The American Journal of Clinical Nutrition 118 (2023) 114–120

The American Journal of CLINICAL NUTRITION

journal homepage: https://ajcn.nutrition.org/

Original Research Article

Association between Hemoglobin and Elevation among School-aged Children: A Verification of Proposed Adjustments

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A B S T R A C T

Background: Anemia is defined by a hemoglobin (Hb) concentration lower than normal based on cutoffs specific to age, sex, and pregnancy status. Hb increases with elevation as an adaptive response to lower blood oxygen saturation, thus, adjusting Hb concentrations for elevation is necessary before applying cutoffs.

Objectives: Recent evidence among preschool-aged children (PSC) and nonpregnant reproductive-aged women (WRA) suggests that current World Health Organization (WHO)-recommended Hb adjustments for elevation need updating. To confirm these findings, we examined the cross-sectional association between Hb and elevation among school-aged children (SAC).

Methods: Using data from 9 population-based surveys, we examined 26,518 SAC aged 5−14 y (54.5% female) with data on Hb and elevation (−6 to 3834 m). We used generalized linear models to assess the association between Hb and elevation under varying conditions, including controlling for inflammation-corrected iron and vitamin A deficiency (VAD). Hb adjustments for each 500-m increase in elevation were estimated for SAC and compared with existing adjustments and those estimated for PSC and WRA. We evaluated the impact of these adjustments on anemia prevalence.

Results: Hb concentration (g/L) was positively associated with elevation (m). The SAC-elevation adjustments were consistent with those reported among PSC and WRA and suggest current recommendations may under-adjust Hb for those residing at lower elevations (<3000 m) and over-adjust Hb for those residing at higher elevations (>3000 m). Among the surveys included, the proposed elevation adjustments increased anemia prevalence among SAC by 0% (Ghana and United Kingdom) to 15% (Malawi) relative to current elevation adjustments.

Conclusion: Results confirm that current recommended Hb adjustments for elevation may need updating, and anemia prevalence among SAC may be higher than currently estimated. Findings will inform the WHO's reexamination of global guidelines on the use of Hb adjustments for anemia assessment and may result in improved identification and treatment of anemia.

Keywords: anemia, hemoglobin, elevation, school-aged children, BRINDA

Introduction

Anemia, a common global health problem, is defined by a hemoglobin (Hb) concentration lower than normal. It is generally accepted that iron deficiency is the primary cause of low Hb concentration in many settings; however, other causes include micronutrient deficiencies in vitamins A, B2, B12, and folate [1], as well as nonnutritional causes such as acute and chronic diseases, blood loss, genetic blood disorders, and infections such as HIV, tuberculosis, and malaria [2]. Hb cutoffs to determine anemia are specific to age, sex, and pregnancy status. Moreover, Hb increases with elevation as an adaptive response to lower blood oxygen saturation [3,4]. Thus, adjusting Hb concentration for elevation is necessary before applying cutoffs [1].

In 1989, Hb adjustments for elevation were initially published [5] based on data from two sources: the CDC Pediatric Nutrition

Abbreviations: AGP, α-1-acid-glycoprotein; BRINDA, Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia; GIFTS, Girls'Iron-Folate Tablet Supplementation; Hb, hemoglobin; ID, iron deficiency; NNMSS, Nepalese National Micronutrient Status Survey; PedNSS, Pediatric Nutrition Surveillance System; PSC, preschool-aged children; SAC, school-aged children; SIVESNU, Sistema de Vigilancia Epidemiológicade Salud y Nutrición; RBP, retinol-binding protein; SF, serum ferritin; SR, serum retinol; sTfR, soluble transferrin receptor; VAD, vitamin A deficiency; WRA, women of reproductive age.

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https://doi.org/10.1016/j.ajcnut.2023.04.014
Received 7 February 2023; Received in revised form 7 April 2023; Accepted 11 April 2023
Available online 13 April 2023

Surveillance System (PedNSS) where data were collected from 1974 to the mid-1980s among low-income, mostly White children aged 2–4 y, and a 1945 publication by Hurtado et al. [6] examining indigenous Peruvian men residing at high-elevations. The WHO subsequently adopted these adjustments in 2001 [7]. Because these data sources were not diverse by age, sex, race/ethnicity, life-course stage (e.g., pregnancy status), or country, they did not account for potential confounding factors such as micronutrient status, and were > 50 y old, there was a question as to whether the WHO global elevation adjustments were appropriate across all population groups.

