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Iron biofortification interventions to improve iron status and functional outcomes

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This analysis was conducted to evaluate the evidence of the efficacy of iron biofortification interventions on iron status and functional outcomes. Iron deficiency is a major public health problem worldwide, with a disproportionate impact on women and young children, particularly those living in resource-limited settings. Biofortification, or the enhancing of micronutrient content in staple crops, is a promising and sustainable agriculture-based approach to improve nutritional status. Previous randomised efficacy trials and meta-analyses have demonstrated that iron-biofortification interventions improved iron biomarkers; however, no systematic reviews to date have examined the efficacy of biofortification interventions on health outcomes. We conducted a systematic review of the efficacy of iron-biofortified staple crops on iron status and functional outcomes: cognitive function (e.g. attention, memory) and physical performance. Five studies from three randomised efficacy trials (i.e. rice, pearl millet, beans) conducted in the Philippines, India and Rwanda were identified for inclusion in this review. Iron status (Hb, serum ferritin, soluble transferrin receptor, total body iron, α-1-acid glycoprotein) was measured at baseline and endline in each trial; two studies reported cognitive outcomes, and no studies reported other functional outcomes. Meta-analyses were conducted using DerSimonian and Laird random-effects methods. Iron-biofortified crop interventions significantly improved cognitive performance in attention and memory domains, compared with conventional crops. There were no significant effects on categorical outcomes such as iron deficiency or anaemia. Further studies are needed to determine the efficacy of iron-biofortified staple crops on human health, including additional functional outcomes and other high-risk populations.

Iron: Biofortification: Anaemia: Functional outcomes

Iron deficiency is a major global public health problem, despite extensive investment in interventions for its prevention and treatment. Iron deficiency is the most common micronutrient deficiency worldwide, with the greatest burden in women of reproductive age and young children(1,2). Iron is essential for brain development, myelination, growth and cognitive function(3). Inadequate iron status has been associated with adverse health outcomes, including deficits in cognitive function (i.e. concentration, short-term memory, reaction time)(4,5), as well as reduced physical work capacity and endurance(6,7).

Biofortification is a promising and sustainable agriculture-based intervention with the potential to improve

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Abbreviations: MeSH, Medical Subject Headings; RCT, randomised controlled trial; SF, serum ferritin; TBI, total body iron.
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nutritional status worldwide, particularly in vulnerable populations(8). It differs from conventional fortification approaches in that it aims to increase micronutrient levels in staple crops during plant growth, rather than through manual means during grain processing. The method involves the targeted breeding of staple food crops to increase their intrinsic micronutrient content(8,9). This approach allows for leveraging existing markets and delivery systems while vulnerable populations are not required to change consumption behaviours in order to receive more diverse, nutritious diets. Increasing the micronutrient content of staple foods items (that constitute the main portion of the diet) through biofortification can be beneficial even if the increase in micronutrient content is small(9). In this review, biofortification refers to the process by which the vitamin and mineral content of staple crops is increased through agronomic practices, conventional plant breeding or modern biotechnology(8).

Previous research demonstrated that iron biofortification interventions were efficacious in improving iron biomarkers(10), and a recent review concluded that iron-biofortified staple crops are efficacious in improving iron status and further highlighted the need to assess functional outcomes(10). However, to date, no systematic reviews have been conducted to examine the efficacy of biofortification interventions on health outcomes.

This review was conducted to examine the efficacy of iron-biofortified staple food crop interventions on improving iron status and functional outcomes, including cognitive performance and physical performance. We conducted meta-analyses to combine findings from included randomised trials to inform public health programmes and to incorporate biofortification as a strategy to target iron deficiency in at-risk populations.

Methods

Types of studies

Controlled trials (i.e. randomised, quasi-randomised), with randomisation at the individual or cluster level, were eligible for inclusion in this review. Research studies that had only been published in abstract form were considered for inclusion if sufficient information was provided to determine eligibility, study design and quality.

Types of participants

We included studies of participants from the general population (including pregnant or lactating women), without respect to participant sex, age, nationality or race. We excluded studies of interventions targeted towards participants with critical illnesses or severe co-morbidities.

Types of interventions

We included studies that examined the efficacy of iron-biofortified staple crops on health outcomes. Interventions providing iron-biofortified staple crops that were not GM (non-GMO), in comparison to conventional crops, were considered without any restrictions on population characteristics or country of location. Only interventions with a duration of at least 28 d were considered.

Types of outcome measures

The primary outcomes examined in this review are presented in Table 2.

Iron status. Primary functional outcomes were: (1) anaemia, defined as Hb concentrations below 120 g/l, in accordance with WHO criteria, adjusted for smoking and altitude, where applicable; and (2) iron deficiency, defined as serum ferritin (SF) <15·0 μg/l in primary analyses; and as total body iron (TBI; mg/kg), as calculated by Cook's Equation(11), <0·0 mg/kg and soluble transferrin receptor >8·3 mg/l in additional analyses.

Functional outcomes. Primary functional outcomes were: (1) cognitive function, as defined by the study authors (e.g. formal tests addressing reaction times and accuracy of responses in tasks targeting attention, memory and other cognitive domains); (2) physical performance, as defined by the study authors (e.g. output produced per work hour, such as wages earned when dependent on production output); and (3) other functional outcomes, as defined by the trial authors (e.g. education/academic achievement, emotional health, psychomotor development).

Other outcomes. Any adverse effects (as defined by study authors) were considered as secondary outcomes.

Search methods for identification of studies

We conducted a structured literature search with the use of MEDLINE electronic databases. Relevant Medical Subject Headings (MeSH) terms were used to identify published studies on 2 August 2018, with no language or date restrictions. The MeSH terms used are summarised in Table 1, and the search strategy PRISMA is summarised in Fig. 1. Additional sources were identified from bibliographies of published studies and from manual searches of related articles in references. An additional search was conducted to find review articles, which were examined to cross-reference other relevant studies. Search results were screened by two independent reviewers (A. F., L. S. H.) to determine if studies met the inclusion criteria.

