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Evidence of the effectiveness of flour fortification programs on iron status and anemia: a systematic review

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Abstract

Context.—More than 80 countries fortify flour, yet the public health impact of this intervention on iron and anemia outcomes has not been reviewed.

Objective.—The objective of this systematic review was to review published and gray literature pertaining to the impact of flour fortification on iron and anemia.

Data Sources.—A systematic review was conducted by searching 17 databases and appealing for unpublished reports, yielding 1881 documents.

Study Selection.—Only studies of government-supported, widely implemented fortification programs in which anemia or iron status was measured prior to and ≥12 months after initiation of fortification were included.

Data Extraction.—Details about the design, coverage, compliance with national standards, and evaluation (e.g., anemia prevalence before and after fortification) of flour fortification programs were extracted from the reports.

Data Synthesis.—Thirteen studies describing 26 subgroups (n = 14 for children ≤15 y, n = 12 for women of reproductive age) were included. During the period from pre- to postfortification (and as difference-in-difference for those studies that included a control group), there were statistically significant decreases in the prevalence of anemia in 4 of 13 subgroups of children

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Author contributions. H.P. conceptualized the study. H.P., M.K.S., and Z.M. developed the study protocol. H.P. completed the database search and managed the documents obtained from the search and e-mail appeal. H.P., M.K.S., and R.S. reviewed all documents, extracted information from them, and completed the analysis; Z.M. served as arbiter during this process. H.P. wrote the first draft; all authors critically reviewed the content and approved the final manuscript.

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and in 4 of 12 subgroups of women of reproductive age as well as significant decreases in the prevalence of low ferritin in 1 of 6 subgroups of children and in 3 of 3 subgroups of women of reproductive age.

Conclusions.—Evidence of the effectiveness of flour fortification for reducing the prevalence of anemia is limited; however, evidence of effectiveness for reducing the prevalence of low ferritin in women is more consistent.

Keywords

enrichment; ferritin; hemoglobin; maize flour; wheat flour

INTRODUCTION

Food fortification is one of the leading public health interventions recommended to prevent and control micronutrient deficiencies.[1] Staple foods and condiments are among the foods most commonly fortified with vitamins and minerals. Wheat flour was the first cereal-grain product to be widely fortified, and the first cereal-grain recommendations issued by the World Health Organization (WHO) pertained to maize and wheat flour.[2] As of 2015, 83 countries have mandated wheat-flour fortification; 14 of these have simultaneously mandated maize-flour fortification.[3] Most of these countries mandate fortification of wheat and maize flour with at least iron and folic acid, with a few exceptions: Australia does not require flour fortification with iron, and Congo, Nigeria, the Philippines, the United Kingdom, and Venezuela do not require fortification of flour with folic acid.

The public health impact of fortification of wheat flour with iron as implemented in government programs has been incompletely documented. A review of efficacy and effectiveness trials found that fortification of staple foods with iron increased hemoglobin levels and serum ferritin levels and decreased anemia prevalence in children, but not in women[4]; however, the effect of specific staples could not be determined. A review of efficacy trials showed that iron fortification of food increased hemoglobin levels in children less than 10 years of age,[5] but the effect of specific staples could not be determined. Per another systematic review of efficacy trials conducted with "apparently healthy (nondiseased) individuals, families or communities," iron-fortified wheat flour and rice increased hemoglobin levels.[6] A desk review of flour fortification programs concluded that most programs that fortify with iron use nonrecommended forms of iron that have low bioavailability (n = 50 of 78 programs) and hence would be "expected to have little impact on iron status at the national level."[7] However, no systematic reviews have been completed on the post hoc effectiveness of flour fortification on iron status or anemia.

The objectives of this systematic review were to answer the following questions about flour fortification (wheat flour alone or combined with maize flour) (Table 1[8]): 1) In effectiveness settings, does flour fortification improve iron status and anemia?; 2) Is there a difference, by age group, in the impact of flour fortification on iron status and anemia?; 3) Are there differences in iron status and anemia if WHO recommended iron compounds are used for flour fortification?; and 4) If programs are well implemented, does flour fortification improve iron status and anemia?

METHODS

The PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines for systematic reviews were followed[8] (see Table S1 in the Supporting Information online). The study design drew heavily from the Cochrane protocol published for fortification of maize flour,[9] although no review protocol was developed for the current study. The following types of studies were included: nonrandomized controlled trials; prospective observational studies that had a control group, such as cohort studies (prospective and retrospective) and controlled before-and-after studies; and prospective observational studies that did not have a control group, including before-and-after studies. Studies were included if there was a biochemical measurement of the primary outcomes (listed below) before fortification began (prefortification) and a measurement at least 12 months after fortification began (postfortification). The following documents were excluded: review articles, conference abstracts, letters to the editor, and presentations. If there were multiple documents from the same country's experience, only the most recent and comprehensive paper was included. The participants included in the review consisted of the general population older than 2 years (including pregnant women) from any country.

The following interventions were included: wheat flour (alone or in combination with maize flour) fortified with iron; flour to which micronutrients were added during production of the flour; interventions that were part of a government program; and interventions that included any of the primary outcomes (listed below). The following interventions or studies were excluded: interventions that were provided only in an experimental capacity; interventions in which fortification took place at the point of use (e.g., micronutrient powders); studies of biofortified crops (biofortification); and in vitro, animal, or human bioavailability studies. Studies of interventions targeting participants with a critical illness or severe comorbidities were also excluded.

The primary outcomes of interest were as follows: hemoglobin concentration, anemia as defined by studies (e.g., hemoglobin below a cutoff and adjusted for altitude or other factors), iron status using any biomarker (e.g., ferritin, transferrin saturation, soluble transferrin receptor, soluble transferrin receptor-ferritin index, total iron-binding capacity, serum iron), and iron deficiency as defined by studies (e.g., biomarker below or above a cutoff and adjusted for inflammation). Because ferritin is not normally distributed in populations in which significant iron deficiency is present, geometric means were reported, if available; however, if only arithmetic were published, these were assessed. The secondary outcomes of interest were the biomarkers of any other nutrients added to flour (e.g., serum or red blood cell folate for folic acid) and the deficiency of nutrients as defined by studies (e.g., nutrient level below or above a cutoff).

The systematic review had two components: a search in electronic databases and an e-mail appeal. For the electronic searches, no date or language restrictions were imposed. Using the terms "wheat fortification" in English and in Spanish (for the IBECS [Índice Bibliográfico Español en Ciencias de la Salud][10] and SciELO [Scientific Electronic Library Online][11] databases), the following databases were searched on May 31, 2013: Cochrane Central Register of Controlled Trials,[12] MEDLINE,[13] Embase,[14] Web of Science,[15] CINAHL

(Cumulative Index to Nursing and Allied Health Literature),[16] POPLINE,[17] AGRICOLA,[18] BIOSIS Previews,[19] OpenGrey,[20] Bibliomap,[21] TRoPHI (Trials Register of Promoting Health Interventions),[22] IBECS,[10,11] Global Health Library,[23] Indian Medical Journals,[24] Native Health Research Database,[25] and ProQuest Dissertation and Theses.[26] Email appeals for unpublished fortification evaluations were sent on June 4, 2013, and August 12, 2013, to approximately 2500 individuals in a listserv managed by the Food Fortification Initiative and representing public, private, and civic organizations.