WHO is currently reviewing global guidelines for anemia and has identified hypoxia and elevation affecting Hb concentrations as a priority topic [8]. Recent evidence among preschool-aged children (PSC; 6–59 mo) and nonpregnant women of reproductive age (WRA; 15–49 y) suggests that current WHO-recommended Hb adjustments for elevation may need updating. A recent analysis [9] of pooled population-based survey data from 14 countries examined the association between Hb and elevation in an effort to define Hb adjustments; these proposed Hb adjustments were compared with current WHO guidelines. This analysis [9] concluded that adjustments were similar among PSC and WRA, although the current recommendations under-adjust Hb at low elevations and over-adjust Hb at high elevations. Children aged 5–14 y were not included in these analyses.

To date, there has been no study focused on nonpregnant school-aged children (SAC). School-age children should be considered to strengthen the case for updating WHO adjustments. Addressing this specific population group could confirm the reproducibility of proposed adjustments for PSC and WRA and provide insights on if and how Hb should be adjusted for elevation among SAC. The purpose of our study is to examine the association between Hb and elevation among WRA and SAC aged 5–14 y using contemporary, multinational, population-based survey data, and recommend updated adjustments.

Methods

Data sources and study population

The Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project, a multi-agency and multinational partnership, pooled data from national and subnational representative surveys to examine the relationship between inflammation and nutrition biomarkers and identify factors associated with anemia in highly prevalent groups [10]. Information on survey selection is available on the project website https://www.brinda-nutrition.org/thebrindastory. Six surveys (representing 5 countries) with available data on SAC were included. Three additional population-based surveys with requisite data were included to increase diversity and the number of children residing at higher elevations, namely, the Guatemalan Sistema de Vigilancia Epidemiológicade Salud y Nutrición (SIVESNU, 2017), the Nepalese National Micronutrient Status Survey (NNMSS, 2016), and the Ghanaian Girls' Iron-Folate Tablet Supplementation (GIFTS, 2019) program survey [11]. From the 9 surveys (representing 8 countries) combined, a total of 27,404 children aged 5–14 y were potentially eligible for analysis. All surveys were conducted with appropriate ethical approval. CDC reviewed this analysis, which was conducted consistent with applicable federal law and CDC policy.

Variables

Children who were missing data on elevation or Hb (n = 825) were excluded from the analysis. Elevation at the household or cluster was a continuous value in all countries except for the United Kingdom, where it was set at 80 m for all individuals based on the average elevation of the 10 most populous areas [9]. Hb measures were completed at the time of blood collection using point-of-care photometers (HemoCue) for all surveys, using either venous blood (Colombia, Ecuador, Guatemala, Malawi, Nepal, and the United Kingdom) or pooled capillary blood (Ghana and Mexico). Hb concentrations >210 g/L or <40 g/L (n = 3) were defined as biologically implausible and excluded from the analyses. Anemia was defined as Hb concentration <115 g/L for children aged <12 y and <120 g/L for children aged 12–14 y after adjusting for elevation [1]. Adjusting for elevation includes subtracting the indicated elevation adjustment from an individual's Hb measure before applying anemia criteria. Smoking status was not generally assessed among SAC, and thus, not examined.

Iron deficiency (ID), vitamin A deficiency (VAD), and malaria status were examined as potential confounding factors associated with both Hb and elevation. Iron deficiency was assessed in all surveys and defined as serum ferritin (SF) < 15 μg/L [12]. If data were missing on SF (n = 14), soluble transferrin receptor (sTfR) > 8.3 mg/L was used to identify ID [13]. Among children with data on Hb and elevation, there were 58 records where both SF and sTfR were missing. For simplicity, these records were excluded from the analysis so that all children in our primary dataset had complete data on Hb, elevation, and ID status (n = 26,518). Vitamin A status was assessed in all surveys, except for the Colombian and Mexican surveys in 2006. For the subsample with vitamin A biomarker data (n = 10,429), VAD was defined as either serum retinol (SR) <0.70 μmol/L or the equivalent survey-specific cutoff for retinol-binding protein (RBP) determined by comparing RBP and SR within each survey (Malawian <0.46 μmol/L; Guatemalan <0.63 μmol/L; Nepalese <0.64 μmol/L; Ghanaian <0.70 μmol/L). Nutrition biomarkers were corrected for inflammation using the BRINDA regression method. Specifically, SF, SR, and RBP were corrected for C-reactive protein (CRP) (and alpha-1-acid-glycoprotein [AGP], where available) for each survey; survey-specific tenth deciles for AGP and CRP were used [14,15]. Malaria status was assessed only in Ghana, Malawi, and Nepal using rapid test kits. For the purpose of identifying an apparently healthy population (no ID, VAD, or known malaria), SAC with a positive malaria test were considered to have "known malaria." In addition, ID, VAD, and known malaria were all inversely correlated with Hb (−0.09, −0.08, and −0.19, respectively; all $P < 0.0001$) and elevation (−0.03, −0.07, and −0.04, respectively, all $P < 0.0001$).

