

Format for ANSWERING REVIEWERS



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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 20211-review.doc).

Title: Nutritional determinants of anemia among adults in Eastern China

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The manuscript has been improved according to the suggestions of reviewers:

Review 1

An interesting paper that should be accepted, since it attempts explaining a treatable condition anaemia, and suggests that it is not the commonly considered -iron deficiency - that actually causes this condition. Authors should: i) consider whether hereditary haemoglobinopathy plays a role in anaemia in Eastern China since thalassemia can cause anaemia with elevated serum ferritin and is a common condition in the Chinese population. ii) provide examples around the world where riboflavin (and magnesium) insufficiency has been established as the cause of anaemia since they suggest that in Eastern China it is in fact the inadequate dietary intake of riboflavin (and magnesium) that causes the anaemia

-Responses: Thank you very much for the positive comments and suggestions.

1. The prevalence of HFE is rare in the Chinese population based on HFE gene mutation data. Please see “hereditary haemoglobinopathy is rare in the Chinese population⁽⁴⁾”

2. We have added more references to the relationship between riboflavin and anemia.

See text “A recent trial in China showed that retinol and riboflavin supplements decreased the prevalence of anemia in pregnant women also taking iron and folic acid supplements⁽²⁵⁾. In UK, it has been found that riboflavin supplementation improves hematologic status among women aged 19-25 years with moderate riboflavin deficiency⁽²⁶⁾.”

3. We are not aware of studies using magnesium supplement to treat anemia. However, we have cited another study from China showing an inverse association between serum magnesium level and anemia. See text: “Data from CHNS also shows that serum magnesium is inversely associated with anemia in both men and women⁽²⁹⁾.”

Review 2

The authors review data suggesting that anemia in this particular region of China may not be due to iron deficiency but due to other factors such as riboflavin and magnesium deficiency or related to MSG intake. In the Abstract: I am not sure if riboflavin can be described as a micronutrient. “Over the past several decades, the prevalence of anemia decreased substantially but remains high”. Why, in the context of their findings, is the prevalence of anemia decreasing? What relevance can this have in strengthening their findings?

-Response: Thank you very much for the questions. Although we do not completely know the causes, the rapid nutrition transition in China was accompanied by the prevalence of anemia decreasing during the past decades.

This may suggest a role of nutrition in the etiology of anemia in the region. That is why we synthesize the evidence generated in the region.

According to the nutrition text book, we believe riboflavin is a micronutrient.

They mention that iron-rich soy sauce is used to treat anemia despite the fact that the actual cause may not be iron deficiency. Can the authors comment on the efficacy of this iron enriched soya supplementation? Does it have a positive effect on anemia after all, or is the benefit negligible?

-Response: A population intervention trial using iron fortified soy sauce was conducted in a different province of China (Chen J et al. Studies on the effectiveness of NaFeEDTA-fortified soy sauce in controlling iron deficiency: a population-based intervention trial. *Food Nutr Bull* 2005; **26**(2): 177-86; discussion 87-9.). Due to the substantial regional differences of food habits in China, it is unknown whether the evidence generated from that province will be applicable in our study region. A recent study shows that the association between dietary intake and anemia is different between migrant students and local students in the region (Hu S et al. Disparity of anemia prevalence and associated factors among rural to urban migrant and the local children under two years old: a population based cross-sectional study in Pinghu, China. *BMC Public Health* 2014; **14**: 601.).

Any data in using riboflavin supplementation in clinically improving anemia will strengthen their case. It may be worth expanding on this in the clinical sense.

-Response: Reviewer one raised the same question. We have added extra information in the text: “A recent trial in China showed that retinol and riboflavin supplements decreased the prevalence of anemia in pregnant women also taking iron and folic acid supplements⁽²⁴⁾. In UK, it has been found that riboflavin supplementation improves hematologic status among women aged 19-25 years with moderate riboflavin deficiency⁽²⁵⁾”.

“Although Tofu intake was inversely associated with persistent anemia during follow-up, it was positively related to incident anemia but inversely related to anemia resolving”. Why is this so? Is tofu also enriched with iron, or how does tofu affect iron, ferritin or Hb levels?

-Response: Thank you for the questions. We have discussed the potential mechanisms. Please see text: “The cause for incident anemia or anemia resolving may be different to the persistent anemia. An inverse association between Tofu intake and persistent anemia may be explained by several mechanisms: 1) Tofu intake was positively associated with magnesium intake⁽¹⁶⁾; 2) Tofu intake is inversely associated with blood lead levels in the Chinese population⁽¹⁷⁾; and 3) soy intake is inversely associated with inflammation biomarkers⁽¹⁸⁾”.

They say: “However, when riboflavin intake is adequate, iron intake is not a determinant of anemia”... So then, if riboflavin intake is adequate, what is the cause of anemia in these patients?

-Response: At the population level, we are unable to tease out what is the cause of anemia among those with adequate riboflavin intake. However, the proportion of adequate riboflavin intake is very low as shown in Figure 3.

What dietary recommendations do they make? Increase riboflavin and magnesium intake, or regulate use of MSG? How would we know in practical terms that the intake is adequate for prevention of anemia and that it will not cause excessive elevation of Hb? Are these recommendations possible in the local culture? In short, the authors should comment further on the translational aspects of their findings, and not merely state that iron is not the main cause of anemia.

-Response: Given the fact that there is a limited number of studies on the topic in the region, we hesitate to make recommendations. However, we can conclude that anemia is related to diet and certain micronutrients intake.

Spelling error: "The possible mechanisms linking MSG and anemia may include the increased secretion of gastric acid and leptin": it should be 'increased secretion'...

-Response: Thank you. Change has been made.

Review 3

This manuscript discussed "Nutritional determinants of anemia among adults in Eastern China" based on the available data. It is well written, and will be interesting to readers of this journal.

-Response: Thank you very much for the very positive comments.

Thank you again for publishing our manuscript in the *World Journal of Translational Medicine*.

Sincerely yours,

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