·667	73·2	
Low risk of bias	16	7·999	5·981	10·016	<0·001	560·216	97·3	
Target group								0·038
Children	18	9·556	7·536	11·575	<0·001	398·669	95·7	
Infants/toddlers	1	7·400	−0·389	15·189	0·063	0·000	0·0	
Women	3	2·345	−2·833	7·523	0·375	8·576	76·7	
Intervention type								0·949
Iron	9	8·427	5·103	11·751	<0·001	115·670	93·1	
Iron+vitamins/minerals	13	8·564	5·948	11·181	<0·001	418·547	97·1	
Iron Compounds								<0·001
Electrolytic iron	8	8·074	5·490	10·658	<0·001	127·457	94·5	
Ferrous bisglycinate	1	1·470	−5·386	8·326	0·674	0·000	0·0	
Ferrous fumarate	2	9·760	4·999	14·522	<0·001	23·607	95·8	
Ferrous sulphate	4	7·856	3·632	12·079	<0·001	8·339	64·0	
H-reduced elemental iron	2	−0·655	−6·537	5·227	0·827	0·034	0·0	
NaFeEDTA	5	13·663	10·401	16·925	<0·001	70·425	94·3	

of the random effects model showed that flour fortification significantly increased serum ferritin level. The overall effect size was 8·544 μg/l (95 % CI: 6·767, 10·320; $P < 0·001$) (Table 9, Figure S7). Subgroup analysis indicated that trial quality ($P = 0·258$) and type of intervention ($P = 0·949$) had no significant effects on the results. However, there were significant differences between target groups ($P = 0·038$) and between the type of iron compounds ($P < 0·001$). In particular, flour fortification significantly increased the mean ferritin level in children, and in trials which used the electrolytic iron or ferrous fumarate or ferrous sulphate, or NaFeEDTA (Table 9).

11. Effect of iron-fortified flour on geometric mean ferritin level: controlled trials (data not shown)

Fourteen controlled trials reported geometric means of serum ferritin level. After the interventions, there were 1147 subjects in the intervention groups and 1115 in the

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Table 10 Meta-analysis of the effect of iron-fortified flour on the prevalence of anaemia in controlled trials

Differences of changes in the prevalence of anaemia	Random effects model and 95 % CI					Test for heterogeneity		P-differences between subgroups
Stratification variable	Number of trials	Point estimate	Lower limit	Upper limit	*P*-value	*Q*-value	*I*-squared	
Overall	27	−0·081	−0·117	−0·044	<0·001	8178·317	99·7	
Quality								0·246
High risk of bias	3	−0·022	−0·127	0·083	0·678	14·716	86·4	
Low risk of bias	24	−0·088	−0·124	−0·051	<0·001	6958·915	99·7	
Target group								0·484
Children	14	−0·081	−0·129	−0·033	0·001	3000·883	99·6	
Infants/toddlers	7	−0·108	−0·177	−0·040	0·002	3614·194	99·8	
Women	6	−0·045	−0·122	0·033	0·260	12·399	59·7	
Intervention type								0·653
Iron	9	−0·069	−0·131	−0·007	0·029	1313·652	99·4	
Iron+vitamins/minerals	18	−0·087	−0·131	−0·042	<0·001	6099·967	99·7	
Iron Compounds								0·002
Electrolytic iron	10	−0·030	−0·072	0·011	0·151	571·323	98·4	
Ferric pyrophosphate	1	−0·106	−0·233	0·021	0·102	0·000	0·0	
Ferrous fumarate	7	−0·138	−0·186	−0·090	<0·001	1797·863	99·7	
Ferrous sulphate	3	−0·099	−0·175	−0·022	0·011	145·642	98·6	
H-reduced elemental iron	2	0·022	−0·068	0·111	0·634	90·675	98·9	
NaFeEDTA	4	−0·134	−0·198	−0·071	<0·001	188·249	98·4	

control groups. Begg's funnel plot was symmetrical, suggesting no publication bias ($P = 0·443$) and Egger's linear regression test ($P = 0·199$) confirmed this result. There was significant heterogeneity among the trials ($I^2 = 54·7\,\%$, $P = 0·007$). The results of the random effects model showed that fortification significantly increased the geometric mean serum ferritin level. The overall effect size was 9·091 μg/l (95 % CI: 5·291, 12·891; $P < 0·001$). Subgroup analysis showed that intervention type ($P = 0·884$) and type of iron compounds ($P = 0·837$) had no effects on the results, but there were significant differences between the quality of trials ($P < 0·001$) and between the target groups ($P < 0·001$). Flour fortification significantly increased the geometric mean ferritin level in trials with low risk of bias, and in children and infants/toddlers.