Two reviewers independently screened the titles of the documents retrieved from the database search and e-mail appeal to discard those that were irrelevant (Figure 1). Two reviewers then independently screened the abstracts of potentially relevant documents to discard those that were irrelevant. The full text of each potentially relevant document was read independently by two reviewers. From relevant documents, the reviewers independently extracted approximately 20 pieces of information related to study location, study design, design and implementation of the fortification program, and outcomes assessed (see Table S2 in the Supporting Information online).

The extracted information was analyzed qualitatively. Specifically, the statistical significance of changes in outcomes of interest as reported in the studies was noted (i.e., reduction in anemia prevalence or no reduction in anemia prevalence). Additionally, the fortification program from each study was categorized on the basis of whether it met WHO recommendations[2] for flour fortification with regard to type and amount of iron. The nutrition outcomes from the studies that did and did not meet the WHO recommendations were compared.

RESULTS

The database search yielded 2621 documents; when duplicates were eliminated, 1768 documents remained (Figure 1). Titles were reviewed independently, and 149 documents were selected for abstract review. Of these, 48 full-text documents were retrieved and reviewed. Of these, 7 were included in the analysis; 1 Portuguese-language document[27] was reviewed by only 1 author (H.P.). The e-mail request yielded 123 documents. After deletion of duplicate documents, 113 documents remained. Titles were reviewed independently, and 86 documents were selected for abstract review. Of these, 55 full-text documents were reviewed. Of these, 6 were included in the analysis.

Description of documents

The documents selected for in-depth review presented evaluations of flour fortification programs in 13 countries: Azerbaijan, Brazil, China, Fiji, India, Iran, Kazakhstan, Mongolia, Nepal, Sri Lanka, Tajikistan, Uzbekistan, and Venezuela (Table 2[27–39] and Table S2 in the Supporting Information online). Most reported fortification of wheat flour only (n = 10), of wheat and maize flour (n = 2), and of wheat, maize, and millet flour (n = 1). Nine documents were published and 4 were available in the gray literature. The documents described 13 studies. Most studies (n = 9) were designed as pre–post independent cross-sectional surveys with or without a comparison group; 4 were pre–post cohort studies with or without a comparison group. Four of the studies employed a comparison group.

Most studies presented data gathered at the subnational level; the only national-level data reported were for Fiji[35] and Uzbekistan[34] (Table 2). Four studies presented results for multiple subgroups (i.e., age, region, or type of iron); in total, 26 subgroups were reported. For example, Tazhibayev et al.[30] reported 5 subgroups: children 2 to 15 years in Azerbaijan, Kazakhstan, Mongolia, Tajikistan, and Uzbekistan. Nestel et al.[36] published reports for 6 subgroups: preschool children 9 to 71 months who consumed wheat flour fortified with electrolytic iron, preschool children 9 to 71 months who consumed wheat flour fortified with reduced iron, schoolchildren 6 to 11 years who consumed wheat flour fortified with electrolytic iron, schoolchildren 6 to 11 years who consumed wheat flour fortified with reduced iron, nonpregnant women who consumed wheat flour fortified with electrolytic iron, and nonpregnant women who consumed wheat flour fortified with reduced iron.

The 2 population groups represented by the studies were children ≤15 years (n = 14 subgroups) and women of reproductive age (n = 12 subgroups) (Table 2 and Table S2 in the Supporting Information online). The prefortification measurement was taken as early as 1992 in Venezuela[33] and as late as 2009 in Nepal[37]; most studies gathered baseline data between 2000 and 2009 (Table 2). The sample sizes in the studies ranged from a low of 80 children aged 2 to 15 years[30] to a high of 9189 children aged 2 to 5 years[27] (Table 3).

All 13 programs added iron to flour (Table 4 and Table S2 in the Supporting Information online). In 2 countries, fortification legislation allowed 2 or more iron compounds to be used in the programs that were evaluated. Brazil[31] permitted ferrous sulfate, ferrous fumarate, reduced iron 325 Tyler mesh, electrolytic iron 325 Tyler mesh, NaFeEDTA (ferric sodium ethylenediaminetetraacetate), and iron bisglycinate chelate for wheat and maize flour, and Venezuela[33] allowed ferrous fumarate and electrolytic iron for maize flour.

Alignment of programs with WHO recommendations for flour fortification

All of the fortification programs included in this review began before WHO recommendations for wheat and maize flour fortification were issued in 2009.[2] The recommendations for iron fortification depend on the per capita intake of the flour to be fortified and the extraction level of flour (i.e., whether it is refined or whole grain). The iron compound used in fortification was in line with WHO recommendations for 8 of 13 countries (Table 4). For the concentration of iron, 2 of the 13 countries reported adding at least the WHO-recommended levels to the flour.

Primary outcomes and age groups

The ferritin level (mean/median), prevalence of low ferritin, hemoglobin level (mean), and prevalence of anemia, stratified by subgroup, are shown in Table 3. Table 5[40] summarizes these primary outcomes. For children 15 years of age and younger, there were statistically significant increases in ferritin and hemoglobin for 3[30,33] of 6 and 5[30,39] of 12 subgroups, respectively, from the pre- to the postfortification periods. For children, there were statistically significant decreases in the prevalence of low ferritin and anemia for 1[30] of 6 and 4[30] of 13 subgroups, respectively. For women of reproductive age, there were statistically significant increases in ferritin and hemoglobin for 5[28,29,32,35] of 5 and 6[28,29,35,37–39] of 11 subgroups, respectively. There were statistically significant decreases in the prevalence of low ferritin, anemia, and iron-deficiency anemia for 3[32,35] of 3, 4[35,38,39] of 12, and 0 of 2, subgroups, respectively, in women of reproductive age.

Primary outcomes and WHO flour fortification recommendations

The relationship between adding the WHO-recommended iron compounds and at least the WHO-recommended iron levels and having the expected outcomes was assessed. Only 2 subgroups[30,35] met both WHO recommendations (iron type and concentration). Anemia prevalence decreased in both subgroups and ferritin improved in 1, but not the other.

Program implementation information

Most documents (n = 9) provided some evidence on the implementation of the flour fortification program under study: evidence of either compliance with standards or coverage of fortification (Table 6). The compliance and coverage information was not reported in a standard manner across studies, nor are there guidelines to classify compliance and coverage (e.g., as inadequate or adequate) information. Thus, it was not possible to link the compliance and coverage information with outcomes.

