Note: This is a rougher stage internal document that has not undergone our formal vetting process.

A closer look at the impact of iron supplementation on cognitive ability in children

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Summary

What I did

I searched for updates to our views on the cognitive effects of iron supplementation in children in two ways:

1. I examined the meta-analysis Low et al. 2013 more closely and considered the randomized controlled trials (RCTs) that underlie it.
2. I performed scientific literature searches for meta-analyses and primary RCTs published since Low et al. 2013.

What I found

I identified several reasons to be skeptical of Low et al. 2013 that I was not previously aware of.

The scientific literature search did not provide a significant update for our purposes.

What I believe about iron supplementation and cognition

I am fairly convinced that iron supplementation tends to increase general cognitive ability in children who have low iron status. Reasoning:

- It seems biologically plausible. Iron is a key part of hemoglobin, an important transport molecule for oxygen, and iron deficiency has a well-documented ability to impair physical performance. Iron also plays many other important roles in biochemistry throughout the body, including the brain.
- Low et al. 2013 is the only recent meta-analysis of randomized controlled trials I identified that covers a pertinent age range (5-12 years) and does not have limitations that severely restrict its informativeness for our purposes. In a subgroup analysis of six RCTs, it reports that iron supplementation increases general cognitive ability by 0.29 standard deviations (95% confidence interval 0.07 to 0.51) in children with anemia, a rough marker of iron deficiency. This translates approximately to a 4.4-point increase in IQ. Children without anemia did not benefit from iron supplementation, which is what the

biology predicts. Although I am often skeptical of subgroup analyses, in this case it has a clear and compelling biological rationale.

- I identified limitations of Low et al. 2013 that lead me to increase my internal and external validity adjustments (below), but these are not fatal concerns in my opinion. My primary concern is that the trials with largest effect sizes all come from one research program in India in the 1980s. However, there is enough consistency across trials in different locations to be somewhat reassuring. Among the six trials that reported data from anemic subjects, all reported positive effect sizes, although only one was individually statistically significant. These trials were conducted in India, Thailand, Indonesia, and Mali.

These updates also impact our internal and external validity adjustments for the impact of iron supplementation in adults, since our estimates in adults derive in part from our estimates in children. This is reflected in the new external and internal validity adjustments below.

Recommended changes to our CEA (implemented)

As a result of this work, I recommend more severe internal and external validity adjustments for our estimates of the cognitive effects of iron in children and adults:

- Internal validity adjustment for children: 0.8 to 0.7
- External validity adjustment for children: 1.0 to 0.7
- Internal validity adjustment for adults: 1.0 to 0.85
- External validity adjustment for adults: 0.65 to 0.6

A closer look at Low et al. 2013

Our iron supplementation, fortification, and biofortification CEAs that include cognitive benefits in children rely on the findings of a meta-analysis, Low et al. 2013. This meta-analysis includes randomized controlled trials (RCTs) of daily (≥ 5 days/week) iron supplementation in children 5-12 years old, nearly all in low- or middle-income settings.

It reports the following cognition-related outcomes:

- Iron supplementation improved global cognitive performance in nine studies (SMD of 0.50; 95% confidence interval 0.11 to 0.90). This represents measures including IQ tests, “author-adapted scales of global cognitive performance”, and “overall school performance”.[1] This is the most inclusive outcome.

[1] “Global cognitive performance was reported in 9 studies: 5 studies used IQ (tests: Raven Progressive Matrices, Wechsler Intelligence Scale for Children [WISC], Test of Non-verbal Intelligence 2nd Edition), 3 studies used authoradapted scales of global cognitive performance (visual memory, digit span, mazes