Data collection and analysis

Selection of studies. A standardised form for data extraction was developed, piloted and used to ensure accurate data extraction from included studies. Data from studies identified as potentially eligible upon screening were extracted independently by two authors (A. F., L. S. H.). All discrepancies were resolved through discussion and consultation with an additional review author (J. L. F. or S. M.). Extracted information included: study characteristics (i.e. year of study, duration of intervention, kind of iron-biofortified foods, setting, inclusion and exclusion criteria, recruitment strategy, sample size, rates of attrition), population characteristics (e.g. sex, age, occupation, socio-economic status) and

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Table 1. MEDLINE search strategy

Search	Query	*n*
#1	Search (Biofortification[MeSH] OR food, fortified[MeSH] OR Biofortif*[tiab] or fortif* [tiab] or bioengineer* [tiab] or bio-engineer* [tiab] or nutritionally enhance*[tiab] OR nutritional enhance*[tiab])	25526
#2	Search (Iron[MeSH] OR iron[tiab])	192782
#3	Search (Iron[MeSH] OR iron*[tiab])	195667
#4	Search (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab])	4308794
#5	Search (#1 and #3 and #4)	971
#6	Search (animals[MeSH] NOT humans[MeSH])	4481132
#7	Search (#5 not #6)	881

MeSH, Medical Subject Headings.
The search was conducted on 2 August 2018.

Table 2. Primary outcomes for iron status and functional parameters

Continuous	Categorical
Hb, g/l	<120 g/l
Anaemia	Hb < 120 g/l
SF, μg/l	<15·0 μg/l
sTfR, mg/l	>8·3 mg/l
TBI, mg/kg*	<0·0 mg/kg
Iron deficiency	Primary analysis: SF < 15·0 μg/l Secondary analysis: TBI < 0·0 mg/kg and sTfR > 8·3 mg/l
Cognitive function	As defined by study authors, e.g. formal tests assessing reaction time or number of accurate decisions in response to attention, memory and other cognitive tasks
Physical performance	As defined by study authors, e.g. wages earned when dependent on production output

SF, serum ferritin; sTfR, soluble transferrin receptor; TBI total body iron.
* TBI = –(log10 (sTfR (mg/l) × 1000/SF (μg/l)–2·8229)/0·1207) (Cook's Equation)(11).

all outcomes reported (e.g. iron status, anthropometric, cognitive function, physical performance, any adverse effects and any other outcomes reported by the study authors). We contacted study authors to request any data that were either missing or required additional clarifications.

Risk of bias and quality assessment. Risk of bias was independently assessed by two authors (A. F., L. S. H.), using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. The protocol was registered in PROSPERO (CRD42018118329), the international prospective register of systematic reviews of the University of York and the National Institute for Health Research.

For each randomised trial, potential sources of bias were examined, including selection, performance, detection, attrition, reporting and other potential biases. Methods used for random sequence generation and allocation concealment were examined for potential selection biases; methods for blinding of study participants and personnel were examined for performance biases; methods for blinding outcome assessors were examined for detection bias; completeness of data and study attrition were examined for potential biases; study protocols and methods sections were compared with reported results to examine for potential reporting bias; and any other concerns identified that could potentially introduce bias were identified. For each study, each of the aforementioned areas was evaluated and classified into low, high or unclear risk of bias.

Data synthesis. Statistical analyses were conducted in the Cochrane Review Manager software (RevMan v5.3 2014), and meta-analyses were conducted using random-effects models (DerSimonian and Laird method). Weights used in meta-analyses are reported in each figure.

Subgroup analyses. Where data were available, we planned to conduct the following subgroup analyses for primary outcomes: baseline anaemia (e.g. Hb < 120 *v.* ≥120 g/l) and baseline iron deficiency (e.g. SF < 15·0 *v.* ≥15·0 μg/l; TBI < 0·0 *v.* ≥0·0 mg/kg) status.

Results

This review summarises findings from randomised efficacy trials investigating the effects of iron-biofortified staple food crops on iron status, cognitive performance and work performance. Our structured search identified 881 abstracts, of which 873 were excluded during initial abstract screening (i.e. insufficient intervention length, interventions without biofortified crops, not randomised control trials). Eight publications (from four studies) underwent full-text screening; three publications (from two studies) were excluded due to the use of non-

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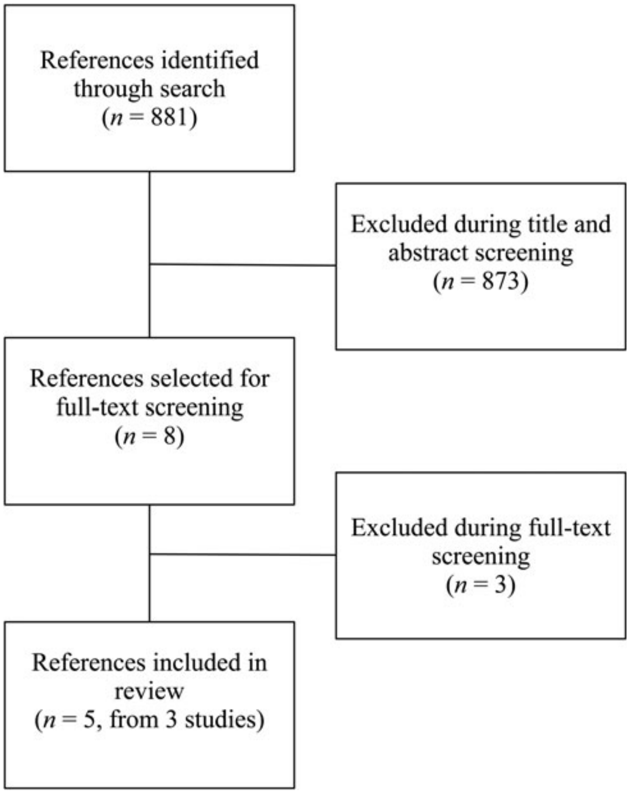

Fig. 1. PRISMA flow diagram.

biofortified foods. A total of five publications from three randomised efficacy trials were included in this review; the PRISMA flow diagram is presented in Fig. 1.

Randomised efficacy trials

Three randomised efficacy trials assessing the performance of iron-biofortified staple food crops on iron status have been conducted and their results published to date. The staple food crops used in those trials were rice, beans and pearl millet. Two of the studies measured cognitive performance in a subset of participants *via* behavioural tasks assessing memory and attention (Tables 2 and 3).