12. Effect of iron-fortified flour on the prevalence of anaemia: controlled trials

Twenty-seven controlled trials reported data on the prevalence of anaemia. After interventions, there were 3636 subjects in the intervention groups and 3314 in the control groups. Begg's funnel plot was symmetrical, suggesting no publication bias ($P = 0·416$), but Egger's linear regression test indicated there was publication bias ($P = 0·010$). There was significant heterogeneity among the trials ($I^2 = 99·7\,\%$, $P < 0·001$). The results of the random effects model showed that flour fortification significantly reduced the prevalence of anaemia. The overall effect size was −0·081 (−8·1 %) (95 % CI: −0·117, −0·044; $P < 0·001$) (Table 10, Figure S8). Subgroup analysis indicated that trial quality ($P = 0·246$), target group ($P = 0·484$), and type of intervention ($P = 0·653$) had no significant effects on the results. There was significant differences between the type of iron compounds ($P = 0·002$), and flour fortification significantly reduced the prevalence of anaemia in trials that used ferrous fumarate or ferrous sulphate, or NaFeEDTA (Table 10).

13. Effect of iron-fortified flour on the prevalence of ID: controlled trials

Twenty-three controlled trials reported data on the prevalence of ID. After interventions, there were 2838 subjects in the intervention groups and 2533 in the control groups. Begg's funnel plot was symmetrical, suggesting no publication bias ($P = 0·526$), in agreement with the results of Egger's linear regression test ($P = 0·219$). There was significant heterogeneity among the trials ($I^2 = 99·9\,\%$, $P < 0·001$). The results of the random effects model showed that fortification significantly reduced the prevalence of ID. The overall effect size was −0·120 (−12 %) (95 % CI: −0·189, −0·051; $P = 0·001$) (Table 11, Figure S9). Subgroup analysis indicated that trial quality ($P = 1·0$), target group ($P = 0·170$), and type of intervention ($P = 0·723$) had no significant effects on the results. There was a significant difference between types of iron compounds ($P = 0·002$), and flour fortification significantly reduced the prevalence of ID when ferrous fumarate or ferrous sulphate, or NaFeEDTA was used (Table 11).

14. Effect of iron-fortified flour on the prevalence of IDA: controlled trials

Fifteen controlled trials reported data on the prevalence of IDA. After interventions, there were 2242 subjects in the intervention groups and 2018 in the control groups. Begg's funnel plot was symmetrical, suggesting no publication bias ($P = 0·138$), in agreement with the results of Egger's linear regression test ($P = 0·290$). There was significant heterogeneity among the trials ($I^2 = 100\,\%$,

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Table 11 Meta-analysis of the effect of iron-fortified flour on the prevalence of ID in controlled trials

Differences of changes in the prevalence of ID	Random effects model and 95 % CI					Test for heterogeneity		P-differences between subgroups
Stratification variable	Number of trials	Point estimate	Lower limit	Upper limit	*P*-value	*Q*-value	*I*-squared	
Overall	23	−0·120	−0·189	−0·051	0·001	24539·181	99·9	
Quality								1·000
Low risk of bias	23	−0·120	−0·189	−0·051	0·001	24539·181	99·9	
Target group								0·170
Children	13	−0·091	−0·184	0·002	0·056	17460·458	99·9	
Infants/toddlers	4	−0·267	−0·434	−0·099	0·002	2407·629	99·9	
Women	6	−0·085	−0·223	0·052	0·225	346·016	98·6	
Intervention type								0·723
Iron	8	−0·137	−0·256	−0·018	0·024	4812·283	99·9	
Iron+vitamins/minerals	15	−0·111	−0·198	−0·024	0·013	18676·754	99·9	
Iron Compounds								0·002
Electrolytic iron	6	0·033	−0·079	0·145	0·566	587·024	99·1	
Ferric pyrophosphate	1	−0·083	−0·358	0·192	0·554	0·000	0·0	
Ferrous fumarate	5	−0·223	−0·345	−0·100	<0·001	9916·467	100·0	
Ferrous sulphate	4	−0·180	−0·319	−0·041	0·011	138·553	97·8	
H-reduced elemental iron	3	0·020	−0·139	0·179	0·805	31·182	93·6	
NaFeEDTA	4	−0·276	−0·414	−0·139	<0·001	962·010	99·7	