- In subgroup analysis, iron supplementation improved global cognitive performance in six studies of children who were anemic at baseline (SMD 0.29, 95% confidence interval 0.07 to 0.51), but not in four studies of children who were not anemic (SMD 0.01, 95% confidence interval -0.10 to 0.11).
- In five studies that specifically reported measures of intelligence quotient (IQ), iron supplementation did not have a significant effect on this measure of cognitive performance (SMD of 0.36; 95% confidence interval of -0.22 to 0.95[2]), although there was a modest trend toward improvement (p = 0.2).
- In subgroup analysis, iron supplementation increased IQ in three studies of children who were anemic at baseline (**SMD of 0.30**, 95% confidence interval of 0.01 to 0.60[3]), but not in two studies of children who were not anemic (SMD 0.01, 95% confidence interval -0.12 to 0.13[4]).
- On more granular tests of cognitive ability, iron supplementation improved scores on the maze test and clerical task, but not digit span, visual memory, math or language tests.[5]

Superficially, this appears to paint a reasonably compelling picture that iron supplementation improves cognitive performance in children, and that this is only observed in those who have anemia, a marker of possible iron deficiency.

Our iron CEAs have focused on the bolded estimate representing IQ in children who are anemic. Although that finding rests on only three trials, it is nearly identical to the estimate for global cognitive performance that rests on six trials. It is worth noting that all estimates suggesting improved cognitive performance have wide confidence intervals that approach zero.

We have often found that we update negatively on meta-analysis findings when we examine them in greater detail. To investigate this possibility, we examined the trials underlying them.

Trial	Subjects	Baseline iron status	Intervention	Measure of intelligence	Findings	Notes
Seshadri 1982 (study 2)	28 Indian boys 5-6 years old	Hemoglobin of 96.2-98.2 g/L (anemic	Iron and folic acid supplements twice daily for 60	Wechsler intelligence scale for children	Supplementation significantly increased	Experimental design was confounded by folic acid and did not

test, clerical task tests with maximum scores of 40), and 1 study used overall school performance." Low et al. 2013, Pg. E793.
[2] Converted from IQ points to SMD for consistency with other measures.
[3] Converted from IQ points to SMD for consistency with other measures.
[4] Converted from IQ points to SMD for consistency with other measures.
[5] "Compared with children in the control group, children who received iron supplementation had superior performance on the maze test (MD 1.30, 95% CI 0.9 to 1.7; p < 0.001, I2 = 0%, 4 studies, n = 288) and clerical task scores (SMD 0.44, 95% CI 0.14 to 0.75; p = 0.005, I2 = 30%, 4 studies, n = 290). There was no difference between iron supplementation and control for other measures including digit span, visual memory score, math scores and language test scores (Appendix 2)." Low et al. 2013, Pg. E796.

	“from a low socio-economic group”	on average)	days vs. placebo. Supplements delivered a daily total of 40 mg iron and 0.2 mg FA.	adapted into Gujarati (IQ)	hemoglobin by 23 g/L relative to control. Supplementation significantly increased verbal IQ, performance IQ, and total IQ (+11) relative to control, although the between-group difference in change over the supplementation period was a bit smaller (IQ +8).	satisfy inclusion criteria of the meta-analysis: “We included studies that provided iron supplementation along with a second intervention (cointervention), provided that the cointervention was applied identically in the control arm.”
Gopaldas 1985	210 Indian boys 8-15 years old	“Iron status unknown. Subgroups: anemic, nonanemic”	30-40 mg ferrous sulfate per day vs. placebo for 60 days. Translates to 6-8 mg iron per day (skeptical).	“Author-adapted scale”. Low et al. states that this includes “clerical task test, visual memory test, digit span test and maze test”.	Supplementation significantly increased global cognitive performance by SMD of 0.75. It non-significantly increased global cognitive performance by SMD of 0.98 in children with anemia and 0.63 in children without anemia.	Unable to obtain abstract or full text. Information drawn from Low et al. 2013. The iron per day figure is suspiciously low; I suspect a possible confusion between mass of ferrous sulfate and mass of elemental iron.
Seshadri 1982 (study 1)	94 Indian boys and girls 5-8 years old “from a low socio-economic group”	Hemoglobin of 102-107 g/L (anemic on average)	20 mg iron and 0.1 mg folic acid supplement once daily for 60 days vs. no intervention	Wechsler intelligence scale for children adapted into Gujarati (IQ)	Data are reported in 3 age groups. All supplemented groups saw significant 9-16 g/L increases in hemoglobin and in verbal IQ, performance IQ, and total IQ (+20-23) relative to control. However, the between-group difference in change over the supplementation period was smaller (IQ +7-13). When examining iron deficient vs. replete subgroups, there was no consistent difference.	They did not use a placebo pill for the control group and the investigators were not blinded. The intervention groups started off with substantially higher total IQ, making the between-group difference in change more informative.