Iron-biofortified rice consumption in religious sisters in the Philippines. A double-blind randomised controlled trial (RCT) was conducted to examine the efficacy of iron-biofortified rice (*Oryza sativa*) consumption on parameters of iron status in 192 religious sisters living in ten convents around metro Manila, Philippines(12). Parameters of work performance or cognitive function were not assessed in this study or related sub-studies. Participants were randomly assigned to daily *ad libitum* consumption of iron-biofortified rice (3·21 mg/kg Fe, n 92) or a local variety of conventional rice (0·57 mg/kg Fe, n 100) for 9 months. This resulted in a 17 % difference in total iron consumed in the iron-biofortified group compared with the control group throughout the intervention period. Iron status (Hb, SF, soluble transferrin receptor, TBI, α-1-acid glycoprotein) was measured at base- and endline (9 months). *Iron status.* At baseline, 28 % of participants were anaemic (Hb $<$ 120 g/l) and 34 % were iron deficient (SF $<$ 15·0 µg/l). In analyses among non-anaemic participants, iron-biofortified rice consumption increased SF ($P = 0{\cdot}02$) concentrations and TBI ($P = 0{\cdot}05$) during the trial, representing a 20 % increase after controlling for baseline values and daily rice consumption.

Iron-biofortified pearl millet consumption in adolescents in India. A double-blind RCT examined the efficacy of iron-biofortified pearl millet (*Pennisetum glaucum*) consumption among 246 adolescents (age 12–16 years) in Maharashtra, India (NCT02152150)(13). Adolescents daily consumed 200–300 g of either iron-biofortified (86 mg/kg Fe, n 122) or conventional (21–52 mg/kg Fe, n 124) pearl millet in the form of *Bhakri* flatbread during the 6-month follow-up. Iron status (Hb, SF, soluble transferrin receptor, TBI, C-reactive protein, α-1-acid glycoprotein) was measured at base-, mid- (4 months) and endline (6 months). *Iron status.* At baseline, 28 % of adolescents were anaemic (Hb $<$ 120 g/l) and 43 % were iron deficient (SF $<$ 15·0 µg/l). Iron-biofortified pearl millet significantly increased SF concentrations and TBI levels after 4 months compared with conventional pearl millet. The effects of iron-biofortified pearl millet on iron status were also greater among adolescents who were iron deficient at baseline, compared with those who were not iron deficient. *Cognitive outcomes.* In a subset of 140 study participants (n 88 in biofortification group, n 52 in control group), with the lowest ranked SF concentrations, measures of cognitive function were evaluated at base- and endline (6 months)(14). The measures consisted of attention (i.e. simple reaction time, go/no-go, attentional network) and memory (i.e. composite face effect, cued recognition) tasks (Table 4). In the cognitive subset, 33 % of participants were anaemic and 50 % were iron deficient at baseline. The group consuming iron-biofortified pearl millet demonstrated greater improvement in cognitive measures of both attention and memory, compared with the group consuming conventional pearl millet. Specifically, the iron-biofortification intervention significantly improved all three measures of the attentional network task, i.e. alerting, orienting and conflict, compared with the conventional pearl millet group, which also showed a decline in performance in orienting and conflict. Furthermore, participants in the iron-biofortification group showed significant improvements in the cued recognition task (suggesting an improved ability to adapt to increasing workload), compared with the conventional group. Overall, findings from these analyses indicate a benefit of consuming iron-biofortified over conventional pearl millet on measures of attention and memory.

Iron-biofortified bean consumption in iron-depleted Rwandan women of reproductive age. A double-blind RCT was conducted to determine the efficacy of iron-biofortified bean (*Phaseolus vulgaris*) consumption among 195 iron-depleted (SF $<$ 20·0 µg/l) female university students (18–27 years) in Huye, Rwanda

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Table 3. Characteristics of randomised efficacy feeding trials of iron-biofortified crops

Setting	Manila, Philippines[12]		Maharashtra, India[13,14]		Huye, Rwanda[15,16]	
Population	Adult female (18–45 years), religious sisters in ten convents		Male and female adolescents (12–16 years) living in three hostels		Adult female (18–27 years) university students on campus	
Study design	Randomised efficacy trial		Randomised efficacy trial		Randomised efficacy trial	
Randomisation	By individual		By individual		By individual	
	Iron-biofortified rice		Iron-biofortified pearl millet (*Bhakri* and *Shev*)		Iron-biofortified beans	
Intervention*	High iron	Control	High iron	Control	High iron	Control
Iron content (mg/kg-dry) per crop	10	2	86	21–52	86	50
Iron intake from staple (mg/d)	1·8	0·4	17·6	5·7	13·5	8·0
Per cent of total dietary iron	18	5	90	81	64	46
Length of feeding	9 months		6 months		4·5 months	
Sample size feeding	*n* 192 Iron-biofortified: *n* 92 Control: *n* 100		*n* 246 Iron-biofortified: *n* 122 Control: *n* 124		*n* 195 Iron-biofortified: *n* 94 Control: *n* 101	
Outcomes						
Iron status	Hb, serum ferritin, sTfR, α-1-acid-glycoprotein		Hb, serum ferritin, sTfR, CRP, α-1-acid-glycoprotein		Hb, serum ferritin, sTfR, CRP, α-1-acid-glycoprotein	
Cognitive function						
Subset selection	–		Participants from main study with lowest serum ferritin at screening and with complete baseline and endline cognitive data		Participants from main study with lowest serum ferritin at screening and with complete baseline and endline cognitive data	
Sample size subset	–		*n* 140		*n* 150	
	–		Iron-biofortified: *n* 88 Control: *n* 52		Iron-biofortified: *n* 72 Control: *n* 78	
	–		Three attention (simple reaction time, go/no-go, attentional network) and two memory (composite face effect, cued recognition task) tasks		Three attention (simple reaction time, go/no-go, attentional network) and two memory (Sternberg memory search, cued recognition task) tasks	
Other functional outcomes	Not reported		Not reported		Not reported	

AGP, α-1-acid-glycoprotein; CRP, C-reactive protein; SF, serum ferritin; sTfR, soluble transferrin receptor.

* Modified from(27).

