Summary

Introduction

- The effect of iron fortification on the risk of iron deficiency in FH's program might differ from the effect estimated in the meta-analysis for several reasons:

    1) The quantity of iron intake from fortified products consumed in the academic studies might be different to the level in FH's program.

    2) Conditional on the quantity of iron intake, the amount of iron absorbed might differ between the meta-analysis and FH's program, for several reasons:

        a) Different fortification compounds and vehicles may have different absorption rates. FH uses NaFeEDTA in wheat flour, but the academic studies use many different fortification compounds (e.g. NaFeEDTA, ferrous sulphate, ferrous fumarate, ferric pyrophosphate, electrolyte irons and others) in many different vehicles (e.g. rice, salt, sauce, milk and others).

        b) Certain substances inhibit the absorption of iron (e.g. tannins and phytates), and certain substances enhance the absorption of iron (e.g. ascorbic acid - i.e. vitamin C). The beneficiaries of FH's program might consume different levels of inhibitors/enhancers alongside the fortified foods compared to the recipients in the academic studies.

        c) It is possible that the level of absorption also depends on baseline levels of iron in the blood (absorption rates may be higher when initial iron levels are

lower).

3) Conditional on the amount of iron absorbed, it is possible that iron has a greater effect on health outcomes (including averting risk of iron deficiency) for a lower initial iron status.

Bottom-line

- I have made an adjustment for (1) and (2a).
- I have not made an adjustment for (2b) because we don't have information on the diets that the FH or academic study beneficiaries consume alongside the fortified foods.
    - Stephan believes that diets across developing countries typically contain a high level of phytates, and he does not have reason to believe that absorption inhibitors differ between the meta-analysis and FH context.
- I have not made an adjustment for (2c) because we don't have information on baseline iron levels for FH or academic study beneficiaries.
- For (3), we assume that the relationship is linear.
    - We don't have much information on the shape of the relationship between iron absorbed and health effects for different initial levels of iron status, and from a very quick look into it Stephan wasn't convinced there was strong evidence against a linear relationship.
- Bottom-line:
    - Fortify Health's beneficiaries **intake approximately 41.8%-66.8% as much iron** as in the academic studies. The academic studies add iron to fortified foods at a higher concentration.
    - However, FH deliver iron through the NaFeEDTA fortification compound, which is typically absorbed at a greater rate than the fortification compounds used in the academic studies (approx 1-15 times greater rate depending on the compound used in the particular study).
    - After adjusting for the difference in absorption rates by fortification compound, **my best guess is that 121%-167% as much additional iron is absorbed into the body through FH's program compared to the academic studies**. See cells B43 and C43 in this spreadsheet.
    - We therefore believe that the effect of FH's program on iron deficiency will be greater than the academic estimates. However, the quantity of iron delivered in FH's program is much lower than in iron supplementation programs, and accordingly we expect the effect on iron deficiency to be lower. Bounding the cost-effectiveness of FH's program using the academic effect size estimates from iron fortification and iron supplementation, **we believe that FH's program is 9.5-14.4x cash, with a very rough best guess at about 11x cash.**

1) Differences in quantity of iron intake

- I contacted an author of the meta-analysis (Prof. Sachdev) who sent me this document.[1] I combine the information in that document with the information from Online Supplementary Table 2.
- I have used that to back out an estimate of average additional quantity of iron intake from fortified foods in the studies in the meta-analysis in this spreadsheet:
    - I take the 21 studies included in the meta-analysis regression on the iron deficiency outcome variable (from which we take the effect size estimate).
    - I use the information in the Online Supplementary Table 2 to estimate the quantity of additional iron intake from the fortified food in each of the underlying studies. To do so, I use the "Fortification intake per day (mg)" (column E). I believe this column tells us the weight of additional elemental iron that is consumed through the fortified food per day (in this spreadsheet, I have explained why I believe that, as well as in this footnote[2]).
    - I then estimate the weekly and the annual additional iron intake in each study (see below for a discussion about aggregation over time).
    - I then take a weighted average of the weekly/annual figures across the studies, using the meta-analysis weights that Prof. Sachdev sent me (see column B).
    - Note that there is no information on either the fortification intake per day or fortification frequency (days per week) for 3/21 studies, and so I just take a weighted average across the remaining 18 studies.
    - Aggregating annually, I find that the average additional quantity of iron intake in the studies = 1903.30mg per year (see cell I28). Aggregating weekly, I find that

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[1] The document he sent tells us which of the studies in the meta-analysis were included in the regression on the iron deficiency outcome variable (which is the regression from which Stephan takes the estimate in the CEA), and what each study's meta-analysis weight was in that regression.

[2] I looked at a few e.g.s in more detail to double check:

a) Thuy et al. 2003 fortifies fish sauce with 1104g of NaFeEDTA for every 160 litres of fish sauce. That means 6.9g of NaFeEDTA/litre. Participants eat 10mL of fish sauce once per day as part of a mid-morning snack with rice or noodles. That means 0.069g of NaFeEDTA per day (through a single snack), or 69mg of NaFeEDTA. ~15% of NaFeEDTA is Fe - so participants consume 15% x 69 = ~10mg of additional iron per day.

- "A concentration of 1 mg Fe as NaFeEDTA/mL of fish sauce was achieved in the factory by mixing 1104 g NaFeEDTA with 160 L fish sauce for 2 h before bottling"; "Ten milliliters of fish sauce, which was either fortified with iron (iron-fortified group) or not fortified (control group), was added to a midmorning snack that was based on noodles or rice and served in the factories", see Thuy et al. 2003.

b) Zimmerman et al. 2005 fortifies cookies or bread. See column 1 in Table 1 which outlines the ingredients used to make cookies. Sum all the values of non-iron ingredients, plus hydrogen reduced iron (for example), which is I think nearly 100% Fe. Then there is 2.83g of iron per 4,982.9g of cookie. Participants eat 4 cookies per day, each weighing 5g (i.e. 20g of cookie). So then participants consume (2.83/4982)*20*1000 = ~11mg of additional iron per day.

c) Moretti et al. 2006 fortifies rice. They mix ferric pyrophosphate at a rate of 200mg Fe per kg of rice, and participants eat 100g of rice per day. This means participants are taking in 20mg of Fe per day.

- "The premix was mixed with local rice (Sona Masuri; Bangalore Rice Traders) in 50-kg batches at a 1:50 ratio to result in a fortification level of 200 mg Fe/kg rice", "The rice meals were packed into color-coded plastic lunch boxes; the daily portion of rice per lunch was 100 g dry rice. This provided 20 mg Fe as MGFP in the iron-fortified meals", see Moretti et al. 2006.

the average additional quantity of iron intake in the studies = 58.49mg per week (see cell J28).