Seshadri 1989 (study 4)	130 Indian girls 8-15 years old. “Underprivileged.”	Hemoglobin of 102.8-103.9 g/L (anemic on average)	60 mg iron per day as ferrous sulfate vs. placebo for two 60-day periods separated by two months. Reported results are from the end of the second supplementation period.	Author-adapted scale composed of visual recall, digit span, mazes, a clerical task, and a total score	Supplementation significantly increased hemoglobin by 19 g/L relative to control. Supplementation significantly increased maze, clerical, and total cognitive score (+3.6) relative to control, but not visual recall or digit span. (Low et al. translates this to SMD of +0.37). In subgroup analysis,effect on total cognitive score was only significant in anemic girls, but n was small in nonanemic group.	The meta-analysis appears to have described the cognitive test incorrectly. Cognitive test results are not in IQ units.
Kashyap 1987	130 Indian girls 8-15 years old. “Underprivileged.”	Hemoglobin of 104.2 g/L (anemic on average)	60 mg iron per day as ferrous sulfate vs. placebo for two 60-day periods separated by two months	Author-adapted scale composed of visual recall, digit span, mazes, a clerical task, and a total score	Results similar to Seshadri 1989 (study 4), except cognitive benefit was no longer significant at 12 months (4 months after the end of the second supplementation period).	I’m nearly certain this is the same study as Seshadri 1989 (study 4), due to several study details being identical and Seshadri citing Kashyap when discussing subject characteristics. Baseline and outcome values are very similar but not identical, for unknown reasons. SEM values are very different, also for unknown reasons.
Soemantri 1989	130 rural Indonesian boys and girls 8.1-11.6 years	Hemoglobin in nonanemic groups 132.1 - 133.0; in anemic groups 96.8 - 97.7. Hematocrit and transferrin saturation also reflected lower iron	2 mg/kg iron per day as ferrous sulfate vs. placebo for 3 months. Works out to about 56 mg of iron per day on average.	Raven’s colored progressive matrices (IQ), educational achievement test with language, math, biology, and social science sections	Supplementation increased hemoglobin by 32.9 g/L in the anemic group and also increased hematocrit and transferrin saturation. Little change in IQ but educational achievement tests tended to improve. No tests of statistical	

		status in anemic groups.			significance were performed. Possible iron status and cognitive benefits persisted 3 months after the withdrawal of supplementation.	
Ayoya 2012	406 Malian boys and girls 7-12 years with schistosomiasis	Hemoglobin less than 120 g/L (anemic)	Praziquantel (antihelminthic drug); praziquantel plus iron; praziquantel plus multiple micronutrients; praziquantel plus iron plus multiple micronutrients 5 days per week for 12 weeks. Iron was ferrous sulfate containing 60 mg of iron. Multiple micronutrient tablets contained 12 mg of iron.	School grades	No effect of iron treatment on grades	Placebos were not used for control conditions, potentially introducing bias.
Sungthong 2004	397 Thai boys and girls 6-13 years	Hemoglobin of 121.2 - 121.8 g/L (non-anemic on average)	60 mg iron as ferrous sulfate 5X/wk, 1x/wk, or placebo for 16 weeks. 400 mg albendazole (antihelminthic) at baseline and 11 wk for all groups.	Test of Nonverbal Intelligence, second edition (IQ). Language and math assessed by school exam.	Hemoglobin increased 3.1 (5X/wk) and 2.3 g/L (1X/wk) relative to placebo. Ferritin increased more markedly in iron groups, particularly 5x/wk. IQ declined 3 points in the 5x/wk group relative to placebo. No effect on language or math scores.	
Pollitt 1989	1,358 Thai boys and girls 9 - 11 years	Hemoglobin of 99-129 g/L depending on group (iron-deficient anemic, iron-depleted, iron-replete). Iron-deficient anemic group had low	200 mg albendazole at baseline and 3 months for all groups. 10 mg iron per day for 2 wk, followed by 20 mg per day for 14 wk, as ferrous sulfate, vs. placebo.	Raven's colored progressive matrices (IQ).	Hemoglobin (+14 g/L), ferritin, and transferrin saturation increased in iron supplemented iron-deficient anemic group relative to placebo. Hemoglobin, ferritin, and transferrin saturation increased in all	