Table 4. Cognitive assessment instruments and respective memory and attention domains

Task	Targeted domain	Assessed variable(s)	Details
Simple reaction time	Simple attention	Reaction time, ms	Participants are asked to press a button in response to the onset of the visual task stimulus. Involves no discrimination or decision-making
Go/no-go	Simple sustained attention and response control	Reaction time, ms	Neutral stimuli are randomly assigned to be either the go or the no-go stimulus Participants are asked to press a key with their dominant hand in trials when the go stimulus is presented, and to withhold a response in trials when the no-go stimulus is presented
Attentional task	Low-level attentional capture (alerting) Mid-level spatial selective attention (orienting) High-level control (conflict)	Reaction time, ms →Zero cues →Two cues →Alerting →Centre cue →Spatial cues →Orienting →Consistent flankers →Inconsistent flankers →Conflict	The task is a modified flanker task which is intended to probe three functions of attention in the context of information that is nominally irrelevant to the performance of the task Participants are presented with informative or uninformative visual cues regarding the location of an upcoming test stimulus and are required to press a button to indicate whether a centrally presented arrow is pointing to the left or right while disregarding flanking visual distractors on either side of the stimulus
Composite face effect	Influence of semantic memory on visual selective attention	Reaction time, ms →Hit rate, proportion →False alarm rate, proportion →Sensitivity, SD →Bias, SD	Participants are presented with facial stimuli with the top and bottom parts either being the same or different faces and the parts being aligned *v.* misaligned. The critical comparison involves stimuli in which the top and bottom portions are drawn from familiar *v.* unfamiliar faces. The canonical effect is that identification of one half of a target face is impaired when the two parts of the face are aligned relative to when they are misaligned; this performance decrement is only expected when the top and bottom parts are drawn from two familiar faces
Cued recognition	Memory	Reaction time, ms new items old items →Sensitivity, SD →Bias, SD →Percentage change in capacity, %	The task is a variation on the classic recognition memory paradigm, in which the participant is presented with a set of visual stimuli to be memorised. The participant is subsequently tested on those stimuli and an equal number of previously unseen stimuli, and asked to judge for each stimulus as to whether it was previously seen (old item) or not (new item). The stimuli may be partially covered; the amount of available visual information thus ranges from 50 to 100 %
Sternberg memory search	Memory	Reaction time, ms Intercept (new, old) Slope (new, old)	The task measures the rate with which memory for very recent information can be searched Participants are instructed to memorise graphical symbols, followed by presentation of a test stimulus. The participant indicates whether the stimulus was among the set of preceding stimuli The search rate differs systematically for old (previously encountered) rather than new (not previously encountered) information

(NCT01594359)(15). Participants received either iron-biofortified (86 mg/kg Fe, *n* 94) or conventional (50 mg/kg Fe, *n* 101) beans twice daily for 128 d (i.e. 4·5 months). Iron status (Hb, SF, soluble transferrin receptor, TBI, C-reactive protein, α-1-acid glycoprotein) was measured at base-, mid- (random serial sample) and endline (4·5 months). *Iron status.* At baseline, 37 % of women were anaemic (Hb < 120 g/l) and 86 % were iron deficient (SF < 15·0 µg/l). The iron-biofortified bean intervention significantly increased Hb concentrations by 3·0 g/l (from 121 to 124 g/l), SF concentrations by 5·5 µg/l (from 10·0 to 15·4 µg/l) and TBI by 1·5 mg/kg (from −0·7 to 0·8 mg/kg). In contrast, in the conventional intervention group, Hb concentrations decreased by 1·2 g/l (123–122 g/l), SF concentrations increased by 3·7 g/l (from 10·0 to 13·6 g/l) and TBI increased by 1·0 mg/kg (from −0·7 to 0·3 mg/kg). *Cognitive outcomes.* In a subset of 150 study participants (*n* 72 from the biofortification group, *n* 78 from the control group) with the lowest SF concentrations at baseline, measures of cognitive function were evaluated at base- and endline (4·5 months)(16). In the cognitive assessment sub-study, a total of 43 % of participants were anaemic and 92 % were iron deficient at baseline. Cognitive outcomes assessed were attention (i.e. simple reaction time, go/

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	A	B	C	D	E	F	G
India (13)	?	+	+	?	+	+	+
Philippines (12)	?	+	+	?	?	?	+
Rwanda (15)	?	+	+	+	+	+	+
India (14)	-	+	+	?	+	+	-
Rwanda (16)	-	+	+	+	+	+	+

Fig. 2. Risk of bias assessment for all included studies. Risk of bias was assessed by two authors independently and classified as either low (+), high (–) or unclear (?) for each respective domain. (A) Random sequence generation (selection bias); (B) allocation concealment (selection bias); (C) blinding of participants and personnel (performance bias); (D) blinding of outcome assessment (detection bias); (E) incomplete outcome data (attrition bias); (F) selective reporting (reporting bias); (G) other bias. Numbers in parentheses indicate listed references.

no-go, attentional network) and memory (i.e. mnemonic performance: Sternberg memory search, cued recognition). Iron-biofortified bean consumption predicted a 17 % larger change in the reaction time for the selective spatial attention and improved efficiency and specificity of both memory retrieval and memory search, compared with consumption of conventional beans.

Meta-analyses

Based on the evidence generated by these randomised trials, we conducted meta-analyses to examine the efficacy of iron-biofortification interventions on iron status and functional outcomes. We used a meta-analytical approach to estimate a summary measure for the potential benefit of consuming different iron-biofortified staple crops, with the aim to inform future efficacy trials and effectiveness studies.

Risk of bias in included studies. Risk of bias was assessed for all included studies in the meta-analysis and is presented in Fig. 2. In the three main randomised trials included, risk of bias was classified as low for most criteria. Participants were randomly assigned to interventions, but the sequence generation for randomisation was not described in any of the trials. Both participants and field personnel were blinded to the intervention in all three randomised trials, but blinding procedures used in RCT conducted in India(13) and the Philippines(12) were not clearly described. Furthermore, in the Philippines trial, it was not clear if all outcomes were reported as specified, as the study protocol and trial registration were not available. In the two sub-studies focusing on cognitive performance, participants were selected based on their iron biomarkers at baseline (e.g. iron deficiency or SF < 15·0 μg/l), indicating a high selection bias. Furthermore, the two intervention groups in Scott *et al.*(14) demonstrated baseline differences in iron status parameters indicating a high risk of other bias.

All three of the RCT reported iron status outcomes, two studies reported on cognitive outcomes in the domains of attention and memory, and none of the studies reported on physical performance or other functional outcomes.

Effects of interventions on iron status. A previous review reported results for Hb, SF and TBI concentrations(10). Findings demonstrated improvements in SF concentrations and TBI concentrations (but not Hb), with additional potential to benefit in individuals who were iron deficient at baseline(10). *Anaemia.* We conducted meta-analyses of data from the three included randomised trials, examining the efficacy of iron-biofortified interventions on anaemia and iron deficiency at endline. The effects of iron-biofortified staple crops on anaemia (Hb < 120 g/l) are presented in Fig. 3. There were no significant effects of iron-biofortified interventions on anaemia at endline (anaemia, OR 0·83, 95 % CI 0·58, 1·19). *Iron deficiency.* The effects of iron-biofortified staple crops on iron deficiency defined based on SF and TBI are presented in Fig. 4 (SF < 15·0 μg/l) and Fig. 5 (TBI < 0 mg/kg), respectively. There were no significant effects of iron-biofortified interventions on iron deficiency at endline (SF < 15·0, OR 0·86, 95 % CI 0·61, 1·23; TBI < 0 mg/kg, OR 0·82, 95 % CI 0·55, 1·21).