DISCUSSION

This was the first review of effectiveness studies describing the public health impact of implementing the fortification of wheat flour only, or the fortification of both wheat flour and maize flour, on iron status and anemia. Given the large number of fortification programs, few documents were identified from the published and gray literature. That is, few effectiveness evaluations of flour fortification programs have been completed for iron status and anemia. Subgroup analyses indicate that flour fortification is associated with consistent reductions in low ferritin prevalence in women, but not in children. Further, a reduction in anemia prevalence was observed in only one-third of the subgroups of women and children studied. There is insufficient evidence to evaluate whether programs that followed WHO iron recommendations for flour fortification had better outcomes. While most studies reported on some degree of compliance with national standards or coverage of fortification programs in the study area, this information could not be used to assess whether programs were well implemented, nor was it possible to link program implementation information with outcomes achieved.

In public health practice, the design of a program can affect its impact. All of the studies reviewed initiated fortification before global recommendations for flour fortification were issued.[2] As part of the deliberations to establish those recommendations, Hurrell et al.[7] assessed the design of flour fortification programs worldwide with respect to iron compounds and iron levels. They concluded that, of 78 countries with wheat-flour fortification programs at the time (e.g., mandatory, voluntary, World Food Program, and planned), only 9 were using recommended compounds or levels. Thus, few of the programs would be expected to have a positive impact on iron status. In the current analysis, 8 of 13 countries used the recommended iron compound, while only 2 of the 13 countries reported adding minimum iron levels. In those countries that used recommended iron compounds and levels, 1 of 2 subgroups showed reductions in the prevalence of low ferritin, and 2 of 2 subgroups had reductions in anemia prevalence. Taken together, these results suggest that more countries should be encouraged to design their fortification programs in line with WHO recommendations and to evaluate their fortification programs and adjust them as necessary.

Program implementation is another factor that contributes to program impact. Most studies reported information on program implementation, but the results for compliance and coverage varied widely. For example, in Venezuela, the iron level in commercial flour samples contained 80%–120% of expected levels, suggesting strong compliance.[33] In contrast, in Azerbaijan, 25% of study women reported using fortified wheat-flour products in their homes, suggesting poor coverage.[30] A case study from Fiji offers potential insights into the importance of program implementation.[35] In Fiji, high compliance (flour samples met 91.7%–123.3% of the standard for iron) was reported, and WHO recommendations for iron compounds and levels were followed; this combination may have led to positive outcomes (reduction in the prevalence of low ferritin and anemia among women of childbearing age). These results suggest that two factors are important for countries with flour fortification programs: 1) compliance with and coverage of the program, in addition to the design of the program, should be documented; and 2) information on compliance and coverage should be used to determine when to evaluate the potential health impact of a program (i.e., when compliance and coverage are consistently high, and when the program is optimally designed in relation to international recommendations).

Most studies assessed hemoglobin levels or the prevalence of anemia; 5 used these biomarkers alone to evaluate the success of the fortification program.[27,31,36–38] Biomarkers specific to iron or folate status, for example, were assessed infrequently (n = 7 for iron[28–30,32–35] and n = 4 for folate[28,30,34,35]). Researchers who have assessed multiple nutrition indicators as well as hemoglobin have found that anemia may not be principally due to iron deficiency (e.g., <10% of anemia among preschool children and nonpregnant, nonlactating women in Bangladesh[41] was caused principally by iron deficiency) or other nutrient deficiencies (e.g., anemia may be caused by bacteremia, malaria, hookworm infestation, HIV infection, or the $G6PD^{-202/-376}$ genetic disorder[42]). In these cases, flour fortified with iron, folic acid, and other nutrients will have a limited impact on hemoglobin levels and anemia prevalence. For these reasons, the sole use of anemia biomarkers to assess the impact of flour fortification should be discouraged, and the use of biomarkers specific to the nutrients added to flour should be encouraged.

Study design influences both the ability to detect improvements in nutritional outcomes and the ability to attribute results to an intervention implemented on a large scale. Most studies were pre–post independent cross-sectional surveys, and most did not have a comparison group. Both of these factors preclude any changes observed in health outcomes from being unequivocally attributed to an intervention. When a study's design limits the ability to attribute results to the intervention, confidence in assigning some contribution of the intervention to the results can be strengthened if there is adequate information about program implementation.[43] Researchers have developed program-implementation pathways to express their a priori expectations of how a program will lead to improvements in measurable health outcomes.[44] Then, they measure indicators along the implementation pathway to conclude whether it is more or less likely that the program contributed to the outcomes observed.

Some of the studies in this review included data on iron compounds and levels as well as information on program compliance and coverage, which are important elements along the program-implementation pathway for flour fortification.[45] For example, Fijian investigators reported the addition to flour of the recommended iron compound at the recommended level, evidence that flour was adequately fortified (based on measurement of samples from mills, retail outlets, or households), and the intake of flour-containing foods in sufficient quantities to fill nutrient gaps in the diet.[35] This study reported reductions in the prevalence of both low ferritin and anemia. This example suggests that program evaluations should be designed to measure inputs and outputs of the fortification program (as elucidated through a program-implementation pathway) in addition to health impacts. Such information can add plausibility to findings about the impact of fortification on health outcomes if the study design precludes attributing causality to fortification.

This review has several limitations. The number of documents obtained was small and included no African countries, thus compromising the generalizability of the results. The design of most studies precludes attributing improvements in health outcomes to flour fortification. Moreover, the lack of information on program implementation adds to this problem in some cases. The presentation of findings by subgroup resulted in some studies contributing many more data points to the analysis than others, potentially biasing the findings. Furthermore, subgroup analyses resulted in small sample sizes that limited the ability to detect meaningful effects.

In turn, this review has several strengths. This was the first attempt to assess the effectiveness of flour fortification on iron and anemia outcomes. A rigorous search strategy of both the published and the gray literature was followed, which permitted inclusion of several unpublished studies. Program-specific information that could influence health outcomes, such as the iron compounds used, the levels of iron added, compliance with national standards, and coverage of the program, was systematically assessed.

