COMMENTARY

The systematic review by Gera and Sachdev rightfully address an important unresolved issue. Iron deficiency is the major micronutrient deficiency world-wide and the international community has repeatedly called for action to correct it. In many countries strategies are implemented to increase iron consumption or by supplementing specific target groups. One concern has been the safety issue in particular in malaria endemic areas. The present paper concludes that providing extra iron is safe with regard to incidence of infections. Interestingly, the authors' conclusions regarding malaria is consistent with those of another review of the available evidence on the risks and benefits of iron supplementation in malarious areas carried out by INACG in 1999 (cited by [1]). Iron supplementation is not associated with a significant increase in the risk of clinical malaria, although it increases the odds of being slide-positive for malarial parasitaemia at end of the supplementation period.

Safety is however much broader than incidence for infections. Absorption of oral iron is related to the degree of deficiency, which is translated in the number of intestinal iron receptors. Absorption is however never completely switched off , meaning that there is a risk of iron overload for person carrying the haemochromatosis trait [2] . How important this is, is up to now not clear. . The authors rightfully mention that iron is a very potent free radical generator. But at the same time a numerous mechanisms exist to provide protection against free radical damage [3]and it is only when the balance between free radical generation and protection is broken that specific damage is generated. The best know case being kwashiorkor [4]. The protective mechanism are either enzyme based in which minerals such as zinc, manganese and selenium are essential elements or more indirect using the electron scavenging properties of vitamins such a E and A, carotenes or polycyclic molecules now referred to as antioxidants. Deficiencies of nutrients that act as antioxidants can compromise cell-mediated immunity. The observed variation in response to iron supplementation between control and supplemented groups in the different studies analysed in the paper by Gera and Sachdev could thus be attributable to a concomitant shortage of factors that in the presence of iron protect against free radical damage. Most of the mentioned micronutrients have also in their own right been implicated in decreased disease resistance.

Methodologically the authors have accomplished an impressive piece of work, particularly in their effort to limit publication bias. But as they mention in the discussion, a striking limitation of the analysis is the wide statistical heterogeneity between studies. This heterogeneity is barely a surprise when one considers the important clinical and methodological variations among trials. The authors did model the heterogeneity by performing a random-effect analysis. But still the relevance of pooling results from studies with so obvious different characteristics (setting and consequently risk of infection, age range, route of administration and duration of the iron supplementation, specificity of case definition) is questionable. It can be argued that random-effect analysis is simply a means of combining "apples and pears", and that investigating sources of heterogeneity is more informative than pooling [5]. Fortunately this is what the authors attempted to do by stratified analysis and meta-regression analysis. None of the study characteristics included in the meta-regression could explain the heterogeneity, although some important covariates such as dose or age group were not included. But the question of heterogeneity is maybe not so

important. When considering the forest plot for incidence rate ratio of illnesses, the treatment effect, if any,
is weak in most of the individual studies, the estimate being very close to 1 for all the big studies. Thus, the overall conclusion that iron supplementation is safe seems to be guaranteed at least regarding the investigated infectious diseases.

Reference List

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