Effects of interventions on cognitive function. We conducted meta-analyses of data from the included RCT, examining the efficacy of iron-biofortified interventions on measures of cognitive function, attention and memory. *Attention.* The effects of iron-biofortified staple crops on cognitive measures of attention are presented in Fig. 6. A significant improvement in performance (as indicated by a reduction in reaction times) in the iron-biofortified *v.* the conventional groups was found in the go/no-go task (reaction time −0·25, 95 % CI −0·48, −0·01) and the following of attentional tasks: two cues (reaction time −0·25, 95 % CI −0·49, −0·02); alerting (reaction time −0·33, 95 % CI −0·67, 0·00); spatial cues (reaction time −0·35, 95 % CI −0·61, −0·10); orienting (reaction time −0·37, 95 % CI −0·61, −0·13). Iron-biofortified crop interventions significantly improved overall performance in tasks assessing the cognitive domain attention (reaction time −0·22; 95 % CI −0·32, −0·12) (Fig. 6). *Memory.* The effects of iron-biofortified staple crops on cognitive measures of memory are presented in Fig. 7. Participants in the iron-biofortification groups demonstrated significantly reduced reaction times in the cued recognition task (reaction time −0·57, 95 % CI −0·81, −0·33); the Sternberg memory search with new items (reaction time −0·33, 95 % CI −0·65, −0·01); and the composite face effect (reaction time −0·38, 95 % CI −0·72, −0·03). Iron-biofortified crop interventions significantly improved overall performance in tasks assessing the cognitive domain memory (reaction time −0·42, 95 % CI −0·57, −0·27).

Discussion

The findings from these meta-analyses highlight the potential of iron-biofortification interventions to improve cognitive performance with respect to attention and memory domains in vulnerable populations. This may inform the development of future trials and effectiveness

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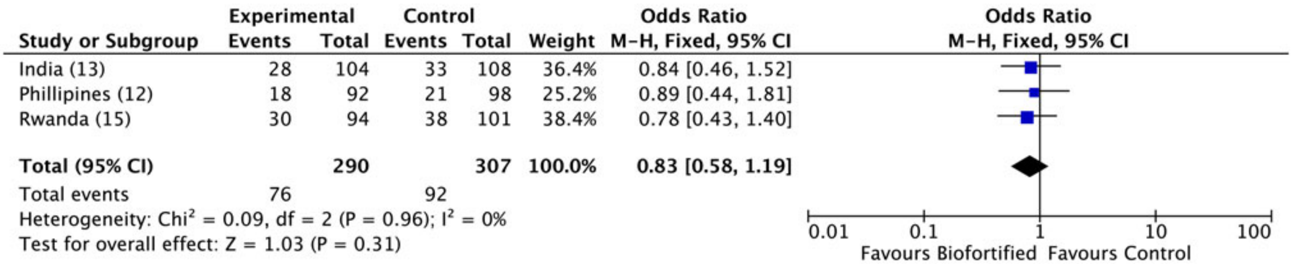
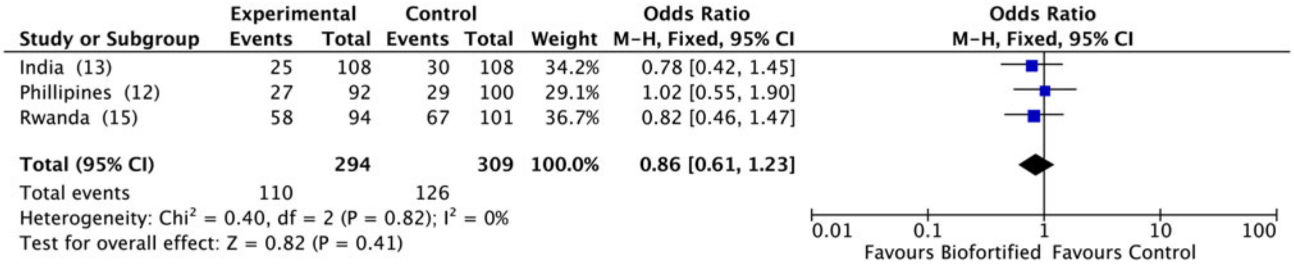


	Experimental		Control			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
India (13)	28	104	33	108	36.4%	0.84 [0.46, 1.52]
Phillipines (12)	18	92	21	98	25.2%	0.89 [0.44, 1.81]
Rwanda (15)	30	94	38	101	38.4%	0.78 [0.43, 1.40]
Total (95% CI)		**290**		**307**	**100.0%**	**0.83 [0.58, 1.19]**
Total events	76		92			

Heterogeneity: Chi^2 = 0.09, df = 2 (P = 0.96); I^2 = 0%
Test for overall effect: Z = 1.03 (P = 0.31)

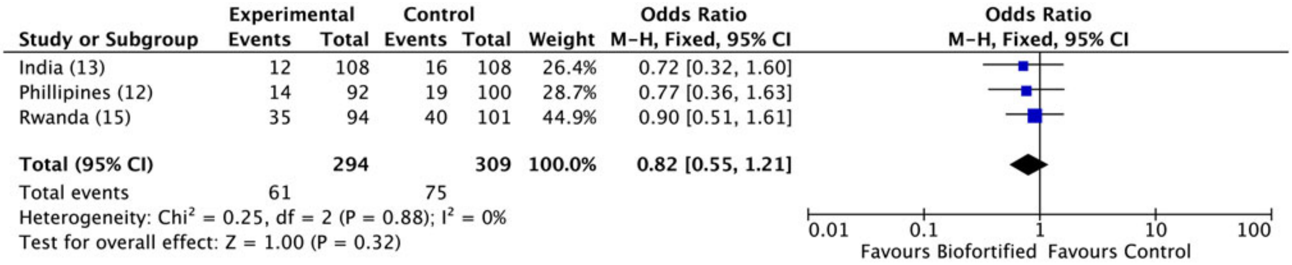
Fig. 3. Effect of iron-biofortified crop interventions on anaemia (Hb < 120 g/l). Numbers in parentheses in the study/subgroup column indicate listed references.