$P < 0·001$). The results of the random effects model showed that fortification significantly reduced the prevalence of IDA. The overall effect size was −0·209 (−20·9 %) (95 % CI: −0·384, −0·034, $P = 0·019$) (Table 12, Figure S10). Subgroup analysis indicated that target group ($P = 0·860$), type of intervention ($P = 0·072$), and type of iron compounds ($P = 0·966$) had no significant effect on the results. However, flour fortification significantly reduced the prevalence of IDA in both low-risk and high-risk trials ($P < 0·001$) (Table 12).

Discussion

Food fortification is a common public health strategy used to reduce iron deficiency. As of 2013, food fortification was mandatory in 133 countries, and the five most commonly fortified foods were salt (43·8 %), wheat flour (32·3 %), cooking oil (14·6 %), maize flour (6·3 %), and rice (3·1 %)[70]. As of 2018, eight-six countries had legislation that mandated cereal grain fortification; sixty-six countries fortify wheat flour alone, fourteen countries fortify wheat flour and maize flour, three countries fortify wheat flour and rice, one country fortifies rice alone, and two countries fortify wheat flour, maize flour, and rice[71]. The success of the food fortification programmes depends on the presence of appropriate legislation and regulations, adequate intake of fortified foods, bioavailability of micronutrients, and programme monitoring and evaluation.

The present meta-analysis evaluated the effectiveness of iron-fortified flour on iron status, with stratification by study design (controlled trials and before-after studies). The results suggest that publications with a controlled trial design had higher quality (lower risk of bias) than the before–after studies. The results also showed that iron-fortified flour increased the haemoglobin levels and serum ferritin levels, and reduced the risk of anaemia, ID, and IDA (IDA only in controlled trials). These findings seem to be consistent with other studies which found that food fortification improved iron status. For example, a review reported that fortified foods had positive effects on haemoglobin and serum ferritin levels, and reduced the risk of anaemia and ID[72]. Another study in 2015 showed that a wheat flour fortification programme was successful in improving iron status and reducing anaemia[43]. Food fortification with several micronutrients, including vitamin A, iron, and other micronutrients, improved the haemoglobin levels of children and improved the ferritin and haemoglobin levels of reproductive-age women and pregnant women[73]. Consumption of fortified foods also improved the haemoglobin levels of children younger than two years-old[74]. Another study showed that each year of consuming iron fortified foods was associated with a 2·4 % reduction in the odds of anaemia prevalence[75]. However, a systematic review concluded there was limited evidence for the effectiveness of flour fortification programmes in reducing the prevalence of anaemia, although these programmes are more effective in reducing the prevalence of ID[76].

The results of our subgroup analysis indicated that high-risk trials in before–after studies and low-risk trials in controlled trials, and trials that used NaFeEDTA resulted in greater responses. However, use of iron with other micronutrients rather than iron alone had no impact on the results.

Fortification programmes that use iron compounds with low bioavailability or only small amounts of iron are often ineffective[77]. Our results indicated that use of NaFeEDTA (which has high bioavailability) was the most important factor assuring effective iron fortification. Thus, we suggest that future food fortification programmes should focus on

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Table 12 Meta-analysis of the effect of iron-fortified flour on the prevalence of IDA in controlled trials