- I then asked FH what level of iron intake they are aiming for with beneficiaries of their program.
    - They told me that they aim to fortify atta with 2.125mg of Fe per 100g of atta (which is the maximum permissible under current Indian government standards).[3]
    - I multiply this by their guess that consumers (at least in Maharashtra) will consume 164g of atta per day to estimate intake per day.
    - I assume that FH's consumers eat atta every day of the week.
    - I therefore estimate that the additional quantity of iron intake for beneficiaries of FH's program is 24.5mg per week (cell H39) or 1271.5mg per year (see cell G39).
- **Bottom line:** Therefore **FH provides** 24.5mg/58.49mg = **41.8%** or 1271.5mg/1903.30mg = **66.8% as much iron intake as the studies in the meta-analysis** (aggregating weekly and annually respectively).

Aggregation over time

- Different studies provide fortified foods for: i) a different number of days per week and ii) a different number of months per year. In order to compare the quantity of iron intake across academic studies (and between the academic studies and FH's program), I therefore need to aggregate the iron intake to a common unit of time.[4]
- Intuitively, the right time period over which to aggregate depends on how gradually the benefits of additional iron intake accumulate. (I.e. for how long does someone with iron deficiency need to consume fortified food before they return to 'normal' iron levels).[5]
- The shortest intervention duration of any of the studies in the meta-analysis is 5.5 months. So if it takes 5.5 months or less of fortified food consumption for someone with iron deficiency to return to normal, then we can just aggregate weekly. Differences in the number of months for which the programs ran do not matter for differences in total additional iron intake. This is the basis for my weekly aggregation procedure - which is to multiply additional iron intake per day (column E) by the number of days/week that recipients eat fortified foods (column F).
- However, it is possible that it takes longer than 5.5 months for an iron deficient person eating fortified foods to return to normal iron levels. I therefore additionally use an annual aggregation procedure. For that, I multiply the additional iron intake per week (column E

[3] See this document (private document) for an outline of why we believe the 21.25mg per kg figure refers to the weight of Fe and not the weight of NaFeEDTA.
[4] As far as we understand, nothing was done in the meta-analysis itself to account for differences in the duration of fortification programs across studies.
[5] Our understanding is that once they return to normal iron levels, that same fortified iron intake can keep them at those levels but isn't going to increase their iron levels further.

x column F) by the number of weeks in the year over which the study took place (using information from column H).[6]

- Our preferred approach is to aggregate annually. Fortify Health sent us one paper which suggests that the bulk of benefits of fortification are attained within the first year and only half of those benefits are achieved within the first 5-6 months (that paper also suggests it is possible that it takes longer than one year for the full benefits to be achieved, see footnote).[7]

2) Differences in iron absorption for a given level of iron intake

a) Fortification compound-vehicle combination

High-level explanation of what I do:

- Iron can be absorbed into the body at different rates from different fortification compounds. As far as I understand it, the key here is whether the iron (Fe) in the fortification compound is held in a state that it can be absorbed into the blood (which is what we care about: the amount of iron that is 'bioavailable' - i.e. enters the circulation and can be actively used by the body).[8]
- Different fortification compounds have different relative strengths in different fortification vehicles (a fortification "vehicle" just refers to the food or drink that is fortified). E.g. iron in NaFeEDTA has a particularly high absorption rate relative to other compounds when fortifying cereal foods, because cereal foods contain a lot of phytates.[9]

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[6] If a study took place for more than one year, I just assume that fortified foods were eaten for the full 52 weeks of the year.

[7] - "Analyses of growth rate of stores under different conditions showed a fast growth from zero iron stores during the first year (reaching about 80% of final amounts) followed by a much slower rate for 2-3 y", see p.623 in Hallberg et al. 1998.
- If it takes longer than one year to accumulate benefits, then it is possible that Fortify Health's program could have a slightly larger effect compared to the studies in the academic literature than our current model suggests if FH are able to continuously provide fortified foods to the same population for multiple years. However, we have not reviewed the methods used in the Hallberg et al. 1998 paper in detail, and we have not reviewed that literature further. Any additional adjustment (by using longer than a one year aggregation) will have very little effect on the bottom line estimate of cost-effectiveness given that a) the bulk of benefits are attained in the first year according to this paper, b) the interventions in some of the academic studies last for more than one year too, and most importantly c) because of the issues discussed in this section.
- Referring to the Hallberg et al. 1998 paper, Hurrell et al. 2010 claim that: "From this report, it can also be estimated that efficacy studies carried out over 5 to 6 months should reach about 40% of final impact, whereas the final impact of studies lasting less than 5 months is too difficult to interpret", p.S9. We are unsure how this 40% figure was estimated.

[8] According to Hurrell et al. 2002 "[iron compounds] differ in...their relative bioavailability (RBV)...Their RBV depends largely on their solubility in the gastric juice during digestion".

[9] Phytates are an inhibitor of iron absorption (as I understand it, phytates bind to iron such that the iron is held in a way that is not easily absorbed by the body). It sounds as though EDTA binds more strongly to Fe than phytates do, and so in NaFeEDTA the iron is protected - i.e. EDTA serves to keep the Fe in a form that the body can absorb.

- In that case we need to adjust the figures for iron intake in (1) to account for the difference in absorption rates between the fortification compound-vehicle combination in FH's program relative to the compound-vehicle combinations in the academic studies.
- Now, the ideal way to do this would be to find studies which directly compare the absorption rate from NaFeEDTA-wheatflour (FH's program) to all other compound-vehicle combinations in the academic studies e.g. ferrous sulphate-milk. However, the only studies that I have read compare across fortification compounds *within the same vehicle*. E.g. rather than compare NaFeEDTA-wheatflour with ferrous sulphate-milk, they compare NaFeEDTA-wheatflour to ferrous sulphate-wheatflour, and NaFeEDTA-milk to ferrous sulphate-milk.
- Therefore, with the information we have, the best that we can do is to make an adjustment for the difference in absorption rates between fortification compounds, within the given fortification vehicles. In other words, for each academic study, I ask: how much better would absorption have been had they used NaFeEDTA (like FH do) within the given fortification vehicle used in the study, instead of the fortification compound that was actually used.
- More specifically, I discount the level of iron intake in each academic study to account for the lower level of iron that was absorbed by participants in the studies compared to the level that would have been absorbed had they hypothetically delivered the same quantity of iron through NaFeEDTA within the same vehicle.
- After making this adjustment I am effectively comparing the academic studies as though they were using NaFeEDTA (in whatever fortification vehicle was used in the study) with Fortify Health's program (which uses NaFeEDTA in wheatflour).
- Possible things left out:
    - Following from the discussion above, I have therefore not accounted for whether a given quantity of iron delivered through NaFeEDTA would have a different absorption rate across fortification vehicles. E.g. suppose we gave Xmg of iron to individual A through NaFeEDTA in milk, and gave Xmg of iron to individual B through NaFeEDTA in wheatflour, would individuals A and B absorb a different amount of iron? I have not read any studies that have asked this question.[10] It seems like this would be a downside risk, since wheatflour is rich in phytates relative to other vehicles, and it's unlikely that phytates have *no* effect on absorption of iron from NaFeEDTA, even if it is much less than the effect on other compounds.[11]