	Experimental		Control			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
India (13)	25	108	30	108	34.2%	0.78 [0.42, 1.45]
Phillipines (12)	27	92	29	100	29.1%	1.02 [0.55, 1.90]
Rwanda (15)	58	94	67	101	36.7%	0.82 [0.46, 1.47]
Total (95% CI)		**294**		**309**	**100.0%**	**0.86 [0.61, 1.23]**
Total events	110		126			

Heterogeneity: Chi^2 = 0.40, df = 2 (P = 0.82); I^2 = 0%
Test for overall effect: Z = 0.82 (P = 0.41)

Fig. 4. Effect of iron-biofortified crop interventions on iron deficiency (serum ferritin < 15·0 μg/l). Numbers in parentheses in the study/subgroup column indicate listed references.



	Experimental		Control			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
India (13)	12	108	16	108	26.4%	0.72 [0.32, 1.60]
Phillipines (12)	14	92	19	100	28.7%	0.77 [0.36, 1.63]
Rwanda (15)	35	94	40	101	44.9%	0.90 [0.51, 1.61]
Total (95% CI)		**294**		**309**	**100.0%**	**0.82 [0.55, 1.21]**
Total events	61		75			

Heterogeneity: Chi^2 = 0.25, df = 2 (P = 0.88); I^2 = 0%
Test for overall effect: Z = 1.00 (P = 0.32)

Fig. 5. Effect of iron-biofortified crop interventions on iron deficiency (total body iron < 0·0 mg/kg). Numbers in parentheses in the study/subgroup column indicate listed references.

studies of the potential impact of iron-biofortified crops on iron status and functional outcomes.

There is limited evidence on the potential efficacy of biofortified crop interventions on functional outcomes, such as cognition and physical performance. Iron is essential for normal brain development and cognitive function including, but not limited to energy metabolism, neurotransmitter production, and myelination(17,18). Several studies, most frequently in rats, have shown that changes in the brain occur in iron-deprived states, and that these changes are associated with deficits in cognitive development(19,20). Accordingly, cognitive impairment is among the most important functional consequences of iron deficiency(21). Iron-deficient infants and children have delayed attention, poor recognition memory, are more likely to be withdrawn from social interactions, and have long-term cognitive deficits. Emerging evidence from longitudinal studies suggest that uncorrected iron deficiency in infancy is associated with persistent cognitive deficits into early childhood, highlighting the importance of correcting these deficits in the critical early years of life(22,23).

Iron trials to examine the effects of iron repletion on cognitive function in human subjects and animals have provided conflicting evidence, and are constrained by limitations in study designs. However, human and animal studies with stronger study designs for causal inference suggest that iron repletion improves cognitive function(24,25).

Findings from this analysis suggest that iron biofortification interventions improved cognitive performance with respect to attention and memory domains. No research to date has been published on the efficacy of iron biofortification on physical performance or other functional outcomes. However, research in this area is forthcoming: the RCT in Rwanda (NCT01594359)(15) and Maharashtra, India (NCT02152150)(13) included evaluation of physical performance as a secondary outcome measure, and a recently completed RCT in young children in Mumbai, India (NCT02233764)(26) included cognition, immune function and growth as outcomes. Previous studies in different populations, including iron supplementation, have demonstrated that iron interventions improved physical work capacity and

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Study or Subgroup	Biofortified Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Simple Reaction Time								
India (14)	−123	115.3776	88	−63	206.3783	52	4.4%	−0.38 [−0.73, −0.04]
Rwanda (16)	−6	59.397	72	−8	61.8223	78	4.7%	0.03 [−0.29, 0.35]
Subtotal (95% CI)			**160**			**130**	**9.1%**	**−0.17 [−0.58, 0.24]**
Heterogeneity: Tau^2 = 0.06; Chi^2 = 3.00, df = 1 (P = 0.08); I^2 = 67%								
Test for overall effect: Z = 0.82 (P = 0.41)								
Go/No-Go								
India (14)	−67	122.5887	88	−30	93.8083	52	4.4%	−0.33 [−0.67, 0.02]
Rwanda (16)	−38	59.397	72	−28	52.9906	78	4.7%	−0.18 [−0.50, 0.14]
Subtotal (95% CI)			**160**			**130**	**9.1%**	**−0.25 [−0.48, −0.01]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.38, df = 1 (P = 0.54); I^2 = 0%								
Test for overall effect: Z = 2.05 (P = 0.04)								
Attention: 0 cues								
India (14)	8	64.8999	88	2	112.57	52	4.4%	0.07 [−0.27, 0.41]
Rwanda (16)	−54	93.3381	72	−47	97.1494	78	4.7%	−0.07 [−0.39, 0.25]
Subtotal (95% CI)			**160**			**130**	**9.1%**	**−0.01 [−0.24, 0.23]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.36, df = 1 (P = 0.55); I^2 = 0%								
Test for overall effect: Z = 0.05 (P = 0.96)								
Attention: 2 cues								
India (14)	−74	129.7998	88	−32	131.3316	52	4.4%	−0.32 [−0.67, 0.02]
Rwanda (16)	−154	93.3381	72	−135	97.1494	78	4.7%	−0.20 [−0.52, 0.12]
Subtotal (95% CI)			**160**			**130**	**9.1%**	**−0.25 [−0.49, −0.02]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.26, df = 1 (P = 0.61); I^2 = 0%								
Test for overall effect: Z = 2.13 (P = 0.03)								
Attention: Alerting								
India (14)	−82	86.5332	88	−32	112.57	52	4.4%	−0.51 [−0.86, −0.16]
Rwanda (16)	−99	76.3675	72	−88	52.9906	78	4.7%	−0.17 [−0.49, 0.15]
Subtotal (95% CI)			**160**			**130**	**9.1%**	**−0.33 [−0.67, 0.00]**
Heterogeneity: Tau^2 = 0.03; Chi^2 = 2.04, df = 1 (P = 0.15); I^2 = 51%								
Test for overall effect: Z = 1.93 (P = 0.05)								
Attention: Center cue								
India (14)	−45	72.111	88	−53	112.57	52	4.4%	0.09 [−0.25, 0.43]
Rwanda (16)	−58	110.3087	72	−58	88.3176	78	4.7%	0.00 [−0.32, 0.32]
Subtotal (95% CI)			**160**			**130**	**9.1%**	**0.04 [−0.19, 0.28]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.14, df = 1 (P = 0.71); I^2 = 0%								
Test for overall effect: Z = 0.35 (P = 0.73)								
Attention: Spatial cues								
India (14)	−57	79.3221	88	−9	121.9508	52	4.4%	−0.49 [−0.84, −0.14]
Rwanda (16)	−193	93.3381	72	−173	79.4858	78	4.7%	−0.23 [−0.55, 0.09]
Subtotal (95% CI)			**160**			**130**	**9.1%**	**−0.35 [−0.61, −0.10]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.16, df = 1 (P = 0.28); I^2 = 14%								
Test for overall effect: Z = 2.71 (P = 0.007)								
Attention: Orienting								
India (14)	−13	86.5332	88	45	168.855	52	4.4%	−0.47 [−0.81, −0.12]
Rwanda (16)	−135	76.3675	72	−115	61.8223	78	4.7%	−0.29 [−0.61, 0.03]
Subtotal (95% CI)			**160**			**130**	**9.1%**	**−0.37 [−0.61, −0.13]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.55, df = 1 (P = 0.46); I^2 = 0%								
Test for overall effect: Z = 3.08 (P = 0.002)								
Attention: Consistent flankers								
India (14)	−1	64.8999	88	−17	112.57	52	4.4%	0.19 [−0.16, 0.53]
Rwanda (16)	−74	101.8234	72	−56	79.4858	78	4.7%	−0.20 [−0.52, 0.12]
Subtotal (95% CI)			**160**			**130**	**9.1%**	**−0.01 [−0.39, 0.36]**
Heterogeneity: Tau^2 = 0.04; Chi^2 = 2.55, df = 1 (P = 0.11); I^2 = 61%								
Test for overall effect: Z = 0.06 (P = 0.96)								
Attention: Inconsistent flankers								
India (14)	−62	79.3221	88	7	140.7125	52	4.3%	−0.65 [−1.00, −0.29]
Rwanda (16)	−139	110.3087	72	−127	88.3176	78	4.7%	−0.12 [−0.44, 0.20]
Subtotal (95% CI)			**160**			**130**	**9.0%**	**−0.38 [−0.89, 0.14]**
Heterogeneity: Tau^2 = 0.11; Chi^2 = 4.70, df = 1 (P = 0.03); I^2 = 79%								
Test for overall effect: Z = 1.44 (P = 0.15)								
Attention: Conflict								
India (14)	−61	72.111	88	24	131.3316	52	4.3%	−0.86 [−1.22, −0.50]
Rwanda (16)	−65	59.397	72	−71	79.4858	78	4.7%	0.08 [−0.24, 0.41]
Subtotal (95% CI)			**160**			**130**	**9.0%**	**−0.38 [−1.31, 0.54]**
Heterogeneity: Tau^2 = 0.42; Chi^2 = 14.87, df = 1 (P = 0.0001); I^2 = 93%								
Test for overall effect: Z = 0.81 (P = 0.42)								
Total (95% CI)			**1760**			**1430**	**100.0%**	**−0.22 [−0.33, −0.12]**
Heterogeneity: Tau^2 = 0.04; Chi^2 = 46.95, df = 21 (P = 0.0010); I^2 = 55%								
Test for overall effect: Z = 4.09 (P < 0.0001)								
Test for subgroup differences: Chi^2 = 12.65, df = 10 (P = 0.24), I^2 = 20.9%								

