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LETTER TO THE EDITOR

Proportion of anemia attributable to iron deficiency in high-altitude infant populations

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Dear Editor,

Anemia is still one of the main unsolved global health problems, affecting 41.7% of preschool children (PSC) [1]. According to WHO, 50% of anemia cases are attributable to iron deficiency (ID) [2]. Based on these statements, most intervention programs use iron supplementation and/or iron food fortification. Nevertheless, anemia prevalence fell since 1990 until 2014, but then stagnated with a tendency to increase in the last years [1]. Recent systematic studies suggest that the proportion of anemia cases attributable to ID is lower than previously assumed. In PSC, 25.0% of anemia cases from 23 countries [3] and 30% from several Latin American countries were attributable to ID [4].

There is no information reported of iron deficiency anemia (IDA) in PSC living in mountain areas. The importance of its study lies in the fact that around 350 million people live in altitudes over 1000 m [5] and as WHO recommends correcting hemoglobin by altitude, the prevalence of anemia increases dramatically [6]. Recent evidence suggests that this correction should not be applied to all high-altitude populations worldwide and despite the intervention is based on iron supplementation, progress in reducing anemia has been modest [7]. Even the anemia prevalence is higher in the mountain than in populations living at lower elevations [7]. The prevalence of anemia in children 6–59 months of age in Bolivia is persistently very high and virtually unchanged between 1998 and 2016, except for an increase in children living at high altitude [8].

In two populations residing in the Peruvian highlands, the anemia prevalence in PSC aged between 6 and 35 months was 67.7% in Puno and 53.2% in Apurimac [7]. These figures are higher than the national average (43.5%). In general, prevalence of anemia is higher in mountain region of Peru than in the rest of the country (Fig. 1a). However, the proportion of anemia attributable to ID in these highland populations is unknown.

We have assessed data from a previous study in Apurimac [9] and our database obtained in Puno aimed to solve the above question. In Apurimac, children aged 10–35 months residing between 2500 and 3699 m above sea level consumed 60 or more sachets of powders of multi micronutrients (MMN) during a period of 6 months [9]. They were compared with a control population not consuming MMN powders. Each sachet contains 12.5 mg iron; 300 ug vitamin A; folic acid 160 ug; vitamin C 30 mg; zinc 5 mg. The iron intervention reduced the prevalence of anemia from 47.4% (control group) to 36% (intervention group).

Subsequently, we have calculated that this value represents about 25% of anemia attributable to ID and the remaining 75% is due to other causes not evaluated. The study showed that mean hemoglobin increased by 0.3 g/dL in the intervention group compared with the control [9]. In populations where anemia is prevalent, the intervention with iron to be successful should result in a mean hemoglobin change of about 1.17 g/dl or higher [2]. The value in Apurimac is around 4 times lower than the expected.

We have assessed a database from 334 children evaluated in the highland region of Puno in the southern part of Peru (average 3800 m above sea level). We found that anemia prevalence was 66.8%, and the prevalence of IDA was 14.7% (Fig. 1b). Then, we estimated the proportion of anemia attributable to ID. According to this, 22% of cases of anemia in children aged 6–