CONCLUSION

This is the first systematic review of the effectiveness of flour fortification on iron and anemia outcomes. There is limited evidence of the effectiveness of flour fortification in reducing the prevalence of anemia; however, evidence of effectiveness in reducing the prevalence of low ferritin in women is more consistent. There is also limited evidence that relates health outcomes with compliance with international fortification recommendations. This review highlights the challenges of evaluating the impact of fortification when implemented on a wide scale. These challenges, along with those related to the design and execution of fortification programs, represent opportunities to strengthen both existing fortification programs and those yet to be implemented.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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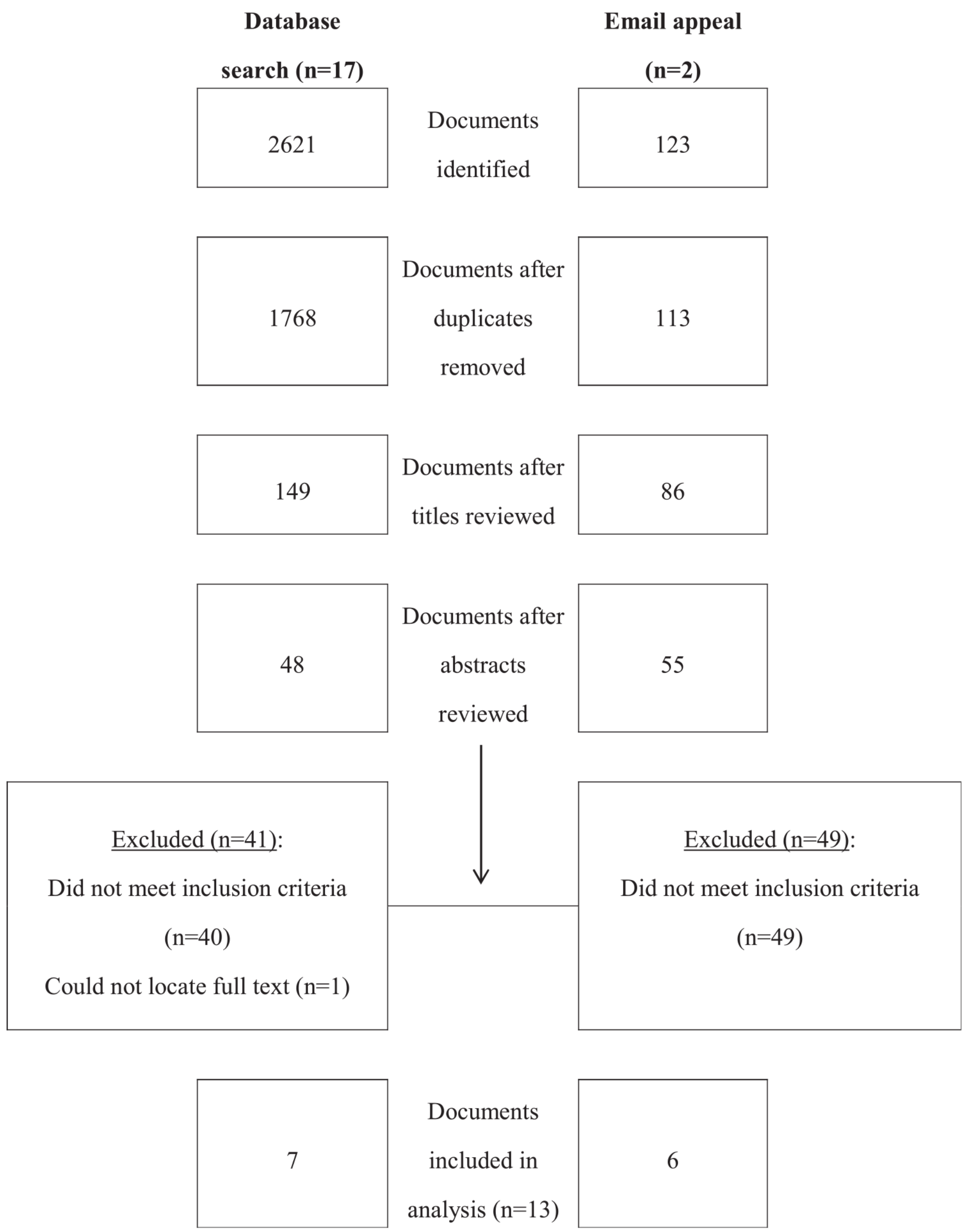

Figure 1.
Flow chart of the search and selection process.

Table 1

PICOS criteria[8] used to define the four research questions

	Question 1	Question 2	Question 3	Question 4
Participants	General population older than 2 y (including pregnant women) from any country			
Intervention	Wheat flour (alone or in combination with maize flour) fortified with iron			
Comparators	Prefortification period vs postfortification period	Children 2–15 y vs women of reproductive age	WHO-recommended iron compounds are used (yes vs no)	Well-implemented programs (yes vs no)
Outcomes	Iron status and prevalence of anemia			
Study design	Nonrandomized controlled trials and observational studies			

Table 2

Description of documents (n = 13) included in the review

Reference	Country (geographic level)	Study design (publication status)	Study population	No. and type of analytic subgroups
Huo et al.[28]	China (subnational, village)	Pre–post cohort study with comparison group (published)	Nonpregnant WRA, 20–60 y	1: WRA
Huo et al.[29]	China (subnational, village)	Pre–post cohort study with comparison group (published)	WRA, 20–60 y	1: WRA
Tazhibayev et al.[30]	Azerbaijan, Kazakhstan, Mongolia, Tajikistan, Uzbekistan (for all countries: subnational, pilot area)	Pre–post cohort study without comparison group (published)	Children, 2–15 y	5: Azerbaijan children, Kazakhstan children, Mongolian children, Tajikistan children, Uzbekistan children
Assuncao et al.[31]	Brazil (subnational, city)	Pre–post independent cross-sectional surveys without comparison group (published)	Children, <6 y	1: children
Sadighi et al.[32]	Iran (subnational, province)	Pre–post independent cross-sectional surveys without comparison group (published)	WRA, 15–49 y	2: WRA from Bushehr Province, WRA from Golestan Province
Costa et al.[27]	Brazil (subnational, municipality)	Pre–post independent cross-sectional surveys without comparison group (published)	Children, 2–5 y	1: children
Layrisse et al.[33]	Venezuela (subnational, municipality)	Pre–post independent cross-sectional surveys without comparison group (published)	Schoolchildren, 7 y, 11 y, and 15 y	1: children
Northrop-Clewes et al.[34]	Uzbekistan (national)	Pre–post independent cross-sectional surveys without comparison group (unpublished)	WRA	1: WRA
National Food & Nutrition Centre[35]	Fiji (national)	Pre–post independent cross-sectional surveys without comparison group (unpublished)	Nonpregnant WRA, 15–49 y	1: WRA
Nestel et al.[36]	Sri Lanka (subnational, tea estates)	Pre–post cohort study with comparison group (published)	Preschool children, 9–71 mo; schoolchildren, 6–11 y; nonpregnant WRA	6: preschool children consuming flour fortified with electrolytic iron; preschool children consuming flour fortified with reduced iron; schoolchildren consuming flour fortified with electrolytic iron; schoolchildren consuming flour fortified with reduced iron; WRA consuming flour fortified with electrolytic iron; WRA consuming flour fortified with reduced iron
Nepali Technical Assistance Group[37]	Nepal (subnational, district)	Pre–post independent cross-sectional surveys without comparison group (unpublished)	WRA, 15–45 y	1: WRA
Fujimori et al.[38]	Brazil (subnational, regional)	Pre–post independent cross-sectional surveys without comparison group (published)	Pregnant WRA	1: WRA
Micronutrient Initiative et al.[39]	India (subnational, district)	Pre–post independent cross-sectional surveys with comparison group (unpublished)	Preschool children and schoolchildren, 5–11 y; adolescent girls, 12–19 y (WRA); pregnant and lactating WRA	4: preschool children, schoolchildren, adolescent girls, pregnant and lactating women

Abbreviation: WRA, women of reproductive age.

