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## Reply to S Rahman and S Ireen

Dear Editor:

We thank Rahman and Ireen for their interest in our recent publication (1). Indeed, we had been surprised to find that the prevalence of anemia was lower than expected in this study site in Bangladesh (2). The control group prevalence in our study was 17.4%, just more than half the 33% prevalence reported in the National Micronutrient Status Survey published in 2013 (3) and substantially lower than the 48.8% prevalence that we found in Kenya (2). We agree with the sentiment in the letter that groundwater iron concentrations are an important contributor to population iron status in Bangladesh, but we are not convinced that this is the reason for the unexpectedly low prevalence of anemia in our study compared with that in other areas of Bangladesh. Because it was shown previously that iron status is correlated with groundwater iron concentration (4), we had purposefully selected an area with low groundwater iron concentrations (5). According to the Bangladesh National Hydrochemical Survey, the majority of groundwater iron concentrations should have been <2 mg/L in our study area, which we illustrated in Supplemental Figure 1. Indeed, median groundwater iron concentration measured in the study area prior to the start of the intervention trial was 0.91 mg/L (IQR: 0.36–2.01 mg/L) (6). Iron deficiency did appear to be a problem in our study area. The prevalence of iron deficiency was 41% (inflammation corrected ferritin <12 μg/L or serum soluble transferrin receptor >8.3 mg/L), which was reduced by 40–60% in the 2 nutrition intervention groups. We have struggled to explain the unexpectedly low prevalence of anemia in this area compared with that of the national survey (3), which included sampling from regions that had much higher groundwater iron concentrations. One possibility that we had considered was that our blood sampling methods differed from those used in the survey, which we erroneously stated had used capillary blood sampling. However, Rahman and Ireen have correctly noted that we did in fact use the same method of venous blood sampling. Nevertheless, it is apparent from our study as well as from the national survey that micronutrient deficiencies are a problem in Bangladesh, regardless of the prevalence of anemia, and that the prevalence likely varies regionally. We recommend that investigators measure groundwater iron concentrations in future studies of iron or other micronutrient interventions.

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## Response to Editorial: Balancing the benefits of maternal nutritional interventions; time to put women first!

Dear Editor:

The editorial (1) accompanying our report of the Women First trial results (2) contained a number of factual misrepresentations. We are writing to clarify, in our view, the most important ones.

The first is the erroneous statement that the overall dropout rate exceeded 50%. As indicated in the CONSORT diagram, of the 7387 randomly assigned women, the dominant reasons for "trial exit" were either becoming pregnant <3 mo into the study or not becoming pregnant within the timeframe the study allowed to meet sample size goals. Only ~30% (average for all arms) left the study during the preconception period due to moving out of the study area or no longer wishing to participate. Of the 44% of the randomly assigned women who conceived ≥3 mo after randomization and who entered the pregnancy phase of the trial ($n$ = 3251), <3% for all arms exited the study. Of those with live births, the primary outcome was obtained for >90% of the participants. Preconception trials are inevitably faced with the inherent challenge of capturing enough pregnancies in the course of the study period to obtain outcomes. To provide relevant context, the percentage of conceptions of those randomly assigned for the Women First trial (44%) is favorably comparable to 2 other recently published preconception trials: the Mumbai Maternal Nutrition Project (3) and the PRECONCEPT trial in Vietnam (4). These trials followed 35% and 36% of randomized participants through pregnancy, respectively.

The second major misrepresentation in the editorial was "the choice of 3 mo as the timing of the preconception intervention," surmising that this choice as a cutoff for preconception supplementation might have limited its impact. In fact, 3 mo was the *minimum* exposure; the actual average duration of exposure to the primary supplement for Arm 1 (preconception) was more than 9 mo. The rationale for that timeframe is available in the protocol article (5) but is also consistent with the other preconception trials, both of which also targeted a 3-mo minimum exposure to intervention (3, 4).

Finally, the comment questioning the value of providing a limited repertoire of micronutrients is puzzling because the primary lipid-based supplement contained >20 micronutrients, including 1000 IU of vitamin D.

We appreciate the opportunity to highlight these apparent misunderstandings in our study design and implementation. All of the details noted previously are included in the primary article for any readers who desire to review them directly.

The authors report no conflicts of interest. Both authors: read and approved the final manuscript.

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## Reply to NF Krebs and KM Hambidge

Dear Editor:

Drs. Krebs and Hambidge have taken issue with my editorial, "Balancing the benefits of maternal nutritional interventions; time to put women first!" (1), citing factual misrepresentation of their article. I regret that issues that I pointed out as possible limitations of the Women First Trial, or indeed other preconception nutrition studies, should have caused umbrage, because this was meant to stimulate scientific debate. Perhaps the text in the editorial could have been clearer on the 3 points highlighted by Drs. Kreb and Hambidge, and here I take the opportunity to explain further.

Firstly, as stated, the 4 sites varied greatly in context and maternal nutrition status (reflected in BMI and height), a point that the authors themselves recognize (2). However, these factors were not taken into account in designing a study with site-specific power for addressing primary outcomes. The acceptability of a minimum intake of only 12 wk as sufficient duration of intervention in a malnourished and possibly micronutrient-deficient population is difficult to justify. The ostensible rationale for the choice of this lower limit in the published protocol is from a 10-y-old animal study (3). Although the mean ± SD intake duration of the lipid nutrient supplement received by women in the preconception period in group 1 was 37.3 ± 21.5 wk, there was a subgroup (numbers not clearly specified) who only received the supplement for barely 3–4 mo, and once one takes the 88% compliance into account in group 1, the overall exposure to the intervention in the prepregnancy period could be really limited in an already small and disparate group of subjects. It can be debated what the optimal duration of prepregnancy nutrition intervention exposure is, but in our large effectiveness trial of a life skills and nutrition intervention in rural Pakistan, we have specified a minimum 6 mo of intervention exposure (4).

The second point on "drop outs" was also related to the aforementioned considerations. If preconception nutrition intervention studies were designed to start early and aimed to achieve optimization of dietary (and micronutrient) intakes through basic measures such as poverty alleviation programs and promotion of intake of fortified foods/staples (5), we would not face the conundrum of trying to address maternal nutrition through the lens of birth outcomes only. Admittedly, the Women First trial had to recruit a cohort and obtain the maximum number of births within a finite period, but one could argue that obtaining study endpoints in only one-third of those recruited missed a huge opportunity of assessing outcomes related to the health and well-being of most, if not all, eligible recruits. Notwithstanding these difficulties in preconception trials, several strategies have been proposed for optimizing recruitment and retention of participants including adequate resourcing for longer, robust studies (6).

Finally, the comment on the limited repertoire of micronutrients was indeed in relation to the calcium and vitamin D (and possibly also iron) intake through the lipid nutrient supplement. The supplement