Statistical analysis

Using generalized linear models, we assessed for a nonlinear association between Hb and elevation as previously reported [9] and assessed for effect modification by age (5–9 y, 10–14 y) or sex (male, female). We then examined the association between Hb and elevation under varying model specifications. The first model examined the crude association between Hb and elevation for individuals with data on ID. The second model examined the association between Hb and elevation, controlling for ID. The third model examined the crude association between Hb and elevation for individuals with data on both ID and VAD. The fourth model examined the association between Hb and elevation, controlling for both ID and VAD. The fifth model was restricted to an apparently "healthy" population, including individuals with no ID, VAD, or known malaria (n = 8596). A separate "healthy" model was examined without consideration of malaria ("healthy" is defined as no ID and no VAD only, n = 9073); results were nearly identical to the model that included malaria and thus are not shown. All

models were controlled for age (continuous), sex, and survey (to account for potential unmeasured confounding variables and the underlying differences in mean Hb associated with each location). Because each survey contributed a different proportion of data when pooled together, to maximize geographic representation for each model, data from each country were weighted to equalize representation across countries. We used SAS 9.4 to conduct all analyses, with statistical significance considered at $P < 0.05$ (main effects) and $P < 0.15$ (interactions). The proportion of explained Hb variance (R^2) and the adjustment equation were reported for each model. Using the adjustment equations, the Hb adjustment and 95% confidence interval for each 500-m increase in elevation were calculated and compared with adjustments derived from the 1989 CDC equation [5,16] and the recently proposed adjustments among other age groups [9].

To characterize the impact of the proposed adjustment criteria on anemia prevalence, we compared the population prevalence of anemia for each survey using the proposed equation for SAC with the existing adjustments using the 1989 CDC equation. Prevalence estimates accounted for the complex survey design; the Taylor linearization method was used to obtain an unbiased estimate that incorporated the original sampling weights, strata, and cluster, where applicable.

Results

Hb and elevation

Of the 27,404 records from 8 countries, 26,518 (96.8%) had the minimally required data for analysis (Supplemental Figure 1). A summary of the included surveys, elevation ranges, availability of specific biomarker data, and proportion with ID or VAD is presented in Table 1. Elevations ranged from −6 m to 3834 m, with 13,009 (49.0%) of SAC residing below 500 m and 2779 (10.5%) residing at or above 2500 m. Overall, 14,452 (54.5%) of SAC were females, ID was more prevalent (11.5%) than VAD (4.4%), and 13,688 (51.6%) were aged 5–9 y.

We tested for a nonlinear association between Hb and elevation by including a quadratic term (elevation^2), which was statistically significant ($P = 0.01$). Thus, this quadratic term was included in all the models. We tested for effect modification by age and sex by including interaction terms with elevation, which was significant for both age*elevation ($P = 0.0009$) and sex*elevation ($P = 0.0001$). We examined the crude model with and without stratification by age or sex and found no meaningful differences in Hb adjustments (Supplemental Table 1). Regardless of model stratification, the difference in Hb adjustment between models was $\leq$ 1 g/L at any given elevation range. For simplicity and to maximize sample size and elevation range across models adjusting for ID and VAD, the remaining results are presented with no age or sex stratifications.