[10] Note - Table 1 in Gera et al. 2012 presents heterogeneity analysis for the effect of fortification on haemoglobin levels (not iron deficiency) by fortification vehicle. But as far as I am aware, those regressions do not control for differences in the quantity of iron intake or differences in the fortification compound across studies - and so can't be used to answer this outstanding question. (For what it's worth, if you believe that those regressions did condition on quantity of iron intake and fortification compound, they would suggest that salt, sauce and milk lead to greater absorption than wheat and rice, so it would seem unlikely that we are underestimating the effect of FH's program. But to be clear - I do not believe that interpretation of those results in Gera et al. 2012).

[11] Stephan said: "Whole wheat is rich in phytate, particularly when it isn't fermented as is the case with typical chapatis. Phytate is the most important inhibitor of iron absorption in most diets. But I don't know

    - As far as I understand, the estimates that I use compare absorption rates of the iron contained in the fortification compound itself only.[12] One paper suggests that NaFeEDTA might additionally increase the absorption of non-heme iron that is contained naturally in the food to which the fortification compound is added too.[13] I have not investigated the evidence base for this claim, and I do not have a good sense for the amount of iron that naturally occurs in e.g. wheatflour.
    - Related to the bullet point above, I guess it's plausible that the fortified food could also affect the absorption of iron from other foods that are consumed alongside the fortified food. Throughout the analysis I am generally only interested in the effect of the fortification compound-vehicle on the absorption of iron *from the fortification compound in the fortified food itself,*[14] because we do not have additional information on the diets of FH's beneficiaries or the participants of the academic studies.

Details of the adjustments for different absorption rates across fortification compounds:

- I make the adjustment for differences in absorption rates across fortification compounds in this spreadsheet.

much about FeEDTA specifically. It's possible that phytate has less effect or no effect on EDTA-bound Fe, but if it had no effect at all this would be unusual. EDTA is a chelator, as is phytate, so I would expect them to compete for Fe. I don't have a confident answer to this but if you put a gun to my head I'd guess that iron absorption would be lower from the whole wheat flour. By how much, I don't know"'

[12] Because I believe that it is only the iron that is added through the fortification compound that is isotopically labelled and counted. See description of isotopic studies below.

[13] "[NaFeEDTA] has been shown to have a further advantage. It can enhance the absorption of the intrinsic non-heme iron in food. In one experiment, ferrous sulphate, which joins the common pool of food iron and NaFeEDTA were fed on separate days in the same type of meal (maize porridge). Iron absorption from the NaFeEDTA-fortified meal was found to be significantly better. However, the iron from ferrous sulphate was as well absorbed as from the NaFeEDTA when they were fed together in the same meal", p.423 in Bothwell and MacPhail 2004.

[14] - E.g. Bothwell and MacPhail 2004 note that Table 1 compares absorption rates between NaFeEDTA and ferrous sulphate "fed together with a variety of cereals eaten singly", p.424.

- To do so, I read the six studies that FH sent me on this topic, in this document. Those studies are: Gera et al. 2012,[15] Bothwell and MacPhail 2004, Hurrell et al. 2000, Hurrell et al. 2002, Hurrell et al. 2010, and Davidsson et al. 2002:
    - I do not know whether those studies are representative of the literature. I have not reviewed the literature myself.
    - I focused on the results which come from "isotopic" studies (see footnote).[16] Those studies specifically try to estimate the relative absorption of a given quantity of iron across different compounds within a given vehicle, which is what we are interested in.
- The absorption discount factors are given in column K.
- In column F of the "Relative absorption rates across compounds" tab, I provide a brief explanation for each absorption discount factor - see those notes for details. The sources of evidence are in column E.
- Broadly speaking, I have: a) used Column 3 of Table 1 in Bothwell and MacPhail 2004 to compare absorption rates between ferrous sulphate and NaFeEDTA (in a vehicle-specific way), and b) then used results described across the other papers (particularly Hurrell et al. 2002) to compare absorption rates between other fortification

[15] I don't believe the heterogeneity analysis in Table 1 of Gera et al. 2012 by fortification compound is particularly useful here. I have therefore focused directly on the isotopic studies. Issues with using Table 1 in Gera et al. 2012 for our purposes here are:

- It is not directly trying to estimate absorption rates, but rather effects on a health outcome (haemoglobin). This is unlikely to be a good proxy for differences in absorption rates, not least because the regression does not seem to control for the level of iron intake (and so differences in haemoglobin levels across fortification compounds might just be driven by differences in the quantity of iron that happened to be in the studies that used different compounds
- Even if we want to directly look at the health outcome, Is haemoglobin the right outcome? We are interested in iron deficiency, but it looks like that wasn't a primary outcome of the study and so they haven't done the heterogeneity analysis on iron deficiency specifically. Can we assume that the results for haemoglobin levels would carry over to iron levels in the blood?
- As far as I can tell, Table 1 estimates a separate effect of each fortification compound (on haemoglobin levels). However, it doesn't test for the statistical significance of the differences across fortification compounds, and the 95% confidence intervals for the estimates don't look particularly tight.

[16] As I understand it, isotopic studies take a very small sample of individuals (e.g. around 10-50) and provide individuals with different fortification compounds. They isotopically label the iron in each fortification compound, meaning that when you later take a blood sample you can work out from which compound the iron came - and therefore understand precisely how much of the iron from each specific compound was absorbed. E.g. describing the studies underlying Table 1 in Bothwell and MacPhail (which I rely on quite heavily): "A number of human studies have been carried out in which the bioavailability of iron from foods fortified with either ferrous sulphate or NaFeEDTA has been compared. A simple protocol was used in the majority of these studies. It involved the addition of radioiron...to test the meal, which was fed on two consecutive days. The relative absorption of the two isotopes was then measured in a blood sample taken two weeks later. Each subject's absorbing capacity was subsquently assessed by measuring the absorption of a reference dose of 3mg 59FeSO47H20 fed together with 30mg ascorbic acid. This made it possible to standardize all individual food absorption values to a reference absorption of 40%, a value assumed to represent borderline iron deficiency. In some recent studies, stable isotopes have been used instead of radioisotopes", p.424.

compounds and ferrous sulphate. I then combined (b) with the conversion from ferrous sulphate to NaFeEDTA (given that none of these studies seem to directly compare NaFeEDTA and compounds other than ferrous sulphate). Note that (b) was not vehicle specific, so I assume that the relative rates of absorption between other compounds and ferrous sulphate is the same across vehicles.