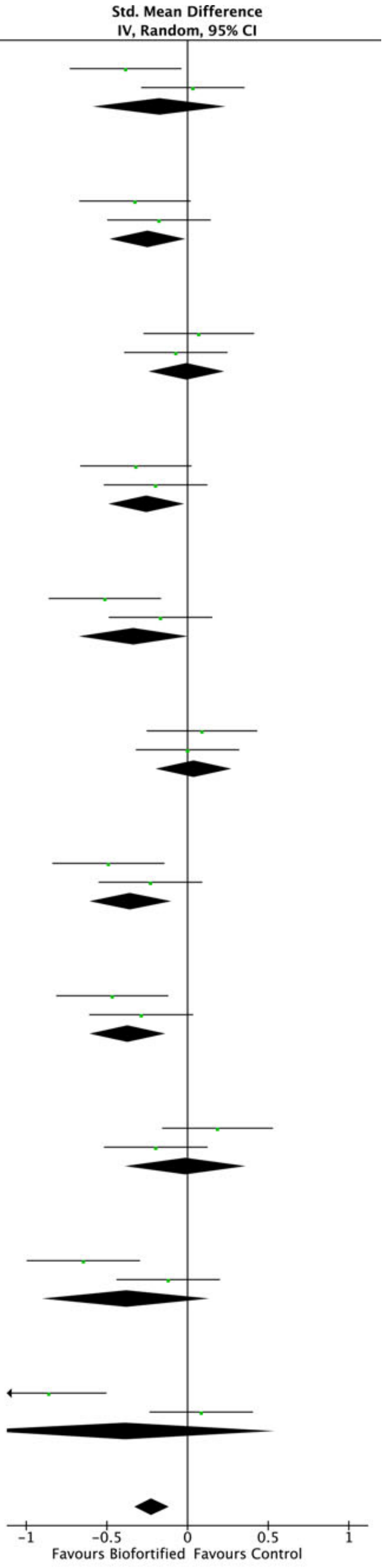

Fig. 6. Effect of iron-biofortified crops on cognitive outcomes: attention domain. Performance was measured as difference in reaction times. Details on the procedures of the performed tests can be found in Table 4. Numbers in parentheses in the study/subgroup column indicate listed references.

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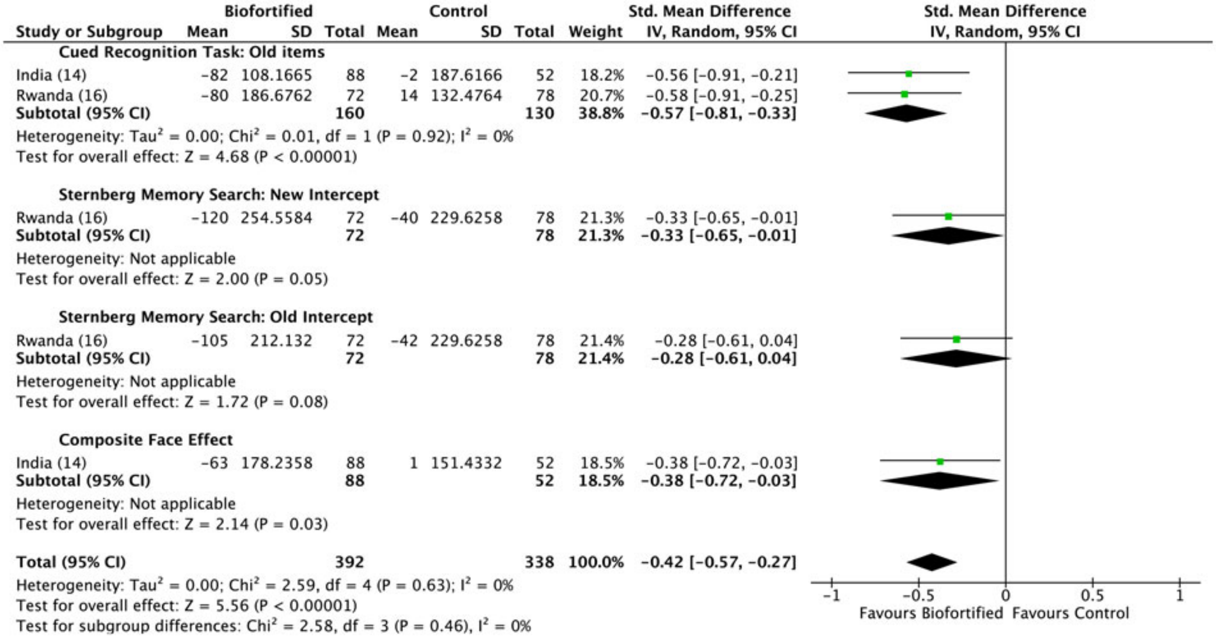