Adjustment equations for each model are presented and visualized in Figure 1. The proportion of R^2 was the highest for model 2 (34%) and lowest for model 5 (28%). The association between Hb and elevation was similar across models, with more variation at elevations >2500 m. Model 1 (crude among individuals with ID data, $R^2 = 33\%$) and model 2 (adjusted for ID only, $R^2 = 34\%$) were nearly identical. Similarly, model 3 (crude among individuals with ID and VAD data, $R^2 = 29\%$) and model 4 (adjusted for ID and VAD, $R^2 = 30\%$) were also similar. Survey-specific associations are illustrated in Supplemental Figure 2. Associations for the Mexican surveys, where pooled capillary blood samples were used to assess Hb, were similar to those where

Table 1
Data source location, elevation range, and data availability

Country	Year	Total sample size	Records with Hb, elevation, and ID data	Elevation, m	Hb, g/L	Age, y	Female, %	Biomarker data available					ID %[1]	VAD %[1]
				Median Range	Mean (SD) Range			SF	sTfR	SR	RBP	CRP	AGP		
Colombia	2010	8604	8604	297 -6 to 3204	140 (15) 65–205	5–14	58	X				X		10.7	
Ecuador	2012	6063	6062	612 0–3834	136 (11) 72–200	5–14	49	X		X		X		3.3	10.5
Ghana	2019	651	621	234 20–367	126 (10) 95–156	10–14	72	X	X		X	X	X	11.4	4.7
Guatemala	2017	1129	878	1023 5–3200	138 (9) 101–175	6–14	51	X	X		X	X	X	5.0	1.5
Malawi	2016	758	751	951 52–1626	124 (14) 42–167	5–14	49	X	X	X	X	X	X	4.3	0.3
Mexico	2006	3660	3660	1160 1–3110	136 (16) 80–184	5–14	58	X	X			X		25.6	
Mexico	2012	4332	3783	1137 0–2973	135 (15) 71–179	5–14	49	X		X		X		14.8	1.6
Nepal	2016	1600	1588	785 46–3542	131 (12) 61–175	10–14	63	X	X		X	X	X	12.1	1.4
United Kingdom[2]	2014	607	571	80 80–80	132 (9) 79–161	5–14	47	X	X	X		X		16.1	1.3
Overall	2006-2019	27,404	26,518	527 -6 to 3834	136 (14) 42-205	5–14	54.5							11.5	4.4

AGP, α-1-acid-glycoprotein; CRP, C-reactive protein; Hb, hemoglobin; ID, iron deficiency (based on inflammation-corrected SF or sTfR if SF was unavailable); RBP, retinol-binding protein; SF, serum ferritin; SR, serum retinol; sTfR, soluble transferrin receptor; VAD, vitamin A deficiency (based on inflammation-corrected SR or RBP) [14].

[1] Proportion observed in data, not weighted to be nationally representative. Denominators: ID = 26,518; VAD = 10,429.

[2] Elevation is assumed to be 80 m based on the average elevation of the 10 most populous areas.