		hemoglobin, ferritin, and transferrin saturation. Iron depleted group had normal hemoglobin but low ferritin and transferrin saturation.			groups, but particularly the iron supplemented iron-deficient anemic group (+14 g/L hemoglobin relative to placebo). “There was no evidence that iron treatment had an effect on IQ or on either of the two educational achievement measures.”	

Closely examining this meta-analysis, including its underlying studies, revealed several concerns:

- Seshadri et al. 1982 (study 2) does not conform to the stated inclusion criteria of the meta-analysis because the intervention included both iron and folic acid, without folic acid in the control group. This seems like a modest concern since we are not aware that folic acid supplementation impacts cognitive ability in children.[6]
- The primary meta-analysis of nine trials included the same trial twice (Seshadri et al. 1989, study 4, and Kashyap et al. 1987). However, the effect size estimate (SMD)[7], number of participants[8], and standard deviation reported in the meta-analysis are substantially different for each instance of this trial. This appears to be explained by 1) inconsistencies in data extraction by the meta-analysis team, and 2) unexplained differences in the data contained in the two papers themselves. I view this as a modest concern because:

[6] In a quick literature search, I identified one meta-analysis of folic acid supplementation trials suggesting that supplementation does not significantly impact cognitive ability in children. I have not vetted this meta-analysis or done a more thorough literature search and it is possible that my views could change with additional investigation. Ip et al. 2017, table 2.

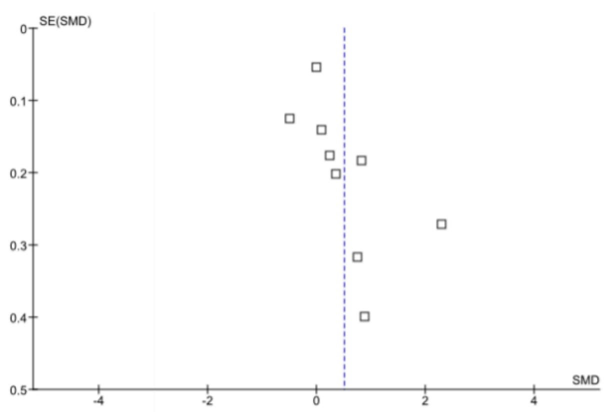
[7] The absolute effect sizes extracted from each study are nearly identical but SMD differs greatly due to different standard deviations extracted (Low et al. 2013, figure 2). I am able to replicate the absolute effect sizes and standard deviations attributed to Seshadri et al. 1989 in the meta-analysis by 1) calculating a weighted mean of endline values for total cognitive score of anemic and non-anemic groups in tables 12 and 13 of Seshadri et al. 1989, and 2) converting SEM of endline values in tables 12 and 13 of Seshadri et al. 1989 to standard deviation and taking a weighted mean of anemic and non-anemic groups. Seshadri et al. 1989 and Kashyap et al. 1987 report substantially different SEM values, despite absolute effect sizes that are nearly identical, and I do not know why.

[8] Low et al. extracted the number of participants that were randomized in Kashyap et al. 1987. In contrast, Low et al. 2013 extracted the number of participants that completed cognitive assessment from Seshadri et al. 1989, which reflects substantial attrition. This is why n differs in Low et al. 2013 (figure 2), despite the fact that Kashyap et al. 1987 and Seshadri et al. 1989 appear to be the same trial.