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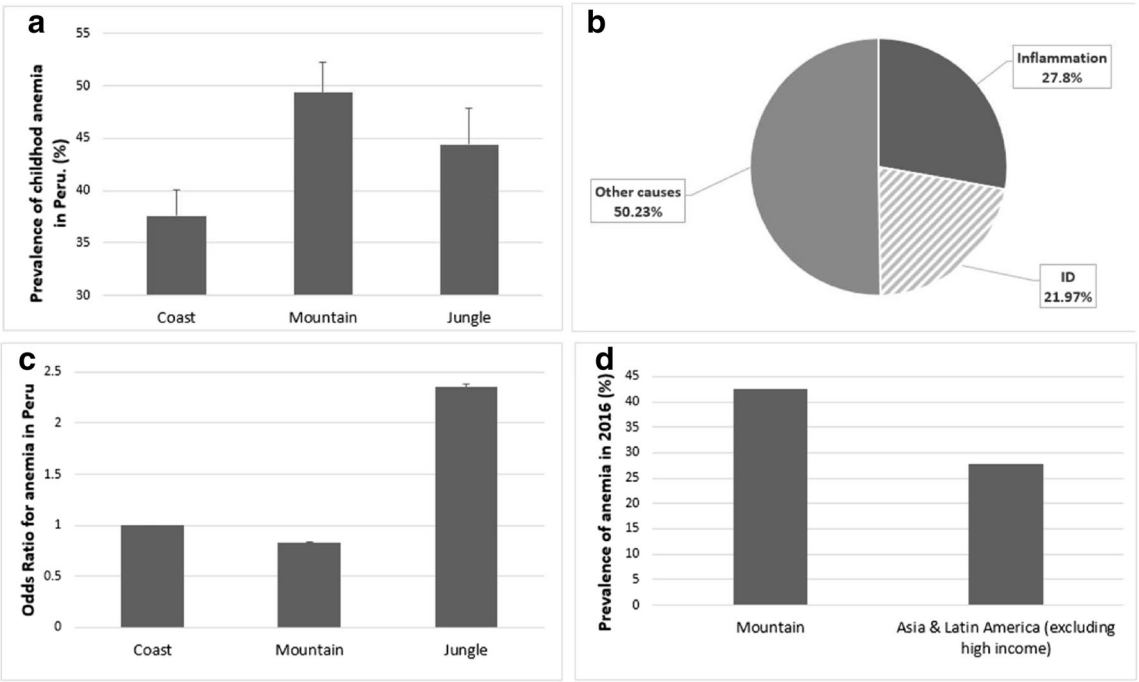

Fig. 1 **a** Prevalence of anemia in Peruvian infants aged 6–35 months according to geographical region of residence. $p < 0.01$ between mountain and coast regions, and between jungle and the coast region. Anemia in mountain places was diagnosed with hemoglobin correction by altitude. Source: INEI, 2019 [7]. **b** Proportion of anemia by causes in Puno, Peru. Total sample included 334 children between 6 and 59 months. From these, 223 children were diagnosed with anemia after Hb correction, whereas 49 and 62 children were diagnosed with iron deficiency anemia (IDA) and inflammatory anemia (IA), respectively. We estimated the proportion of anemia attributable to iron deficiency as (IDA prevalence)/(anemia prevalence) and the proportion of anemia attributable to inflammation as (IA prevalence)/(anemia prevalence). 21.97% of the total cases of anemia were attributable to iron deficiency, 27.8% was attributable by inflammation, and more than half of anemia cases are attributable to other causes no evaluated. Body iron content (BIC) was calculated using measurements of ferritin and soluble transferrin receptor (sTfR) in serum. BIC = (mg/kg) = −[log(sTfR×1000/ferritin)−2.8229)]/0.1207. Serum ferritin levels (ng/mL) were determined using a ELISA kit (Reference: EIA-1872; DRG Instruments GmbH, Germany). Serum soluble transferrin receptor (sTfR)(mg/L) was detected using sensitive ELISA (Reference: EIA-4256; DRG Instruments GmbH, Germany). Inflammatory status was assessed measuring serum interleukin 6 concentration. Interleukin 6 was measured using ELISA kit (Reference: EIA-4640; DRG Instruments GmbH, Germany). Interleukin 6 correlated directly with serum hepcidin ($Y = 0.16X + 0.07$; $r = 0.27$; $p < 0.01$) but not with BIC ($Y = -0.01x + 5.39$; $r = -0.07$; $p > 0.05$). **c** Multivariate analysis to determine odds ratio (OR) for anemia in preschool children (6–59 months) by geographical region in Peru. Data were controlled by intervention with multimicronutrients containing iron supplement, age (months), and stunting. OR at the coast was considered the reference (OR = 1). Confidence intervals at 95 % at the mountain places were 0.81–0.85 (p = 0.0001) and at the jungle region, 2.28–2.42 (p = 0.0001). Anemia in mountain places was diagnosed without hemoglobin correction by altitude. **d** Prevalence of anemia in 8 countries where people live in elevations zones compared with prevalence of anemia in Asia and Latin America countries excluding high income. Population living at high altitudes are from Latin America (Bolivia, Peru) and Asia (Afghanistan, Bhutan, Kyrgyz Republic, Nepal, Pakistan, and Tajikistan). Source: World Bank [1] Figure 1 contains poor quality of text in image. Otherwise, please provide replacement figure file.Higher quality Figure1 has been sent as an attachment to the following email CorrAdmin1@spi-global.com because we could not upload it on this platform.