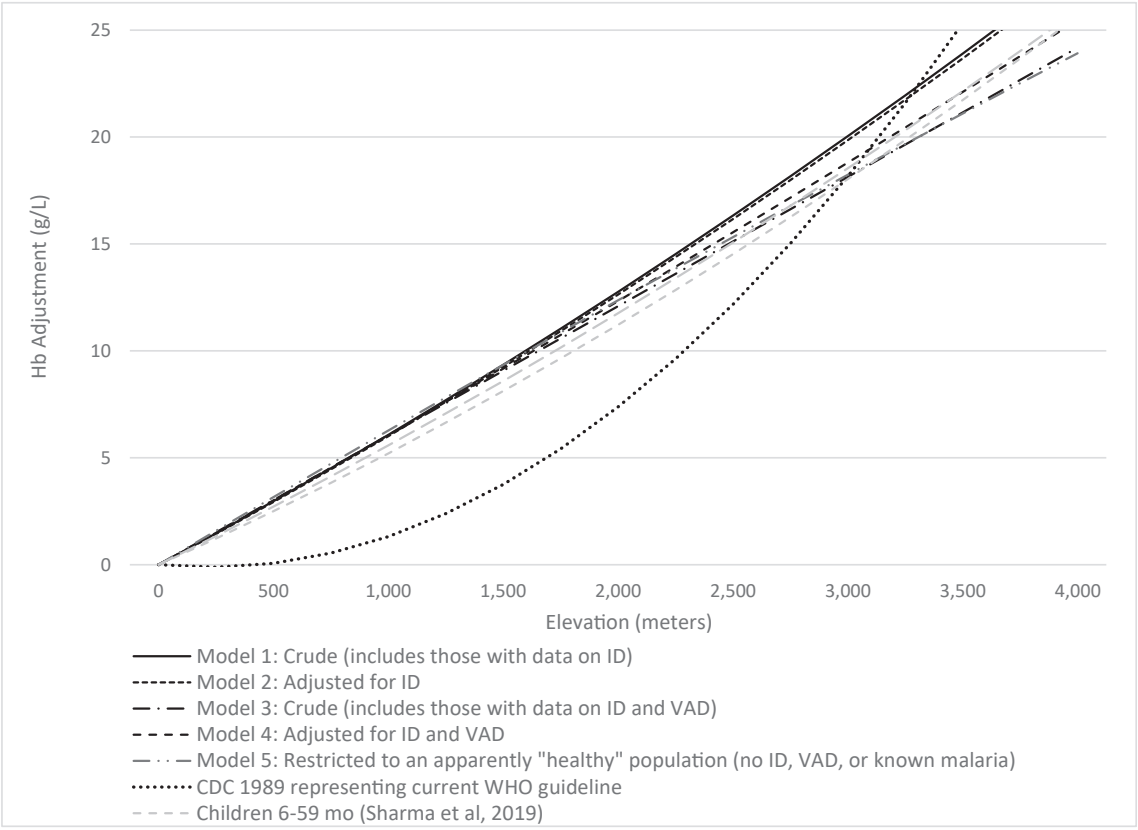

FIGURE 1. Hemoglobin adjustment for elevation among school-aged children aged 5–14 y, by model. All generalized linear models 1–5 included elevation, elevation^2, age (continuous), gender, and survey, and data were weighted to balance country representation. Females were nonpregnant. Models 1 and 2 included 26,518 observations. Models 3 and 4 included 10,429 observations. Model 5 included 8596 observations. Iron deficiency (ID) and vitamin A deficiency (VAD) are based on inflammation-corrected biomarkers [14]. Models among preschool-aged children and nonpregnant women were included for comparison [9].

TABLE 2
Estimated adjustments[1] (95% CI) to hemoglobin (g/L) by 500-m increments in elevation for school-aged children and comparison with current WHO guidelines (based on CDC 1989 equation) and proposed adjustments published for other population groups

Elevation, m	CDC 1989 equation[2]	The SAC model 2: adjusted for ID[3] (95% CI)	The SAC model 4: adjusted for ID and VAD[4] (95% CI)	Sharma PSC[5]	Sharma WRA[6]
<500	0	1 (1, 2)[7]	1 (1, 2)[7]	1 (1, 1)[7]	1 (1,2)[7]
500–999	1[7]	4 (4, 5)	5 (4, 5)	4 (3, 5)	4 (3, 5)
1000–1499	2	8 (7, 9)	8 (6, 9)	7 (5, 8)	7 (5, 9)
1500–1999	5	11 (9, 13)	11 (8, 13)	10 (7, 12)	10 (8, 13)
2000–2499	10	14 (12, 17)	14 (10, 18)	13 (9, 16)	13 (10, 17)
2500–2999	15	18 (15, 21)	17 (12, 22)	16 (11, 21)	17 (12, 21)
3000–3499	22	22 (18, 26)	20 (13, 27)	20 (13, 26)	20 (14, 26)
3500–3999	29	26 (21, 31)	24 (15, 32)	24 (15, 31)	24 (16, 32)

CDC, Centers for Disease Control and Prevention; CI, confidence interval; ID, inflammation-adjusted iron deficiency; PSC, preschool-aged children (6–59 mo); SAC, school-aged children (5–14 y); SE, standard error; VAD, inflammation-adjusted vitamin A deficiency; WRA, nonpregnant women of reproductive age (15–49 y).[1] Adjustment is the amount (g/L) added to the hemoglobin cutoff defining anemia or subtracted from an individual's observed hemoglobin level.

[2] CDC 1989 cutoffs [5, 16] calculated using Hb_adjustment (g/L) = {[−0.032 × (elevation × 0.0032808) + 0.022 Ã— (elevation × 0.0032808)^2] Ã— 10}, where elevation is based on the midpoint of the elevation range (e.g., 1750 m for the 1500−1999 m range).

[3] Proposed cutoffs among SAC (n = 26,518) calculated using Hb_adjust_elevation (g/L) = [0.0057163 (SE 0.0003073) × elevation] + [0.0000003 (SE 0.0000001) × elevation^2], where elevation is based on the midpoint of the elevation range.