    - Kashyap et al. 1987 has the third-largest effect size of the nine trials in Low et al. 2013, and the fifth-largest sample size, so its impact on the nine-trial pooled result is potentially meaningful.
    - It suggests that the authors of Low et al. 2013 were not careful and may have made other errors in their literature search and/or data analysis that I may not have caught.
    - Unexplained differences in the data contained in the two primary papers raise concerns about the quality of the research conducted by this group, which is responsible for five of the nine trials reporting cognitive outcomes.
    - However, Kashyap et al. 1987 is not included in the meta-analysis of six studies only reflecting subjects with anemia. This is the most pertinent analysis for our purposes and it is not affected by this duplication, so this substantially mitigates my level of concern.
- Of the nine trials reporting cognitive outcomes in Low et al. 2013, the five with the largest positive effect sizes, and all four trials that reported a statistically significant positive result, were conducted in India by the same research team. In contrast, the remaining four studies were conducted in Thailand, Indonesia, and Mali and reported smaller, mostly nonsignificant, and in one case significantly negative effect sizes. However, among the six trials that reported data from *anemic* participants, all reported positive effect sizes, although only one was individually statistically significant. Among these six trials, three were conducted outside India, and the trial with the third-largest effect size was conducted in Indonesia (Soemantri et al. 1989), which is reassuring. I view this as a moderate concern because:
    - The overall pooled finding, which incorporates the most trials, may have low external validity to settings other than India, and perhaps even to settings other than 1980s Gujarat. However, this is substantially mitigated by the findings in anemic participants that are less reliant on the Indian studies, while being more relevant to our hypothesis of interest.
    - The positive nine-trial result rests entirely on trials conducted by one research group in the 1980s in Gujarat state, India, that are not consistent with the findings of other independent trials. To believe the pooled result, we have to have a high level of confidence in the quality and relevance of the research of this individual research group. This would be less of a concern if there were several fully independent estimates that were consistent with one another. However, again this is partially mitigated by the pooled finding for anemic participants, which relies on roughly consistent findings across independent studies. I remain somewhat concerned about this because the two trials with the largest effect sizes were from the Indian research group in Gujarat and without these, the pooled result would be substantially smaller and probably lose its statistical significance.
- I did not identify substantial concerns with the pooled IQ result, although it rests on only three trials. The trial with the largest effect size was conducted by the research group in

Gujarat, yet each of the three trials was fully independent and reported positive effects of iron on IQ (although two were not individually statistically significant).

- In addition, Low et al. 2013 performed risk of bias analysis on the nine trials,[9] concluding that "no studies reporting cognitive outcomes were at low overall risk of bias."[10] Study quality ranged considerably, but most manuscripts did not report important pieces of information such as randomization procedures and participant dropout, potentially concealing important sources of bias.
- The authors of Low et al. 2013 suggest that a funnel plot of the nine RCTs in the overall pooled analysis reveals "no asymmetry and no evidence of publication bias",[11] but I disagree with their assessment. In my view, this plot appears asymmetrical, suggesting that publication bias in smaller trials may be inflating effect size (see graph below). However, it is difficult to come to strong conclusions from nine studies, and they did not perform this analysis on the six studies that focused specifically on subjects with anemia. Eyeballing the effect sizes and error bars for these six studies,[12] asymmetry could be somewhat of a concern, but likely less than in the full pooled analysis. This concern is related to the previous concern about the Indian studies, since these are smaller studies reporting larger effect sizes.



In sum, further examination of Low et al. 2013 and its underlying trials revealed reasons for concern that have reduced my confidence in the meta-analysis somewhat. Knowing that we typically have lower confidence in meta-analyses after examining them more closely, we had already applied an internal validity adjustment of 0.8 to these findings in our iron cost-effectiveness analysis. However, I now feel that 0.7[13] is more appropriate.