Table 3

Results for primary outcomes: ferritin level, low ferritin status, hemoglobin level, and prevalence of anemia in 26 subgroups

Reference	Country	Study population (subgroup)	Sample size	Pre- and postfortification marker(s) of iron status	Definition of iron deficiency	Pre- and postfortification prevalence of iron deficiency (%)	Pre- and postfortification hemoglobin levels	Definition of anemia	Pre- and postfortification prevalence of anemia (%)
Huo et al.[28]	China	Nonpregnant WRA, 20–60 y	Intervention, prefortification: 268; postfortification: 213. Control, prefortification: 277; postfortification: 235	Mean (SD): FEP: Control: 46.5 (10.0) μg/dL → 46.1 (10.7) μg/dL. Intervention: 46.4 (10.9) μg/dL → 43.2 (8.9) μg/dL, SSD[a]. Serum iron: Control: 0.80 (0.14) mg/L → 0.81 (0.19) mg/L. Intervention: 0.80 (0.16) mg/L → 0.85 (0.15) mg/L, SSD[a]	NR	NR	Mean (SD): Control: 129.7 (12.2) g/L → 129.8 (13.2) g/L, SNR. Intervention: 129.3 (14.9) g/L → 132.0 (14.3) g/L, SSD[b]	Hb <120 g/L. No reported adjustments	Control: 30.2% → 29.8%. Intervention: 29.5 → 27.2%, SNR
Huo et al.[29]	China	WRA, 20–60 y	Intervention, prefortification: 308; postfortification: 269 Control, prefortification: 298; postfortification: 247	Mean (SD): FEP: Control: 44.5 μg/dL → 46.5 (13.4) μg/dL. Intervention: 42.6 (13.7) μg/dL → 38.9 (7.5) μg/dL, SSD[a]. Serum iron: Control: 0.76 (0.28) mg/L → 0.76 (0.26) mg/L. Intervention: 0.75 (0.27) mg/L → 0.86 (0.16) mg/L, SSD[a]	NR	NR	Mean (SD): Control: 131.9 g/L (13.3) → 131.58 (13.0) g/L. Intervention: 132.2 (13.3) g/L → 135.7 (14.3) g/L, SSD[a]	NR	Control: 13.1% → 14.2%. Intervention: 15.1% → 10.8%, SNR
Tazhibayev et al.[30]	Azerbaijan	Children, 2–15 y	Prefortification: 80; postfortification: NR	Mean (SE): Ferritin: 29.4 (2.0) μg/dL → 36.7 (2.6) μg/dL, NS	Children <5 y: ferritin <12 μg/dL; children >5 y: ferritin <15 μg/dL. No reported adjustments	15.2% → 16.3%, SSD	Mean (SE): 120 (10) g/L → 123 (1) g/L, SSD	6–59 mo: Hb <110 g/L; 5–11 y: Hb <115 g/L; ≥ 12 y: Hb <120 g/L. No reported adiustments	20.9% → 6.3%, SSD

Reference	Country	Study population (subgroup)	Sample size	Pre- and postfortification marker(s) of iron status	Definition of iron deficiency	Pre- and postfortification prevalence of iron deficiency (%)	Pre- and postfortification hemoglobin levels	Definition of anemia	Pre- and postfortification prevalence of anemia (%)
Tazhibayev et al.[30]	Kazakhstan	Children, 2–15 y	Prefortification: 80; postfortification: NR	Mean (SE): Ferritin: 17.6 (1.5) µg/dL → 32.5 (3.8) µg/dL, SSD	Children <5 y: ferritin <12 µg/dL; children ≥5 y: ferritin <15 µg/dL. No reported adjustments	43.8% → 22.9%, SSD	Mean (SE): 114 (2) g/L → 123 (1) g/L, SSD	6–59 mo: Hb <110 g/L; 5–11 y: Hb <115 g/L; ≥12 y: Hb <120 g/L. No reported adjustments	50% → 32.4%, SSD
Tazhibayev et al.[30]	Mongolia	Children, 2–15 y	Prefortification: 80; postfortification: NR	Mean (SE): Ferritin: 38.0 (2.2) µg/dL → 41.8 (4.1) µg/dL, NS	Children <5 y: ferritin <12 µg/dL; children ≥5 y: ferritin <15 µg/dL. No reported adjustments	5% → 16.4%, NS	Mean (SE): 126 (1) g/L → 129 (2) g/L, NS	6–59 mo: Hb <110 g/L; 5–11 y: Hb <115 g/L; ≥12 y: Hb <120 g/L. No reported adjustments	12.5% → 20.3%, NS
Tazhibayev et al.[30]	Tajikistan	Children, 2–15 y	Prefortification: 80; postfortification: NR	Mean (SE): Ferritin: 32.8 (2.0) µg/dL → 48.4 (4.8) µg/dL, SSD	Children <5 y: ferritin <12 µg/dL; children ≥5 y: ferritin <15 µg/dL. No reported adjustments	8.7% → 12.9%, NS	Mean (SE): 107 (2) g/L → 128 (2) g/L, SSD	6–59 mo: Hb <110 g/L; 5–11 y: Hb <115 g/L; ≥12 y: Hb <120 g/L. No reported adjustments	70% → 20.3%, SSD
Tazhibayev et al.[30]	Uzbekistan	Children, 2–15 y	Prefortification: 80; postfortification: NR	Mean (SE): Ferritin: 31.2 (1.6) µg/dL → 25.7 (1.6) µg/dL, NS	Children <5 y: ferritin <12 µg/dL; children ≥5 y: ferritin <15 µg/dL. No reported adjustments	8.1% → 22.6%, NS	Mean (SE): 119 (1) g/L → 132 (2) g/L, SSD	6–59 mo: Hb <110 g/L; 5–11 y: Hb <115 g/L; ≥12 y: Hb <120 g/L. No reported adjustments	31.4% → 16.7%, SSD
Assuncao et al.[31]	Brazil	Children, <6 y	Prefortification (2004): 507; postfortification (2008): 799	NR	Ferritin <12 ng/mL or transferrin saturation <20%	NR	Mean (SE): 113 (1.3) g/L → 111 (0.9) g/L, SSD[c]	Hb <110 g/L. No reported adjustments	30.2% → 42.6%, SSD[d]
Sadighi et al.[32]	Iran (Bushehr Province)	WRA, 15–49 y	Prefortification: 593; postfortification: 600	Mean (SD): Ferritin: 32.8 (48.4) ng/mL → 41.9 (44.3) ng/mL, SSD	Ferritin <10ng/mL. No reported adjustments	22.2% → 15.7%, SSD	Mean (SD): 136 (16) g/L → 129 (14) g/L, SSD	Nonpregnant women: Hb <120 g/L; pregnant women: Hb <110 g/L. No reported adjustments	12.1% → 20.8%, SSD
Sadighi et al.[32]	Iran (Golestan Province)	WRA, 15–49 y	Prefortification: 579;	Mean (SD): Ferritin: 31.5 (42.9)	Ferritin <10 ng/mL. No	26.7% → 14.6%, SSD	Mean (SD): 129 (13) g/L → 125 (11) g/L, SSD	Nonpregnant women: Hb <120 g/L; pregnant	19.3% → 25.6%, SSD