- The key assumptions are:
    - Ratios used:
        - Absorption of iron from NaFeEDTA is 2.1-3.9 times greater than ferrous sulphate, with the exact figure depending on the specific fortification vehicle. These figures come from Column 3 in Table 1 in Bothwell and MacPhail 2004, and have been drawn from other studies in the literature (which are described by Bothwell and MacPhail as isotopic studies).[17]
        - Iron in ferric pyrophosphate is absorbed at half the rate as iron in ferrous sulphate.
        - Iron in ferrous fumarate is absorbed at the same rate as iron in ferrous sulphate.
        - Iron in ferrous gluconate is absorbed at 0.89 times the rate as iron in ferrous sulphate.
        - Electrolyte iron is absorbed at half the rate as iron in ferrous sulphate.
        - Hydrogen reduced iron is absorbed at one fifth the rate as iron in ferrous sulphate.
        - Haem iron is absorbed at the same rate as NaFeEDTA.
    - Other assumptions:
        - I couldn't find studies which compare absorption rates across fortification compounds for salt. It seems unlikely that salt is consumed on its own: I assume that it is typically consumed with staple foods, and many staple foods such as wheat, rice, maize and bread are cereals. I therefore assume that NaFeEDTA is absorbed at a rate three times greater than ferrous sulphate in salt (i.e. take the midpoint of the range 2.1-3.9 for cereals). My logic is that in the presence of phytates from the staple foods, NaFeEDTA would presumably have similar benefits relative to other fortification compounds as were it added to the cereal directly.
        - Like with salt, I was unsure what a "complementary food" was, but assume that it is consumed alongside staples too (and therefore again use the 3:1 NaFeEDTA-ferrous sulphate absorption ratio).
        - I use relative absorption rates across compounds within milk in Table 1 in Bothwell and MacPhail 2004 as a proxy for the relative absorption rates in academic studies that use "infant milk substitute".

b) Inhibitors/Enhancers

[17] Note that I have not vetted those underlying studies.

- We are already implicitly adjusting for the effect of inhibitors/enhancers in the fortified food itself on the absorption of iron from the fortification compound. E.g. this is the reason that absorption of iron from NaFeEDTA is greater than ferrous sulphate in cereals - because cereals contain phytates (an inhibitor).
- I have not adjusted for the possibility that the beneficiaries of FH's program and the participants in academic studies consume different foods alongside the fortified food, and those foods contain different levels of inhibitors/enhancers.[18] I have not made any adjustment for this because:
    - It seems unlikely that there is going to be any data on the level of inhibitors (e.g. tanins and phytates) or enhancers (e.g. vitamin C) in the diet of FH's beneficiaries vs academic study recipients, and so I don't think we can practically do anything else on this.
    - There seemed to be a suggestion in one of the papers I read that this could matter quite a bit (see footnote).[19]
    - Stephan believes that there is unlikely to be a huge difference in the amount of phytates between the diets of FH beneficiaries and the academic studies, because most staple foods in developing countries contain a lot of phytates, and so an adjustment for this probably wouldn't make a huge difference.[20] The possible exception is if tea is drunk significantly more amongst FH beneficiaries in India than the participants in the academic studies, because tea seems to have a large effect on absorption of iron, even from NaFeEDTA (see footnote in the bullet point above). We have no information on diets (but perhaps, very speculatively, seems like it could be a downside risk).

c) Baseline levels of iron in the blood

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[18] As far as I understand it's only inhibitors or enhancers that are consumed at the same time as the fortified food that matters. Consuming inhibitors or enhancers earlier in the day doesn't affect the proportion of iron in fortified food that is consumed in the present moment. As I understand it, the idea is that inhibitors and enhancers bind with iron such that it is held in a less or more bioavailable form. I believe that the impact of inhibitors/enhancers would itself depend on the fortification compound used.

[19] "Some direct evidence of the ability of NaFeEDTA to prevent [phytates] action was obtained in an experiment where bran, a rich source of phytates, was shown to reduce the absorption of iron from ferrous sulphate eleven-fold. In contrast, no such inhibition occurred when bran was fed with NaFeEDTA…In contrast, when NaFeEDTA was given with tea, a seven-fold reduction in iron absorption was noted in one study, while in another tea reduce iron absorption from 11.5% to 1.86% when it was drunk with a low-extraction wheat roll fortified with NaFeEDTA", p.423.

[20] Stephan: "To clarify, inhibitors can potentially matter a lot. I just doubt that there are large differences in the overall concentration inhibitors when comparing the mean of studies represented in the meta-analysis vs. the FH context, and I also think it would be a lot of work to determine this and therefore the effort/benefit ratio is likely poor. It is possible that there would be large differences in phytate across the two contexts for example, but I think it's not the most likely scenario because diets in very poor countries are usually pretty high in phytate from whole grains and legumes. But the tea effect you mention below is concerning. Tea can reduce the absorption of certain minerals but IIRC its effects in the context of normal mixed diets aren't very large. But the specific effect on EDTA-bound Fe you mention below is concerning."

What are the relative levels of iron in the blood comparing between beneficiaries of FH's program and the academic studies?

In the academic studies:

- The meta-analysis reports that the “mean baseline haemoglobin concentration was < or equal to 120g/L in 49 out of 80 (57%) and the geometric mean baseline serum ferritin was < or equal to 20 microg/L in 22 of 47 (47%).” However, a couple of issues:
    - I'm not sure what the right measure is to understand the baseline iron levels in the blood.[21] E.g. Professor. Pachon mentioned that serum ferritin spikes when people are sick (even if they have low iron status), so serum ferritin levels can be misleading.[22]
    - The meta-analysis doesn’t report the baseline iron levels in each underlying study (including anywhere in the online supplementary materials), and so we don’t know what the levels were specifically in the 21 studies included in our meta-analysis regression of interest for iron deficiency.
- I briefly looked at each of the underlying 21 studies. However, baseline iron levels do not seem to be reported in a consistent way across those studies.[23]

In FH's program:

- We don’t know the baseline iron levels for FH’s beneficiaries. FH sent us some information on baseline iron intake at the state level for India in the 2012 National Institute of Nutrition report, on p.17 in this doc. However, iron intake is not the same as iron levels or status (even e.g. proxied by serum ferritin), and so this is not directly comparable.[24]

What is the effect of baseline iron levels on absorption rates?