Differences of changes in the prevalence of IDA	Random effects model and 95 % CI					Test for heterogeneity		P-differences between subgroups
Stratification variable	Number of trials	Point estimate	Lower limit	Upper limit	*P*-value	*Q*-value	*I*-squared	
Overall	15	−0·209	−0·384	−0·034	0·019	138285·539	100·0	
Quality								<0·001
High risk of bias	3	−0·596	−0·759	−0·434	<0·001	12533·304	100·0	
Low risk of bias	12	−0·113	−0·194	−0·032	0·006	7363·631	99·9	
Target group								0.860
Children	10	−0·238	−0·466	−0·010	0·041	130566·479	100·0	
Infants/toddlers	4	−0·180	−0·540	0·180	0·328	1983·659	99·8	
Women	1	−0·038	−0·761	0·685	0·918	0·000	0·0	
Intervention type								0·072
Iron	6	−0·372	−0·600	−0·144	0·001	74595·537	100·0	
Iron+vitamins/minerals	9	−0·101	−0·287	0·085	0·288	7110·931	99·9	
Iron Compounds								0·966
Electrolytic iron	2	−0·138	−0·639	0·362	0·587	2910·019	100·0	
Ferric pyrophosphate	1	−0·056	−0·764	0·652	0·877	0·000	0·0	
Ferrous fumarate	4	−0·165	−0·519	0·189	0·360	4784·567	99·9	
Ferrous sulphate	3	−0·234	−0·643	0·175	0·262	4039·474	100·0	
NaFeEDTA	5	−0·289	−0·605	0·028	0·074	97785·461	100·0	

using bioavailable forms of iron compounds, such as NaFeEDTA. Although NaFeEDTA is more expensive than other forms of iron, its addition to foods enhances the absorption of other iron fortifying compounds, such as sulphate or fumarate[78].

Our study found that iron-fortified flour reduced the prevalence of IDA, but this finding should be interpreted with caution because it was highly dependent on study design. In particular, iron-fortified flour only reduced the prevalence of IDA in controlled trials, not in before-after studies. The global prevalence of anaemia has decreased from 40·2 % in 1990 to 32·9 % in 2010, and IDA is one of the major causes of anaemia, in addition to hookworm, sickle cell disorder, thalassemia, schistosomiasis, and malaria[79]. Thus, iron fortification of foods is only one of the public health strategies needed to control anaemia[80].

The strengths of this meta-analysis are that we performed stratification by study design, we included trials that fortified all types of flours, examined all age groups, and examined both genders, and we examined large numbers of subjects. Our meta-analysis of before-after studies examined haemoglobin levels in 19 083 subjects, ferritin levels in 6790 subjects, anaemia in 23 267 subjects, ID in 7683 subjects, and IDA in 4909 subjects. There were fewer subjects in the controlled trials presumably because these studies are more labour-intensive. There were also several limitations of this meta-analysis. In particular, there was high heterogeneity among most studies, so the results of the random effects models should be interpreted with caution. We found evidence of publication bias among trials with before–after design that investigated the effect of flour fortification on haemoglobin level; however, this bias was unlikely to alter the magnitude of the effect because analysis of measurements of the mean differences in the change of haemoglobin levels indicated no evidence of publication bias. Some of our subgroup analyses only included a small number of trials, so these results should be interpreted with caution. We determined the quality of each trial based entirely on information presented in the published articles; some of these studies might have been rated as having lower bias if we received additional information from the authors. The effect of iron-fortified flour on the geometric mean haemoglobin levels and on the geometric mean serum ferritin levels should also be interpreted with caution because of the small sample sizes. Only a few of the trials that examined serum ferritin concentrations performed statistical adjustment for inflammation. Finally, we used definitions of anaemia, ID, and IDA provided in each publication, and these may have differed among studies.

In general, our findings support the view that iron-fortified flour effectively improves iron status. It should be noted, however, that the magnitudes of some of the differences that were statistically significant were quite small (e.g. significant increases of mean haemoglobin level: (3·360 g/l); hence, health policy-makers must consider whether the small magnitude of this effect is relevant to public health.

Conclusion

This meta-analysis provides evidence that iron-fortified flour increases levels of haemoglobin and ferritin, and reduces the prevalences of anaemia, ID, and IDA (IDA only in controlled trials). There were stronger effects in high-risk trials in the before–after studies, and stronger effects in low-risk trials in controlled trials. Thus, our analysis of controlled trials provided strong evidence supporting the effectiveness of iron-fortified flour. It should be noted that the type of iron compounds used for flour fortification had

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a strong impact on effectiveness, in that NaFeEDTA led to the greatest response. Thus, this meta-analysis found that flour fortification with iron is a useful public health strategy that can improve the iron status of populations. However, further studies are needed to examine the beneficial effect of iron-fortified flour on the prevalence of IDA.

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Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1368980019002179.

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