Reference	Country	Study population (subgroup)	Sample size	Pre- and postfortification marker(s) of iron status	Definition of iron deficiency	Pre- and postfortification prevalence of iron deficiency (%)	Pre- and postfortification hemoglobin levels	Definition of anemia	Pre- and postfortification prevalence of anemia (%)
			postfortification: 652	ng/mL → 47.7 (46.3) ng/mL, SSD	reported adjustments			women: Hb <110 g/L. No reported adjustments	
Costa et al.[27]	Brazil	Children, 2–5 y	Prefortification: 9189; postfortification: 329[e]	NR	NR	NR	Mean (SD): NR → 119.9 (14.3) g/L	Hb <110 g/L. No reported adjustments	30.2–68.8% → 20.9%, SNR
Layrisse et al.[33]	Venezuela	School children, 7 y, 11 y, and 15 y	Prefortification (1992): 282; postfortification (1999): 545	Geometric mean: Ferritin: 13.46 µg/dL → 24.1 µg/dL, SSD	Girls & boys, 7–11 y: ferritin <10 µg/dL; girls & boys, 15 y: ferritin <12 µg/dL. No reported adjustments	37.2% → 15.5%, NS	NR	7 y girls & boys: Hb <115 g/L; 11–15 y girls: Hb <120 g/L; 11 y boys: Hb <125 g/L; 15 y boys: Hb <130 g/L. No reported adjustments	18.1% → 17.1%, NS
Northrop-Clewes et al.[34]	Uzbekistan	WRA	Prefortification: 4333; postfortification: 2584	Geometric mean: Ferritin: NR → 17.1 µg/dL[f], SNR	Ferritin <12 µg/dL. Ferritin adjusted for CRP	NR → 47.5% (95%CI: 45.1–49.9), SNR	Geometric mean (95%CI): NR → 121.6 (120.4–122.7) g/L	1996 and 2008: Hb <120 g/L. In 2008, Hb adjusted for altitude and smoking	60.4% → 34.4% (95%CI: 32.0–36.7), SNR
National Food & Nutrition Centre[35]	Fiji	Nonpregnant WRA, 15–45 y	Prefortification: NR; postfortification: 869	Mean (SD): Ferritin: 51.7 (NR) µg/dL → 76.7 (41.63) µg/dL, SSD	Ferritin <15 µg/dL. No reported adjustments	22.9% → 7.9% (95%CI: 6.3–10.0), SSD	Mean (SD): 122 (NR) g/L → 124.2 (13.7) g/L, SSD	Hb <120 g/L. No reported adjustments	40.3% → 27.6% (95%CI: 24.7–30.7)[9], SSD
Nestel et al.[36]	Sri Lanka	Preschool children, 9–71 mo, electrolytic iron	Intervention, prefortification: 247; postfortification: 146 Control, prefortification: 267; postfortification: 131	NR	NR	NR	Mean (SD): Electrolytic: 122.2 (12.2) g/L → 126.3 (10.7) g/L, NS[h]	Children <60 mo: Hb <110 g/L; children 5–11.9 y: Hb <115 g/L. No reported adjustments	Electrolytic: 16.6% → NR. Control: 18.4% → NR
Nestel et al.[36]	Sri Lanka	Preschool children, 9–71 mo, reduced iron	Intervention, prefortification: 231; postfortification: 81 Control, prefortification: 267; postfortification: 131	NR	NR	NR	Mean (SD): Reduced: 119.9 (15.3) g/L → 125.5 (11.3) g/L, NS[h]	Children <60 mo: Hb <110 g/L; children 5–11.9 y: Hb <115 g/L. No reported adjustments	Reduced: 19.5% → NR. Control: 18.4% → NR

Reference	Country	Study population (subgroup)	Sample size	Pre- and postfortification marker(s) of iron status	Definition of iron deficiency	Pre- and postfortification prevalence of iron deficiency (%)	Pre- and postfortification hemoglobin levels	Definition of anemia	Pre- and postfortification prevalence of anemia (%)
Nestel et al.[36]	Sri Lanka	School children, 6–11 y, electrolytic iron	Intervention, prefortification: 278; postfortification: 180 Control, prefortification: 306; postfortification: 180	NR	NR	NR	Mean (SD): Electrolytic: 129.6 (10.7) g/L → 128.4 (11.6) g/L, NS[h]	Children 5–11.9 y: Hb <115 g/L; children ≥12 y: Hb <120 g/L. No reported adjustments	Electrolytic: 6.1 % → NR. Control: 8.5% → NR
Nestel et al.[36]	Sri Lanka	School children 6–11 y, reduced iron	Intervention, prefortification: 326; postfortification: 152 Control, prefortification: 306; postfortification: 180	NR	NR	NR	Mean (SD): Reduced: 129.2 (10.8) g/L → 129.9 (10.0) g/L, NS[h]	Children 5–11.9 y: Hb <115 g/L; children ≥12 y Hb <120 g/L. No reported adjustments	Reduced: 7.4% → NR. Control: 8.5% → NR
Nestel et al.[36]	Sri Lanka	Nonpregnant WRA, electrolytic iron	Intervention, prefortification: 486; postfortification: 187 Control, prefortification: 541; postfortification: 198	NR	NR	NR	Mean (SD): Electrolytic: 126.2 (17.5) g/L → 125.9 (14.9) g/L, NS[h]	Hb <120 g/L. No reported adjustments	Electrolytic: 22.8% → NR. Control: 29.0% → NR
Nestel et al.[36]	Sri Lanka	Nonpregnant WRA, reduced iron	Intervention, prefortification: 546; postfortification: 180 Control, prefortification: 541; postfortification: 198	NR	NR	NR	Mean (SD): Reduced: 120.7 (18.6) g/L → 122.4 (18.4) g/L, NS[h]	Hb <120 g/L. No reported adjustments	Reduced: 34.4% → NR. Control: 29.0% → NR
Nepali Technical Assistance Group[37]	Nepal	WRA, 15–45 y	Prefortification: 270; postfortification: 570	NR	NR	NR	Mean (SD): 125 (18.8) g/L → 131 (13.5) g/L, SSD	Hb <120 g/L. Hb adjusted for altitude. No reported adjustments	33% → 18%. SNR