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[21] Just flagging that the proportion who are iron deficient is only part of the picture. We really want to know what average iron levels in the blood are. The definition of 'iron deficient' can vary, and even if someone is iron deficient, they can have varying levels of iron in the blood. Then in turn it isn't totally clear to me how to measure 'iron levels', see footnote below.

[22] "Plasma or serum ferritin is also an acute phase protein. That means it increases when we’re sick. So, it’s possible that a sick person with poor iron status will have an artificially inflated ferritin value, which in turn makes them appear to have adequate/high iron status (this is elegantly described here: https://www.ncbi.nlm.nih.gov/pubmed/28615259)", email sent by Prof. Pachon to Fortify Health on 24th May 2019.

[23] Some report baseline serum ferritin levels, some report baseline iron stores, some report baseline proportion who are iron deficient (but definitions of iron deficiency can differ across studies and don’t always seem obviously mentioned). With the time we have, I have not tried to back out a comparable baseline iron level figure – if that is even possible with the information presented in the papers.

[24] We have already made some assumptions about the rate of iron deficiency amongst FH beneficiaries in our CEA, but as mentioned in a previous footnote - the rate of iron deficiency is only part of the picture (we really want to know what the average iron levels are).

- Conventional wisdom is that the rate of iron absorption is greater when iron levels are low.[25]
- I have not read into that literature at all, but a couple of questions/cautions if I was to look into it:[26]
    - Prof. Hurrell mentioned that he's not sure if a simple linear relationship holds when serum ferritin levels are very low.[27]
    - Figure 1a in the Zimmerman et al. article that Pachon refers to in her email (see this doc [private document]) seems to show an inverse relationship between baseline iron levels and absorption for ferrous sulphate, but not ferric pyrophosphate. So it may be that the shape of the relationship depends on the fortification compound.

My rough takeaway

- Given that we do not have information on relative baseline iron levels amongst beneficiaries in the academic studies or FH's program, I don't think we can practically make an adjustment for this, and so I have spent limited time on it.
- However, assuming that iron absorption is greater when iron levels are lower, I have a slight concern that this could be a downside risk for FH's cost-effectiveness because it

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[25] E.g. see this doc (private document):
- "It's a well-established fact that iron absorption is greater when an individual's iron status is lower (versus higher). This was determined through absorption studies. These are usually done with a few people (<50) whose iron stores are known to be low. The study participants consume iron (say from a supplement or from fortification or from another source) that has been isotopically labeled. Then, the researchers take blood draws a few weeks later to measure how much of the isotopically labeled iron remains in the body. This allows them to calculate the absorption of iron from different sources", Prof. Pachon's email to Fortify Health on 24th May 2019. "
- "I do not have time at present to go back and find the early publications but there is little doubt that in normal subjects, free of inflammation, iron absorption increases as serum ferritin decreases and vice versa. Low SF leads to high absorption ; high SF leads to low absorption. We have found this in all our studies", Prof. Hurrell's email to Fortify Health on 27th May 2019.

[26] One additional possible caveat is that Gera et al. 2012 appear to find that the effect of fortification on haemoglobin levels is greater for individuals with initially higher serum ferritin levels (Table 1). However, I don't place much or any weight on this finding, because:
- Looks at haemoglobin levels outcome variable (doubt this is a good proxy for rate of absorption of iron)
- Not clear if it controls for the quantity of iron intake (if not then the results could just be driven by differences in the level of iron intake between the studies where participants had a low or high baseline haemoglobin level)
- No tests of statistical significance across the different baseline levels of intake.

[27] - "This is a straight line relationship and has been widely used to compare Fe absorption between studies. The earlier work was done in the 1970's or before by the Bothwell group and was used by Jim Cook to propose the adjustment to compare between studies where the subjects had different iron stores. I do not think the relationship holds with very low SF values and, while absorption is normally much higher in subjects with IDA, no relationship has been reported between haemoglobin and iron absorption", Prof. Hurrell's email to Fortify Health on 27th May 2019.
- I'm not sure from this exactly what alternative shape relationship he is suggesting.

seems possible that baseline iron levels amongst FH program beneficiaries are higher than in the academic studies:

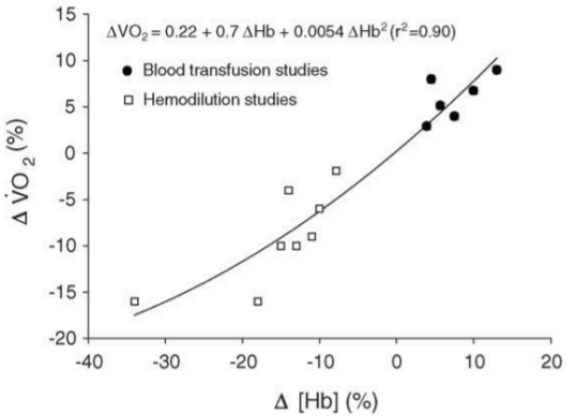
- All but one of the academic studies samples only women and/or children.[28] FH's program produces for the open market, and so a non-negligible fraction of beneficiaries are adult men. My prior is that adult men have considerably lower rates of iron deficiency than adult women and children.[29]
- Several of the academic studies specifically sample individuals with iron deficiency or anemia (e.g.: Cabalda et al. 2009 samples anemic children, Biebinger et al. 2009 samples women with low body Fe stores, Wegmuller et al. 2006 samples children with iron deficiency, Moretti et al. 2006 samples children with iron deficiency or low body iron stores, Zimmerman et al. 2005 samples women with low iron stores). That said, two studies specifically sample children in good health (Stevens et al. 1995 and Olivares et al. 1990).
- Related to the bullet point above, baseline rates of iron deficiency seem quite high in some studies (e.g. 78% iron deficiency in Moretti et al. 2006, 35% in Zimmerman et al. 2003, 27% of men and 58.7% of women in Ballot et al. 1989).
- However, it is possible that iron deficiency is higher in India (where FH works, Maharashtra and West Bengal specifically) than in the countries in the academic studies. The academic studies largely focus on developing countries: Cote d'Ivoire, Philippines, Kuwait, North Korea, Mexico, India, Thailand, Vietnam, Morocco, Chile, Pakistan.[30] However, two studies are from the UK and one from South Africa. That said, many of the studies are from a while ago (I have a weak prior that iron deficiency rates may have decreased over time (as that seems to have occurred in India), but I have not looked at data for these countries specifically).[31]

3) Effect of a given increase in iron absorbed on health

- The effect of a given increase in iron absorbed on health (e.g. the probability of iron deficiency) may differ based on baseline iron levels.