[4] Proposed cutoffs among SAC (n = 10,429) calculated using Hb_adjust_elevation (g/L) = [0.0059666 (SE 0.0004817) × elevation] + [0.0000001 (SE 0.0000002) × elevation^2], where elevation is based on the midpoint of the elevation range.

[5] Proposed cutoffs among PSC (model adjusted for ID and VAD) [9] calculated using Hb_adjust_elevation (g/L) = [0.0048108 (SE 0.0004499) × elevation] + [0.0000004 (SE 0.0000002) × elevation^2], where elevation is based on the midpoint of the elevation range.

[6] Proposed cutoffs among WRA (model adjusted for ID and VAD) [9] calculated using Hb_adjust_elevation (g/L) = [0.0052792 (SE 0.0004508) × elevation] + [0.0000003 (SE 0.0000002) × elevation^2], where elevation is based on the midpoint of the elevation range.

[7] A difference of 1 g/L was not considered meaningful in WHO recommendations [1]; therefore, adjustments may not need to be applied for these elevations.

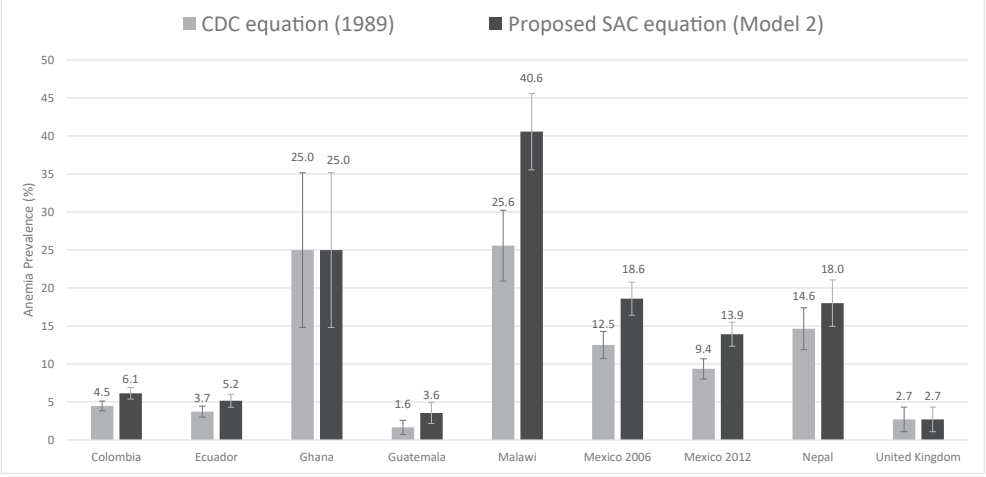

FIGURE 2. Prevalence of anemia among school-aged children (5–14 y) based on different criteria to adjust hemoglobin for elevation. Anemia was defined as Hb <115 g/L for age 5–11 y and Hb <120 g/L for age 12–14 y. Females were nonpregnant. Nationally representative prevalence estimates and 95% confidence intervals accounted for the complex survey design. Taylor linearization method was used to obtain an unbiased estimate incorporating the original sampling weights, strata, and cluster, where applicable. CDC (1989) [5] based on the equation Hb_adjust_elevation (g/L) = {[−0.032 × (elevation × 0.0032808) + 0.022 × (elevation × 0.0032808)2] × 10} [16]. No adjustments were applied to elevations <1000 m. Proposed SAC equation, Hb_ adjust _elevation (g/L) = [0. 0057163 (SE 0.0003073) × elevation] + [0.0000003 (SE 0.0000001) × elevation^2]. No adjustments were applied to elevations <500 m.

venous blood samples were used. Hb adjustments for each 500-m increase in elevation for models 2 and 4 are summarized in Table 2. Adjustments according to the 1989 CDC equation and the recently proposed adjustments for PSC and WRA are also provided for comparison.

Given the negligible difference in derived adjustments of models 2 and 4, model 2 was selected as the proposed equation because it included all surveys, had the highest R^2, and adjusted for at least one indicator of nutritional status. The population prevalence of anemia for each survey based on the 1989 CDC equation and the proposed SAC equation (model 2) is shown in Figure 2. Anemia prevalence was 0%–15% higher when applying elevation adjustments based on the proposed SAC equation compared to the 1989 CDC equation.