Study or Subgroup	Biofortified Mean	Biofortified SD	Biofortified Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cued Recognition Task: Old items								
India (14)	−82	108.1665	88	−2	187.6166	52	18.2%	−0.56 [−0.91, −0.21]
Rwanda (16)	−80	186.6762	72	14	132.4764	78	20.7%	−0.58 [−0.91, −0.25]
Subtotal (95% CI)			**160**			**130**	**38.8%**	**−0.57 [−0.81, −0.33]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0\%$								
Test for overall effect: Z = 4.68 (P < 0.00001)								
Sternberg Memory Search: New Intercept								
Rwanda (16)	−120	254.5584	72	−40	229.6258	78	21.3%	−0.33 [−0.65, −0.01]
Subtotal (95% CI)			**72**			**78**	**21.3%**	**−0.33 [−0.65, −0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.00 (P = 0.05)								
Sternberg Memory Search: Old Intercept								
Rwanda (16)	−105	212.132	72	−42	229.6258	78	21.4%	−0.28 [−0.61, 0.04]
Subtotal (95% CI)			**72**			**78**	**21.4%**	**−0.28 [−0.61, 0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.72 (P = 0.08)								
Composite Face Effect								
India (14)	−63	178.2358	88	1	151.4332	52	18.5%	−0.38 [−0.72, −0.03]
Subtotal (95% CI)			**88**			**52**	**18.5%**	**−0.38 [−0.72, −0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.14 (P = 0.03)								
Total (95% CI)			**392**			**338**	**100.0%**	**−0.42 [−0.57, −0.27]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.59$, df = 4 (P = 0.63); $I^2 = 0\%$								
Test for overall effect: Z = 5.56 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 2.58$, df = 3 (P = 0.46), $I^2 = 0\%$								

Fig. 7. Effect of iron-biofortified crops on cognitive outcomes: memory domain. Performance was measured as difference in reaction times. Details on the procedures of the performed tests can be found in Table 4. Numbers in parentheses in the study/subgroup column indicate listed references.

endurance(6,7), and provide biological plausibility of a potential benefit of iron biofortification on physical performance outcomes. Further research is needed to determine the efficacy of biofortified crop interventions on other functional outcomes and in different high-risk populations.

Findings expand upon previous research on the efficacy of iron-biofortification interventions demonstrating significant improvements in continuous measures of iron status such as SF concentrations; however, in these analyses, no significant effect was observed on categorical measures such as iron deficiency. This may be inherent to the statistical analysis where the power is sufficient to detect significant differences in continuous but not in categorical outcomes; alternatively, the effect size may be too small to move the population distribution adequately to affect anaemia and iron deficiency.

Comparing the effects of biofortification with those of fortification and supplementation should be considered when planning public health programmes and interventions. Although we are not aware of any studies comparing biofortification against conventional fortification or supplementation, meta-analyses of interventions focused on fortification or supplementation suggest larger effect sizes for these approaches. However, it is still unclear whether delivering the extra dose of the nutrients through the food matrix may be beneficial and this was partly the objective behind incorporating functional outcomes in the discussed trials and the meta-analyses. Future public health programmes and interventions should be designed to take advantage of the complementarity of these approaches; for example, in a setting with a high burden of iron deficiency, supplementation may be the preferred short-term intensive approach with fortification or biofortification more of a sustainable long-term maintenance strategy.

This review has several limitations, which warrant caution in the interpretation of findings. For example, only baseline and endline data were included in our analyses, and study durations differed between all studies; studies had heterogeneous designs, including duration, frequency of feeding administration, and included different biofortified crop interventions, risk populations and settings. The diversity of the populations, settings and design of the randomised trials constrains the comparability of findings. This is particularly true for the cognitive performance tests, as the studied populations differed regarding their age and sex (female and male adolescents *v.* female adults), setting (India *v.* Rwanda) and educational level (university students *v.* adolescents attending boarding schools). None of the reported studies assessed the long-term impact of iron-biofortified staple crop administration in children, where changes in the developing haematological and functional parameters may be more pronounced. More studies assessing developmental aspects are needed. Tasks should be standardised between different studies, while still accounting for potential cultural biases in the studied populations. Additional domains of cognitive performance should be considered for testing.

Findings to date from randomised trials suggest that iron-biofortified crops are an efficacious intervention to improve continuous measures of iron status. Furthermore, findings from this systematic review indicate that the consumption of iron-biofortified crops can improve cognitive function, in terms of attention and memory. Future studies are needed to generate the required evidence to successfully scale up biofortification

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efforts for populations in need. Assessment of other functional outcomes and in other high-risk populations is warranted to inform the development and scale-up of biofortified interventions to improve human health.

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Conflict of Interest

J. L. F., J. D. H. and S. M. have received competitive grant funding for conducting randomised efficacy trials of biofortified crops from HarvestPlus. J. D. H. has served as an expert consultant for HarvestPlus. S. M. also has an equity interest in a diagnostic start-up, planning to commercialise his work on point-of-care methods of nutritional assessment.

Authorship

J. L. F., A. F., and L. S. L. wrote the first draft of the manuscript; A. F. and L. S. L. extracted the data in duplicate and conducted data analyses in RevMan; J. L. F., J. D. H., and S. M. provided guidance in the interpretation of findings from data analyses; all authors revised the manuscript and reviewed the final version; J. L. F. has responsibility for final content.

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