Reviewer's report

Title: HFE Gene Variants Modify the Association between Maternal Lead Burden and Infant Birthweight: A Prospective Birth Cohort Study in Mexico City, Mexico

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Reviewer: Fernando E. E Viteri

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This interesting paper is a good attempt to take advantage of a previous study that explored the effect of calcium supplementation on bone lead mobilization during lactation. This fact, however, limits significantly the possibilities of exploring HFE and TF gene variants in a systematic way.

The major weakness of this paper is the fact that the authors do not account for the possibility of the effect of maternal iron status prior to and during pregnancy, including the ingestion of iron from antenatal supplementation. This may influence maternal bone lead burden and mobilization during pregnancy and its effects on the fetus, including birth weight. Another important effect would be on iron and lead absorption and possibly fetal lead deposition. Unfortunately, postpartum maternal haemoglobin is a poor proxy of iron status, especially that during critical periods of pregnancy when its influence on birth weight is clear. In essence, the lack of information on maternal iron status and supplementation during pregnancy introduces a serious confounding factor on the relation between HFG mutations and birth weight. It must be recognized that 21 and 28% of non-pregnant and pregnant Mexican women, respectively, are anemic, the great majority because of iron deficiency. It is also important to note that in Mexican women allele frequency C282Y is lower than that observed in descendents from northern Europe, and that serum ferritin levels and iron overload frequency have not been found different in the presence of HFE allele alterations. Even so, iron status cannot be ignored.

Another confounding factor that is not properly addressed in this paper is the relation between calcium intake and possible bone release of lead. In Mexico, antenatal multimineral and multivitamin supplementation is compulsory, although compliance is far from optimal. In any case, the average calcium intake in a similar sample of Mexican pregnant women was moderately higher than the DRI for calcium (1,000 mg/day) and the higher calcium intake was associated with lower blood and bone lead, even though the dispersion of calcium intake was large. It would have been important to consider calcium intake if this was available.

Are there data available on maternal blood lead besides bone lead? Are they significant covariates?

Even though the homozygous HFE H63D and compound heterozygotes were
removed for good statistical reasons, their results should have been presented
given that they could have been "outliers".

Lastly, some minor editorial corrections or modifications could be suggested:
Indicate that it is maternal bone lead every time bone lead is referred to.
Wild type HFE H63 and not HFE H63D should be indicated as homozygous non-
variant. The same should be for the homozygous wild type genes C282 and
TFP570.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a
statistician.

**Declaration of competing interests:**
I declare that I have no competing interests.