59 months were attributable to ID. Besides, we have calculated the proportion of anemia attributable to inflammation (27.8%) (Fig. 1b). It is probably that in the 50.23% of the remaining cases, anemia could be due to other causes and/or that diagnosis was inaccurate as it has been suggested previously for highlanders [6,10]. Figure 1c shows that odds ratio (OR) for anemia is lower in mountain region when hemoglobin is not corrected by altitude. Interestingly, anemia in the jungle has high OR despite iron intervention suggesting that treatment of anemia in this geographical region should not be based only on iron. Comparing data from World Bank is evident that populations living at high altitude in Latin America and Asia have consistently high prevalence of anemia (Fig. 1d) and this could be due to the correction factor rather than a true anemia.

Iron supplementation could even be severely harmful in populations without ID or when anemia is due to other conditions, as observed for PSC in malaria-endemic settings [4]. It may be necessary to review the continuous practice of attributing 50% of anemia cases to ID and the general use of anemia diagnosis as ID. Finally, studies to quantify and map anemia distribution in different settings are necessary to implement adequate anemia-reduction strategies and interventions should be based on an analysis of country-specific data since ID cannot always be the key determinant of anemia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Research involving human participants The study in Puno involved human participants. The procedures performed in the mentioned study involving human participants were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975 as revised in 2008. GFG and VP did not participate in any study involving human beings presented in the present article. IRB at the Universidad Peruana Cayetano Heredia approved the study using database.

Informed consent An informed consent was obtained from parents before the development of the study in Puno.

References

1. World Bank. Prevalence of anemia among children (% of children under 5) [Internet]. 2016 [cited 2019 Aug 21].
2. Stoltzfus RJ, Mullany L, Black RE (2004) Iron deficiency anaemia. Chapter 3. In: Ezzati M, Lopez A, Rodgers A, Murray C (eds) Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors, pp 1–48
3. Petry N, Olofin I, Hurrell R, Boy E, Wirth J, Moursi M, Donahue Angel M, Rohner F (2016) The proportion of anemia associated with iron deficiency in low, medium, and high human development index countries: A Systematic Analysis of National Surveys. Nutrients. 8(11):693
4. Engle-Stone R, Aaron GJ, Huang J, Wirth JP, Namaste SM, Williams AM, Peerson JM, Rohner F, Varadhan R, Addo OY, Temple V, Rayco-Solon P, Macdonald B, Suchdev PS (2017) Predictors of anemia in preschool children: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr. 106(Suppl 1):402S–415S
5. Huddleston B, Ataman E, de Salvo P, Zanetti M, Bloise M, Bel J, Franceschini G (2003). Towards a GIS-based analysis of mountain environments and populations [Internet].
6. Sarna K, Gebremedin A, Brittenham GM, Beall CM (2018) WHO hemoglobin thresholds for altitude increase the prevalence of anemia among Ethiopian highlanders. Am J Hematol. 93(9):E229–E231
7. INEI (2019). Encuestra Demográfica y de Salud Familiar - ENDES 2019-1.
8. Cordero D, Aguilar AM, Casanovas C, Vargas E, Lutter CK (2019) Anemia in Bolivian children: a comparative analysis among three regions of different altitudes. Ann N Y Acad Sci 1450(1): nyas.14038
9. Aparco JP, Bullón L, Cusirramos S (2019) Impacto de micronutrientes en polvo sobre la anemia en niños de 10 a 35 meses de edad en Apurímac, Perú. Rev Peru Med Exp Salud Publica. 36(1):17–25
10. Gonzales GF, Rubin de Celis V, Begazo J, del Rosario Hinojosa M, Yucra S, Zevallos A, Tapia V (2018) Correcting the cut-off point of hemoglobin at high altitude favors misclassification of anemia, erythrocytosis and excessive erythrocytosis. Am J Hematol 93(1): E12–E16 Please check captured Author names if correct.Refferences are fine.