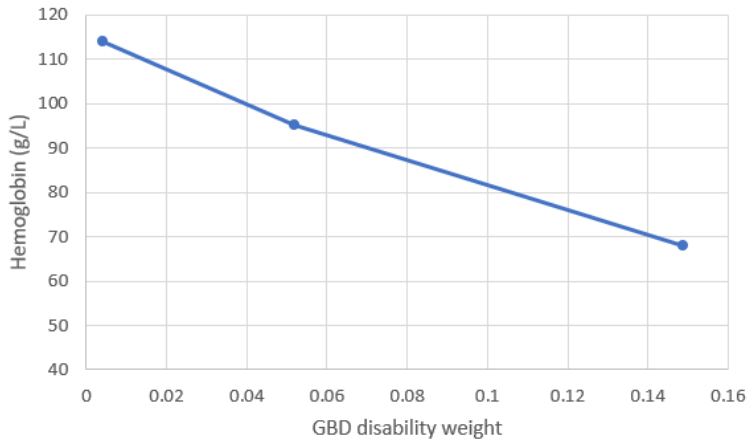
[28] Ballot et al. 1989 samples men and women in South Africa. That said, the iron deficiency rates amongst men in that sample seem pretty high (27% of men had some form of iron deficiency, and 58.7% of women - see Table 3).
[29] E.g. in India, according to the DHS 2015/16 data that FH sent us: 58.5% of children under 5 and 53.1% of women have any anemia, as compared to only 23.3% of men. (Of course this refers to anemia and not iron deficiency specifically).
[30] In addition, a couple of the papers report sampling areas with high rates of anemia (Thuy et al. 2005) or malnutrition (Javaid et al. 1991).
[31] 12 of the 21 studies underlying the effect size that we use were published in 2005, and so would have collected data from before then - so at least 15 years ago or more.

- Stephan had a very quick look into this, and his analysis doesn't seem to provide strong evidence that there is a greater effect at a lower initial nutrition status. Stephan noted the following:[32]
    - "I assessed it in two ways. First, by looking at studies that have examined the relationship between experimental hemoglobin reduction/increase and VO2max, a measure of exercise capacity. Second, by graphing GBD disability weights for mild, moderate, and severe anemia against the hemoglobin levels associated with them. Both approaches have substantial limitations but they were the best ways I could think of to address the question quickly."
    - Here are the data from hemoglobin modification studies (doi.org/10.1016/j.resp.2006.01.014). The relationship is slightly nonlinear but in the opposite direction than expected (i.e., VO2max doesn't get proportionally worse as Hb declines). Furthermore, the nonlinearity seems to depend heavily on a single data point:



- Here is a graph of GBD disability weights for anemia vs. the approximate hemoglobin level that corresponds to them. It's pretty linear.

[32] Stephan also sent a link to an academic paper which contains a figure from Zimmerman and Qaim (2004) which suggests a non-linear relationship between micronutrient intake and adverse health outcome. The formula underlying that figure is H(x) = 1/x – 1/RDA, where H = adverse health outcome and x = micronutrient intake. (I think that figure was derived theoretically.) However, the non-linear relationship described here could just be driven by differences in the rate of absorption at different initial levels of iron (as discussed in (2c), given that the x-axis is "micronutrient intake" and not "micronutrient absorbed".



- The evidence is far from ironclad but what I considered suggests an approximately linear relationship between iron status and disability.

Other complications

- When we talk about being 'iron deficient' it's not entirely clear what we mean. The meta-analysis allows the underlying studies to use different definitions, and we don't know what the definition underlying the GBD compare estimates that we use in our CEA is.
- Different demographic groups have different optimal iron intake (see the "Optimal iron intake" section in this spreadsheet).
- Our CEA assumes that FH's consumers eat all 164g of their daily atta consumption as fortified atta (in which case FH can reach 5,000 consumers per daily metric ton of production). It could be the case that FH's consumers instead consume half their daily atta as FH's fortified atta and half as some other unfortified atta. In that case we might expect FH to reach 10,000 consumers per daily metric ton of production, with each consumer consuming only 82g of atta per day (and so half as much iron). The effect of the two scenarios is only equivalent if the relationship between iron absorbed and health benefits is linear (see discussion above). For the time being we are assuming linearity (FH didn't raise objections to this when I discussed it with them in the context of the number of consumers that they could reach in W.Bengal vs Maharashtra, given the differences in the quantity of consumption across those two states).
- It's possible that the distribution of flour consumption is sufficiently uneven across the population of beneficiaries that a non-negligible proportion of FH's fortified flour is effectively wasted (because some household members consume so much of the fortified flour that they receive limited or no additional health benefits (or worse some adverse health impacts)).[33] We do not have information on the distribution of consumption within

[33] Note that we already make an adjustment in the CEA to ensure that we only count benefits for people who are iron deficient in the first place. So we do not need to make an additional adjustment here for the proportion of atta that is consumed by individuals who are not iron deficient.

households, only mean flour intakes. Stephan conducted a quick BOTEC to see how likely this is to matter:

- Stephan - "BOTEC. 171 grams of atta is about 580 calories. A lean, smallish physically active adult male might consume 2500 calories per day, which would be 4.3X the calories in 171 g of atta. If we assume an upper limit of 2/3 of total dietary calories coming from atta, the rough upper bound intake would be 2.9X the average dose. Times 3.6 mg is 10.3 mg per day from the atta. That's 1.7X the estimated average requirement (EAR) for a young man, in addition to what he will get from other foods. Also, the EAR is based on nutrient intake (not absorption) and there may be more absorption from the FeEDTA. So it could possibly lead to a fairly high intake of iron in a small subset of the population. I'm not sure what the consequences of that might be. My prior is to not be too concerned because we aren't talking about extreme intakes, but I don't feel very confident about that. There is a lit on harmful effects of excess iron status."[34]
- I have not made an adjustment for this because: a) we do not have information on the distribution of flour consumption around the mean, b) this really matters if the relationship between iron intake and health benefits is non-linear and we don't have strong evidence that that is the case, c) if there is a non-linear relationship we would also need to count the disproportionate benefits for beneficiaries who consume less than the average quantity of iron, which acts in the opposite direction.[35]
- Note - as a separate point (relating to the average level consumption not the distribution around the average), if we did model a non-linear relationship between iron intake and health benefits, we would need to additionally adjust for the possibility that consumers do not consume all their flour intake as fortified flour, and that consumers in West Bengal only consume 49g of atta per day on average, both of which would increase cost-effectiveness.
- Further discussion and ideas on next steps is in this document (private document).