Reference	Country	Study population (subgroup)	Sample size	Pre- and postfortification marker(s) of iron status	Definition of iron deficiency	Pre- and postfortification prevalence of iron deficiency (%)	Pre- and postfortification hemoglobin levels	Definition of anemia	Pre- and postfortification prevalence of anemia (%)
Fujimori et al.[38]	Brazil	Pregnant WRA	Prefortification: 6062; postfortification: 6057	NR	NR	NR	Mean (SD): 118 (13) g/L → 119 (12) g/L, SSD	Hb <110 g/L. No reported adjustments	25.5% → 20.2%, SSD
Micronutrient Initiative et al.[39]	India	Pregnant and lactating WRA	Intervention, prefortification: 376; postfortification: 372 Control, prefortification: 378; postfortification: 386	NR	NR	NR	Mean (SD): Intervention: 117.3 (17.1) g/L → 120.4 (17.1) g/L, SSD^{b,i}. Control: 115.2 (16.6) g/L → 112.3 (16.3) g/L, SSD^{b,i}	Hb cut-off NR. Hb adjusted for altitude	Intervention: 52.1% → 44.7%, SSD^{b,i}. Control: 57.3%^{j} → 63.2%, SNR^{i}
Micronutrient Initiative et al.[39]	India	School children, 5–11 y	Intervention, prefortification: 282; postfortification: 368 Control, prefortification: 343; postfortification: 367	NR	NR	NR	Mean (SD): Intervention: 120.6 (13.5) g/L → 125.2 (12.4) g/L, SSD^{b,i}. Control: 115.9 (12.1) g/L → 122.8 (9.8) g/L, NS^{b,i}	Children 5–11 y: Hb <115 g/L; children 12–14 y: Hb <120 g/L; nonpregnant females: Hb <120g/L. Hb adjusted for altitude	Intervention: 59.9% → 45.9%, SSD^{b,i}. Control: 64.4% → 56.9%, SSD^{b,i}
Micronutrient Initiative et al.[39]	India	Adolescent WRA, 12–19 y	Intervention, prefortification: 296; postfortification: 359 Control, prefortification: 328; postfortification: 343	NR	NR	NR	Mean (SD): Intervention: 120.6 (16.5) g/L → 127.4 (14.1) g/L, SSD^{b,i}. Control: 116.4 (16.9) g/L → 120.9 (13.4) g/L, SSD^{b,i}	Children 12–14 y: Hb <120 g/L; nonpregnant females: Hb <120g/L. Hb adjusted for altitude	Intervention: 70.3% → 54.3%, SSD^{b,i}. Control: 79.9% → 75.5%, NS^{b,i}
Micronutrient Initiative et al.[39]	India	Preschool children	Intervention, prefortification: 376; postfortification: 354 Control, prefortification: 364; postfortification: 370	NR	NR	NR	NR	NR	NR

Abbreviations: CI, confidence interval; CRP, C-reactive protein; FEP, free erythrocyte protoporphyrin; Hb, hemoglobin; NR, not reported; NS, not significantly different; SD, standard deviation; SE, standard error; SNR, statistics not reported; SSD, statistically significantly different; WRA, women of reproductive age.

[a]Comparing the postfortification value between intervention and control.

[b]Comparing the postfortification value with the prefortification value.

[c]Hemoglobin across 4 surveys showed a statistically significant linear trend.

[d]Elemoglobin across 4 surveys was statistically heterogeneous.

[e]The sample size is sometimes noted as 459 children (e.g., Table 1) or 329 children (Abstract and Methods section) in the document.[27]

[f]This represents ferritin adjusted for inflammation; geometric mean ferritin unadjusted for inflammation was 17.3 µg/dL.

[g]The 24.7 value is reported in Table 3.5.2 of the document and as 27.7 in the narrative of the same document.[35]

[h]Comparing mean change from pre- to postfortification in the intervention group with the mean change from pre- to postfortification in the control group.

[i]The "difference of the difference" was not statistically tested.

[j]The 57.3 value seems to be erroneously reported as 37.3% in Figure 3 of the document.[39]

Table 4

Comparison of the iron compound and concentration used in fortification programs with WHO recommendations for flour[2] in 13 countries

Country	Reference	Flour	Flour extraction rate	Iron added	WHO recommendations followed[a,b]	
					Iron compound	**Iron concentration**
Azerbaijan	Tazhibayev et al.[30]	Wheat	First grade flour: 61%–72%. Premium grade flour: 55%–60%	First grade: 40 mg/kg as electrolytic iron. Premium grade: 50 mg/kg as electrolytic iron	Yes	Yes
Brazil	Assuncao et al.,[31] Costa et al.,[27] Fujimori et al.[38]	Wheat, maize	Not reported	42 mg/kg as ferrous sulfate, ferrous fumarate, reduced iron 325 Tyler mesh, electrolytic iron 325 Tyler mesh, NaFeEDTA, or iron bisglycinate chelate	Cannot determine	Cannot determine
China	Huo et al.,[28] Huo et al.[29]	Wheat	Not reported, but wheat flour was grade 2 flour	20 mg/kg as electrolytic iron (Huo et al.[28]). 20 mg/kg as NaFeEDTA[b] (Huo et al.[29])	Yes	No[c]
Fiji	National Food & Nutrition Centre[35]	Wheat	Not reported	60 mg/kg as hydrogen-reduced electrolytic iron	Yes	Yes
India	Micronutrient Initiative et al.[39]	Atta wheat	Atta flour: 80%–85%	60 mg/kg (compound not specified)	Cannot determine	Cannot determine
Iran	Sadighi et al.[32]	Wheat	Not reported	30 mg/kg as ferrous sulfate	Yes	Cannot determine
Kazakhstan	Tazhibayev et al.[30]	Wheat	First grade flour: 61%–72%. Premium grade flour: 55%–60%	First grade: 40 mg/kg as electrolytic iron. Premium grade: 50 mg/kg as electrolytic iron	Yes	No
Mongolia	Tazhibayev et al.[30]	Wheat	First grade flour: 61%–72%. Premium grade flour: 55%–60%	First grade: 40 mg/kg as electrolytic iron. Premium grade: 50 mg/kg as electrolytic iron	Yes	No
Nepal	Nepali Technical Assistance Group[37]	Maize, wheat, millet	Not reported	25 mg/kg[d] (compound not specified)	Cannot determine	Cannot determine
Sri Lanka	Nestel et al.[36]	Wheat	Not reported	66 mg/kg as electrolytic iron or reduced iron	No	No
Tajikistan	Tazhibayev et al.[30]	Wheat	First grade flour: 61%–72%. Premium grade flour: 55%–60%	First grade: 40 mg/kg as electrolytic iron. Premium grade: 50 mg/kg as electrolytic iron	Cannot determine	Cannot determine
Uzbekistan	Tazhibayev et al.,[30] Northrop-Clewes et al.[34]	Wheat	61%–72%	40 mg/kg as electrolytic iron	Yes	No
Venezuela	Layrisse et al.[33]	Maize, wheat	Not reported, but wheat flour was “white”	Wheat: 20 mg/kg as ferrous fumarate. Maize: 50 mg/kg as ferrous fumarate until 1994; since then, 30 mg/kg as ferrous fumarate and 20 mg/kg as electrolytic iron	Yes	Cannot determine