Furthermore, given that the largest effects of iron on cognitive ability were reported in Indian trials only, and our cost-effectiveness analysis models sub-Saharan Africa, I believe a more

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[9] Low et al. 2013, table 2.
[10] Low et al. 2013, Pg. E793
[11] Low et al. 2013, supplement 3.
[12] Low et al. 2013, figure 2.
[13] Subjective estimate.

severe external validity adjustment of 0.7[14] is appropriate for IQ in children (formerly 1.0). Since half our estimate of the impact of iron on cognitive ability in adults derives from our estimate in children, I also believe a more severe external validity adjustment of 0.85[15] (formerly 1.0), and a more severe internal validity adjustment of 0.6[16] (formerly 0.65), are appropriate for IQ in adults.

Literature search for more recent meta-analyses

The Low et al. meta-analysis was published in 2013. I performed a scientific literature search for more recent meta-analyses. I searched PubMed with the search terms "meta-analysis iron cognit*" on the "most recent" setting. This returned 38 results. I considered meta-analyses that were published in 2013 and later, report pooled findings from RCTs of iron supplementation in children over two years old, and report cognitive outcomes. This left three meta-analyses:

- Thompson et al. 2013. This meta-analysis represents an age range of 2-5 years, which overlaps little with that of Low et al. 2013 (5-12 years). It focuses on measures of cognitive and motor development rather than cognitive ability.[17] It does not differentiate based on baseline iron status. It pooled two RCTs, reporting that iron supplementation increased measures of cognitive development by a SMD of 0.25 (95% confidence interval 0.06–0.45). Notably, this includes a RCT in rural Zanzibar.[18]
- Wang et al. 2013. This is a Cochrane meta-analysis representing children under age 3 with iron deficiency anemia. It focuses on measures of cognitive and motor development rather than cognitive ability.[19] In five pooled trials lasting up to 30 days, there was no significant effect of iron supplementation on cognitive development. In two trials lasting more than 30 days that were not pooled, one reported a statistically significant improvement of a measure of cognitive development, while a second reported a nonsignificant trend toward improvement. 30 days is a shorter duration than the trials represented in Low et al. 2013, which ranged from 60 days to 16 weeks (see table above).
- Guo et al. 2015. This meta-analysis represents an age range of 5-12 years, which overlaps fully with that of Low et al. 2013. It included five studies, vs. nine for Low et al. 2013, reporting that iron supplementation does not significantly improve global cognitive scores ("Mean difference 1.05, 95% confidence interval [CI] -2.69 to 4.79, P<0.01").[20] I have little confidence in this finding for several reasons:

[14] Subjective estimate.
[15] This is halfway between 0.7 and 1.0.
[16] Subjective estimate.
[17] As measured by tests such as the Bayley Scales of Infant Development. These test how far an infant or toddler has progressed along developmental milestones, rather than testing adult-like cognitive abilities.
[18] Stoltzfus et al. 2001.
[19] As measured by tests such as the Bayley Scales of Infant Development. These test how far an infant or toddler has progressed along developmental milestones, rather than testing adult-like cognitive abilities.
[20] This p-value doesn't make sense.

- The trials measured global cognitive performance using different measures and the authors appear not to have converted these measures into a commensurable scale such as SMD. The results of the meta-analysis are therefore hard to interpret.
- The paper does not differentiate between children who had anemia and who did not.
- It is not clear from the authors' sparse description of their inclusion criteria why they included so many fewer studies than Low et al. 2013.
- The paper has features that make me question its credibility, such as claiming a p-value of less than 0.01 for a finding that is clearly nonsignificant.[21]
- It was published in an online-only open-access journal that was established in 2008, which is a pattern typically associated with very-low-quality journals with weak peer review procedures. It has an impact factor of 1.1, suggesting that its papers are rarely cited.

Overall, I do not believe these meta-analyses provide a significant update beyond Low et al. 2013, for the following reasons:

- Guo et al. 2015 has several features that make me greatly discount its informativeness.
- Thompson et al. 2013 and Wang et al. 2013 focus on cognitive and motor development in children 0-3 years old rather than adult-like cognitive abilities, which are what our cost-effectiveness analysis is based on. These two measures are plausibly related, but I am not sure how closely, nor am I sure whether we should expect them to be impacted similarly by iron supplementation.
- Most of the trials represented in Wang et al. 2013 lasted 30 or fewer days, which is substantially shorter than the trials represented in Low et al. 2013. I do not have a strong sense of the importance of this difference, but it seems plausibly important.