Adjusting the effect size in the CEA

If the relationship between iron absorption and health benefits is linear.

- Depending on how we aggregate, our best guess is that FH provide between 121%-167% as much iron (absorbed into the body) as the studies underlying the meta-analysis.
- One approach to adjusting our CEA is to multiply the effect size that we assume in the general intervention-level iron fortification CEA by this factor (121%-167%). This

[34] FH previously estimated that their beneficiaries eat 171g of atta per day in Maharashtra, but since estimated 164g per day.
[35] Further details in this document (private document).

assumes that the relationship between iron absorbed and health benefits is linear, as we have discussed above.

- Practically doing this:
    - Cell B4 in the CEA tells us the relative risk of iron deficiency with iron fortification, which is 48% (taken from the Gera et al. 2012 meta-analysis). I.e. a person with iron fortification is 48% as likely to be iron deficient as someone without. Put another way, this means that iron fortification reduces a person's chance of being iron deficient (compared to someone without fortified foods) by (1-0.48) = 52 percent.
    - Multiplying that 52 percent effect size by 121% or 167%, and the bottom line is that iron fortification reduces the relative risk of iron deficiency by 63% or 87% respectively.[36]
- This demonstrates an issue with the linear approach:
    - Our intervention-level iron supplementation CEA assumes that daily iron supplementation reduces the relative risk of iron deficiency by 79% (see cell B4 here).
    - Yet it seems as though iron supplementation delivers substantially more iron than iron fortification.[37] If we use the 167% figure (from the annual aggregation procedure), then our FH model predicts that iron fortification, which delivers less iron than iron supplementation, strangely has a considerably greater effect on the risk of iron deficiency (an 87% reduction compared to a 79% reduction).

So what can we do?

- Intuitively, it seems like the effect of iron fortification in FH's program will lie somewhere between the effect of iron fortification in the academic literature (a 52% reduction in relative risk of iron deficiency) and the effect of iron supplementation in the academic literature (a 79% reduction in relative risk of iron deficiency).
- To understand where in that region, I tried to understand the level of iron delivered in the academic studies underlying the iron supplementation effect size estimate that we use in our CEA (Low et al. 2013), in this spreadsheet. Aggregating annually, it appears as though on average[38] roughly 12,269mg of iron is delivered across the year in the iron supplementation studies, compared to 1,903mg in the Gera et al. fortification meta-analysis and 1,271mg in FH's program (note none of these figures are adjusted for differences in absorption - this is just the quantity of iron that is ingested, see footnote).[39] So at first glance, roughly between 6.4-9.7 times as much iron is delivered through iron supplementation than the fortification studies or FH's program.
- However, I do not think we should take that 12,269mg figure too seriously because:
    - As mentioned, I have not adjusted for differences in absorption rates. Iron from ferrous sulphate, iron citrate or whatever unknown compound is used in the Seshadri et al. study delivered through iron supplementation may be absorbed at a different rate than iron from NaFeEDTA fortified in wheatflour or the

[36] To see this, enter 121% or 167% in the cell B5 and look at the output in cell B6.
[37] See this spreadsheet.
[38] This again refers to a weighted average using the meta-analysis weights.
[39] Although FH's program delivers more iron after adjusting for differences in absorption rates, the physical quantity of elemental iron ingested from FH's fortified food is lower than in the academic studies.

compound-vehicle combinations in the academic studies. I have not done any work to understand differences in absorption rates between iron delivered in tablet form and iron delivered through fortified foods.
    - More generally, I have spent very little time looking at that Low et al. 2013 study.
- Fundamentally, I do not believe we are going to get a very satisfactory best guess to this question.
- For the time being, I assume that Fortify Health's program leads to a 60% reduction in the relative risk of iron deficiency, for the following reasons:
    - It seems intuitive to me that the adjusted effect size should be a bit larger than the effect of iron fortification in Gera et al. 2012, but probably closer to that estimate than the estimated effect size of iron supplementation in Low et al. 2013 given the much larger quantities of iron in supplementation.
    - Given the much larger quantity of iron in supplementation, the 60% figure perhaps seems closer to the iron supplementation effect size estimate than seems intuitive. However, if the relationship between iron absorbed and health benefits is non-linear over the range of iron levels between iron fortification and supplementation (as seems likely from this analysis),[40] then we might expect a disproportionately larger effect of a given increase in iron absorbed from the lower levels delivered in fortification.[41]
- As mentioned, this issue suggests that the effect of iron absorbed on health benefits is likely to be non-linear if we consider the wide range of levels of iron delivered between iron fortification and supplementation.
    - Note that elsewhere in the analysis in this document we have assumed that the relationship between iron absorbed and health benefits is linear. It isn't totally implausible that over the range of levels of iron absorption between different iron fortification programs, the relationship between iron absorbed and health benefits is closer to linear than over the range between iron fortification and iron supplementation programs. However, this is clearly a major unanswered question.

Bottom line

- If we assume that the relative risk of iron deficiency with iron fortification in FH's program is 40% (i.e. FH's program causes a 60% reduction in risk of iron deficiency), then FH's program is 11x cash.
- We can bound the cost-effectiveness of FH's program using the iron fortification and iron supplementation meta-analyses:

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[40] Stephan noted that: "There are issues that I think complicate the interpretation of these meta-analyses for our current purposes. I don't think the meta-analyses perfectly reflect the relationship between iron supp and iron status. For one thing, deficiency is measured as a dichotomous variable which itself could make it nonlinear (you can approach a 100% reduction in risk of deficiency but you will probably never quite reach it, due to a subset of people having weird genetics, blood loss, etc). Using a continuous variable like iron dose vs. ferritin level would be more likely to be linear. For another thing, there is incomplete adherence and measurement error in these studies so even if there were a perfect linear relationship between Fe intake and deficiency risk, it wouldn't be reflected perfectly in the studies. There is some theoretical maximum effect size that would be achievable, given these limitations. Supplementation probably approaches that maximum."

[41] I am also partly choosing this figure because it is a round number, it is very speculative.