Discussion

This multinational study confirmed the association between Hb and elevation among SAC, supporting the need to adjust Hb concentrations for elevation to appropriately identify anemia. Furthermore, our findings add to the growing body of evidence [9,17–21], indicating that current WHO recommendations for Hb-elevation adjustments may need updating. Similar to the multinational examination of PSC and WRA [9], our findings indicate that current WHO recommendations (based on the 1989 CDC equation) under-adjust Hb for individuals residing at low elevations (<3000 m) and over-adjust Hb for those residing at high elevations (>3000 m).

Approximately 77% of the world's population resides at elevations below 500 m [22] and may not be subject to Hb adjustment under the assumption that a difference of 1 g/L is not clinically meaningful. A difference of <3 g/L in Hb concentration is generally considered within measurement error [23]. For the 23% of the world's population residing at elevations between 500 m and 3000 m, the prevalence of anemia would increase with the use of the proposed adjustments (e.g., Figure 2, Malawi), whereas for the <1% population residing at elevations above 3000 m, the prevalence of anemia would decrease. The overall impact of updated adjustments on population prevalence at national levels depends on the distribution of residence across the range of elevation (e.g., Figure 2, Ecuador, Nepal).

Our study identified the effect of modification by age and sex on the association between Hb and elevation in SAC. However, the difference in Hb adjustment for each 500 m range was $\leq$ 2 g/L. Similarly, the proposed Hb adjustments for SAC were also within 1–2 g/L of the proposed adjustments for PSC and WRA [9]. If differences of 2 g/L are clinically insignificant, providing a common set of elevation adjustments across all population groups would be the most practical. Similarly, a single adjustment value applied for each 500-m range of elevation (e.g., 11 g/L for 1500–1999 m range) would generally be more practical to use, and the adjustment value estimated at each midpoint would be within 2 g/L of the range endpoints. The use of the model equation to estimate adjustment values at specific elevations may be beneficial if more precision in the adjustment is needed and feasible, such as in research settings or population surveys.

Strengths of our study include the use of a diverse set of population-based surveys covering data from 4 WHO regions, which inherently reflects diverse genetic ancestry. All surveys included measures of inflammation, which improved the identification of ID and VAD, as well as the ability to control for these potential confounders. In addition, models were weighted so that each country was represented equally, and the results were not biased toward surveys with a larger sample size.

Our study had some limitations. First, data at elevations >2500 m were relatively limited. Model results were more variable at high elevations, which may be related to model instability due to fewer data points and/or differences between genetic or epigenetic adaptions to high elevations among indigenous populations [24,25]. In survey-specific models, we found that the association between Hb and elevation became stronger at elevations >2000 m in Colombia relative to other high-elevation regions. It is possible that region-specific adjustments are appropriate for populations residing at these high elevations. Second, the ability to control for VAD and malaria status was limited as these data

were not available for all SAC and for some surveys. Malaria is prevalent in some regions of Ecuador, Guatemala, and Mexico; thus, some SAC may have been misclassified as not having malaria. Although ID, VAD, and known malaria were correlated with both Hb and elevation, compared to crude models, these factors were not observed to be strong confounders. In fact, the Hb adjustments for elevation were nearly identical across all models. Similarly, we were unable to control for other factors, such as vitamin B12 and B9 status or other infections/illness, possibly associated with both Hb concentration and elevation, as these data were not available. The potential impact of unmeasured confounding variables remains unknown.

In conclusion, our data provide additional support that WHO guidelines on the adjustment of Hb concentration for elevation may need updating. In 2019, an estimated 1.8 billion individuals lived with anemia [26]. Improvements in the identification of anemia, and consequently, targeted treatment and public health interventions may reduce the global burden of anemia.

Acknowledgments

The author's responsibilities were as follows – FAK and AJS: analyzed the data, wrote the first draft, and contributed equally to the article; MEJ, AMW, OYA, and PS: ascertained data for the BRINDA project; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Funding

This study was partly funded by the Bill & Melinda Gates Foundation and The United States Centers for Disease Control and Prevention. These organizations had no role in the design or conduct of the study; collection, analysis, or interpretation of the data; or writing of the manuscript.

Data availability

The data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval from the BRINDA Steering Committee and/or country representatives.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of The United States Centers for Disease Control and Prevention.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.04.014.

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