[a]The WHO recommendations for wheat and maize flour specify iron compounds and levels of iron, zinc, vitamin A, folic acid, and vitamin B_{12} to be added to flour.[2] Recommendations depend on per capita intake of flour and the extraction level of flour. For iron levels, “yes” indicates that at least the WHO-recommended iron level was added to the flour. “No” indicates that less than the WHO-recommended iron level was added to the flour.

[b]Without information on per capita flour intake or iron compound, it cannot be determined whether WHO recommendations are followed.

[c]The compound specified in the Huo et al.[29] document is electrolytic iron; however, the first author confirmed that the iron compound used in the study was NaFeEDTA (Junsheng Huo, China Center for Disease Control and Prevention, personal communication).

[d]The concentration for iron added in the Nepali Technical Assistance Group study was obtained from Felix Brooks-Church (Project Healthy Children, personal communication).

Table 5

Statistically significant changes in biological markers of iron status and anemia from flour fortification effectiveness trials, stratified by target population (n = 26 subgroups)

Biological marker	Children ≤15 y (n = 14 subgroups)			Women of reproductive age (n = 12 subgroups)		
	Yes	No	Not assessed[a]	Yes	No	Not assessed[a]
Increased ferritin[b]	3	3	8	5	0	7
Decreased prevalence of low ferritin	1	5	8	3	0	9
Increased hemoglobin	5	7	2	6	5	1
Decreased prevalence of anemia	4	9	1	4	8	0
Decreased prevalence of IDA	0	0	14	0	2	10

Abbreviation: IDA, iron-deficiency anemia.

[a]This outcome was not assessed.

[b]For 2 subgroups in women, the markers of iron status were free erythrocyte protoporphyrin and serum iron, instead of ferritin.[28,29] An improvement in iron status is marked by a decrease in free erythrocyte protoporphyrin and an increase in serum iron[40]; both of these improved and were classified as “yes” for “increased ferritin.” Only 2 documents specified that ferritin was expressed as a geometric mean.[33,34]

Table 6

Implementation evidence reported on flour fortification programs

Reference	Country	Fortification compliance	Fortification coverage
Huo et al.[28]	China	None reported	Intervention group at baseline: of all flour[a] consumed, 51.2% was fortified. Intervention group at last follow-up at 36 mo: of all flour consumed, 62.9% was fortified
Huo et al.[29]	China	None reported	Intervention group at baseline: of all flour[a] consumed, 62.9% was fortified. Intervention group at last follow-up at 36 mo: of all flour consumed, 53.7% was fortified
Tazhibayev et al.[30]	Azerbaijan	At postfortification measurement (round 3), 83%–100% of wheat flour in home was fortified according to iron spot test	At postfortification measurement (round 3), 25% of study women reported using fortified wheat flour products in their homes
Tazhibayev et al.[30]	Kazakhstan	At postfortification measurement (round 3), 15%–20% of wheat flour consumed annually nationwide was fortified and 83%–100% of wheat flour in home was fortified per iron spot test	At postfortification measurement (round 3), 100% of study women reported using fortified wheat flour products in their homes
Tazhibayev et al.[30]	Mongolia	At postfortification measurement (round 3), 15%–20% of wheat flour consumed annually nationwide was fortified and 83%–100% of wheat flour in home was fortified per iron spot test	At postfortification measurement (round 3), 88% of study women reported using fortified wheat flour products in their homes
Tazhibayev et al.[30]	Tajikistan	At postfortification measurement (round 3), 15%–20% of wheat flour consumed annually nationwide was fortified and 83%–100% of wheat flour in home was fortified per iron spot test	At postfortification measurement (round 3), 49% of study women reported using fortified wheat flour products in their homes
Tazhibayev et al.[30]	Uzbekistan	At postfortification measurement (round 3), 35%–40% of wheat flour consumed annually nationwide was fortified and 83%–100% of wheat flour in home was fortified per iron spot test	At postfortification measurement (round 3), 87% of study women reported using fortified wheat flour products in their homes
Assuncao et al.[31]	Brazil	None reported	None reported
Sadighi et al.[32]	Iran	In 2009, flour samples taken from 3 factories in Bushehr Province contained 50–55 mg iron/kg. In 2009,119 flour samples were obtained from bakeries in Golestan Province; 94.1% of samples contained iron	One bread sample was taken per cluster of women in Bushehr Province in 2009; 98.7% of the samples were fortified with iron
Costa et al.[27]	Brazil	None reported	None reported
Layrisse et al.[33]	Venezuela	During the period 1993–1999, analysis of random samples of commercial flour showed 80%–120% contained the expected level of iron	None reported
Northrop-Clewes et al.[34]	Uzbekistan	Among 2503 households where any wheat flour was available, 41.6% (95%CI: 39.2–43.9) of all flour tested was fortified per iron spot test	The overall weighted average coverage of UDM first grade flour in households at the time of the survey was 59.8%
National Food & Nutrition Centre[35]	Fiji	Percent of iron standard met by flour samples tested ranged from 91.7% to 123.3%	None reported
Nestel et al.[36]	Sri Lanka	Mean iron content of flour: 78 ± 15.2[b] mg/kg (electrolytic), 76 ± 6.6 mg/kg (reduced), and 15 ± 1.7 mg/kg (control); 100% and 95% of electrolytic and reduced iron flour was fortified to acceptable levels	None reported

Reference	Country	Fortification compliance	Fortification coverage
Nepali Technical Assistance Group[37]	Nepal	Baseline: iron content in maize flour from 30 household samples was 36.6 mg/kg. Endline II: iron content in maize flour from 60 household samples was 45.3 mg/kg; 81% of 535 flour samples contained added iron per iron spot test	69.7% of women reported consuming fortified flour at endline II
Fujimori et al.[38]	Brazil	None reported	None reported
Micronutrient Initiative et al.[39]	India	None reported	None reported

Abbreviations: CI, confidence interval; UDM, Uzdonmakhsulot, a state joint stock company association for wheat flour.[34]

[a] At baseline, this refers to compensation flour that was to be fortified as part of the program.

[b] Report does not specify whether error is standard deviation or another measure.