    - If FH's program was no more effective at reducing iron deficiency than the academic studies in Gera et al. 2012, then cell B6 = 48%, and cost-effectiveness = 9.5x cash. This can be thought of as a lower bound.
    - If FH's program if as effective at reducing iron deficiency as iron supplementation (according to the Low et al. 2013 study), then cell B6 = 21%, and cost-effectiveness = 14.4x cash. This can be thought of as an upper bound.
- **So the bottom line is that FH's program is somewhere between 9.5x-14.4x cash, with an extremely speculative best guess of 11x cash.**
- To reiterate, this is an important parameter about which we have a lot of uncertainty.

Next steps

If we wanted to go deeper on this investigation, I would focus on the following areas:

i) Next steps on the relationship between iron absorbed and health effects:

- This seems like the single most important area for future research. We don't have a good sense of the shape of this relationship and it could affect our model in several ways as follows:
    - Affects the size of adjustment that we make for the relative effectiveness of FH's program on iron deficiency compared to the academic literature - i.e. where between the bounds of the effectiveness of iron fortification vs iron supplementation in the two academic meta-analyses does FH's iron fortification program lie (as discussed here)?
    - Affects whether we should make an adjustment for the possibility that consumers only eat part of their total flour intake as fortified flour (i.e. if the program reaches a larger number of beneficiaries at a lower dosage than our current model assumes).
    - Similar to the previous bullet point, it affects whether we should make an adjustment for the possibility that consumers in West Bengal (who seem to consume less flour per day than our model assumes) receive a less than optimal dose (but accordingly a larger number of beneficiaries are reached).
    - If the baseline iron levels of FH beneficiaries were different to those in the academic studies, this could also impact the relative effectiveness of FH's program compared to the academic estimates. It's unclear that we will be any better able to get information on those baseline levels in future though.
- We may want to make a distinction between the shape of the relationship across a narrow and low range of iron intakes (such as the difference between quantity of iron across fortification programs, or within fortification programs for consumers consuming a different quantity of the fortified product), and the shape of the relationship across the much wider range of iron intakes between fortification and supplementation programs (which seems more likely to be non-linear as discussed above).
- To the extent that there are greater benefits at lower initial iron levels, it is possible that our model underestimates FH's cost-effectiveness (e.g. if two consumers receive half of

a given dose of absorbed iron, the sum of health benefits across them is greater than if one person received that full dose).

- We could start by looking at Stephan's quick take (above), which did not totally rule out a linear relationship. Stephan also noted that academics tend to assume that the health impacts of a given increase in iron absorbed are non-linear, and are larger for lower initial levels of iron. We have not reviewed the academic literature on this question (I am unsure what empirical evidence has been collected on this question).
- Related to this, we should try to understand how the distribution of atta consumption around the average in FH's program (not true in the academic studies) affects the bottom line in the presence of a non-linear relationship between iron intake and health benefits. See this document (private document) for further details and ideas on next steps.

ii) Next steps on absorption:

- Adjustment for differences in absorption across fortification vehicles:
    - Read into the academic literature to see if anyone has answered the question posed above: Suppose individual A consumed Xmg of iron through NaFeEDTA in milk, and individual B consumed Xmg of iron through NaFeEDTA in wheatflour, would individuals A and B absorb a different amount of iron? I.e. conditional on the fortification compound and the quantity of iron that is ingested, does the fortification vehicle itself lead to differences in the amount of iron absorbed?
- Adjustment for differences in absorption based on differences in baseline iron levels:
    - Try to back out comparable data on baseline iron levels across the studies, or go to other data sources for this information from the countries in question. Compare baseline iron levels between FH and academic study beneficiaries. (Would require collecting/finding relevant info for the FH beneficiaries too).
    - Read into the literature on the shape of the relationship between iron absorption and baseline iron intake, for different fortification compounds.
- Adjustment for the effect of different fortification compounds on intrinsic iron absorbed from the fortified food itself (rather than the compound). For this we would need to:
    - Read into the literature to understand the evidence for that effect, starting from p.423 in Bothwell and MacPhail 2004.
    - Work out the relative levels of intrinsic iron in each of the fortification vehicles used in the academic studies, and in FH's atta.
- Adjustment for differences in absorption based on differences in prevalence of inhibitors/enhancers in people's diets:
    - Collect information on diets in the countries in the academic studies and in FH's program to try to understand the relative levels of inhibitors and enhancers that may be consumed alongside the fortified foods.
    - Read in to the literature to understand the relative effect of inhibitors and enhancers in the presence of different fortification compounds.

Given the issues outlined in this section, in general I suspect that making these additional adjustments wouldn't make a large difference to the bottom line (exceptions described below). In addition, each seems like it would be a time consuming investigation and it's not obvious that the information exists for us to make an adjustment:

- The first and fourth bullet points seem like downside risks (the first - because wheatflour has a greater concentration of phytates than other vehicles and this could still have a little bit of an effect even for absorption of iron from NaFeEDTA; the fourth - because tea allegedly has a large effect on absorption even from NaFeEDTA and we have a very speculative prior that beneficiaries in FH's program in India may drink more tea than in the countries underlying the academic studies).
- The second and third bullet points seem like they could move the estimates in either direction and I don't have a strong prior as to which.

I would therefore focus primarily on further research outlined in (i).

What are the main outstanding downside risks to cost-effectiveness?

If we decide to make a grant, what are the main ways that we could have overestimated cost-effectiveness. In my opinion, they are (in order of importance):

1) Do Fortify Health's beneficiaries consume more tea alongside the fortified foods than the participants in the academic studies? If there is a large difference, it's possible that FH's program could lead to less iron absorbed than the academic studies, in which case cost-effectiveness could fall below the 9.5x "lower bound". (I am specifically worried about tea because one study mentioned above noted a seven-fold reduction in absorption of iron through NaFeEDTA).
2) Are baseline levels of iron intake lower for participants in the academic studies than FH's program? And if so, is absorption greater the lower the initial level of iron? My rough instinct is that baseline iron levels would have to be quite a bit lower in the academic studies for FH's program to end up causing less iron absorption than the academic studies (given our current best guess, unadjusted for this concern, that iron absorbed in FH's program is 167% of the average in the meta-analysis). In that case, it's perhaps unlikely that cost-effectiveness would fall below the 9.5x lower bound, but that's not a strongly held conviction. Nonetheless, I think this is less of a concern than (1).
3) Is the distribution of flour consumption sufficiently uneven that a reasonable proportion of FH's fortified flour is effectively wasted (because it is consumed by household members who have already consumed their optimal dose of iron and so receive no further benefits)? (I have explained above why I have not made an adjustment for this above, but we have little information about it and so it remains a major outstanding question - see here [private document] for some next steps).