Literature search for more recent RCTs

I did not identify reasonable-quality meta-analyses in older children more recent than Low et al. 2013, so I searched for more recent primary RCTs. I searched PubMed with the search terms "(iron OR ferrous) supplement* cognit*" on the "most recent" setting. This returned 354 results. I included all iron supplementation RCTs in children (mean age <18) published after July 2013[22] that isolate the effects of iron and refer to cognitive outcomes in the title or abstract. This left three trials:

- Rezaeian et al. 2014 randomized Iranian high school girls to receive either 10 mg iron per day or placebo, twice a week for 16 weeks. This is a very modest level of

[21] "Mean difference 1.05, 95% confidence interval [CI] -2.69 to 4.79, P<0.01". Guo et al. 2015, Pg. 16108.
[22] The date that Low et al. 2013 searched Embase.

supplementation. At baseline, the girls were mildly anemic. They report that supplementation improved the score on a test of attention (Toulouse-Piéron test), which was the only cognition-related outcome.

- Berglund et al. 2018 is a long-term follow-up of a trial that randomized "marginally low birth weight" Swedish infants to receive 0, 1, or 2 mg per kg body weight per day of iron supplements from 6 weeks to 6 months of age. The manuscript does not report the infants' baseline iron status but states that infants with a hemoglobin level lower than 90 mg/L were excluded.[23] At 7 years of age, there was no detectable impact of iron on a measure of global intelligence, although there was some suggestion that it reduced the risk of behavior problems.
- Gahagan et al. 2019 is a long-term follow-up to a trial that randomized healthy Chilean infants to a low-iron (2.3 mg/L) or high-iron (12 mg/L) formula for 6 months. None of the infants had iron-deficiency anemia at baseline. At a mean age of 16.2 years, "those randomized to iron-fortified formula had lower scores than those randomized to low-iron formula for visual memory, arithmetic achievement, and reading comprehension achievement."[24] It is worth noting that human breast milk is quite low in iron (~0.4 mg/L),[25] so the high-iron formula supplied much more iron than an infant would normally obtain, possibly accounting for its adverse effects.

Overall, these trials do not provide a significant update for our purposes. Two of the trials are long-term follow-up studies of infant iron supplementation and therefore have little relevance to our cost-effectiveness analysis. The third trial reports that iron supplementation improves a measure of attention. This seems broadly consistent with the findings of Low et al. 2013 that iron supplementation improves cognitive abilities in children with anemia, although I am unsure of the relationship between attention and other measures of general cognitive ability such as IQ.

Conclusions

Upon closer inspection, Low et al. 2013 has a number of limitations that were not initially obvious and lead me to recommend reducing our internal and external validity adjustments for the child and adult cognitive effects of iron supplementation. However, since we had already incorporated some amount of skepticism into our estimates *a priori*, these are not large changes and I continue to believe that iron supplementation probably meaningfully increases cognitive ability in children with anemia.

A scientific literature search did not identify evidence that provides a significant update for our purposes.

Here are a few ways in which my conclusions could be wrong:

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[23] Corresponds to moderate anemia in a 6-month-old.
[24] Gahagan et al. 2019, abstract.
[25] According to US Department of Agriculture data.

- It seems possible that hidden sources of bias, particularly in the Indian studies, could be substantially exaggerating effect sizes. This could lead to overestimation of the size of the effect, perhaps to such an extent that we would no longer be convinced that an effect exists at all. I have already incorporated this possibility into my internal validity adjustments.
- It is difficult to assess publication bias in this literature due to the limited number of studies. It seems possible that this could account for the majority of the effect size. I have already incorporated this possibility into my internal validity adjustments.
- The Indian trials may not be outliers but in fact reflect real, externally valid treatment effects. If that is true, our internal and external validity adjustments are too severe.