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The increase in hemoglobin concentration with altitude varies among human populations

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Decreased oxygen availability at high altitude requires physiological adjustments allowing for adequate tissue oxygenation. One such mechanism is a slow increase in the hemoglobin concentration ([Hb]) resulting in elevated [Hb] in high-altitude residents. Diagnosis of anemia at different altitudes requires reference values for [Hb]. Our aim was to establish such values based on published data of residents living at different altitudes by applying meta-analysis and multiple regressions. Results show that [Hb] is increased in all high-altitude residents. However, the magnitude of increase varies among the regions analyzed and among ethnic groups within a region. The highest increase was found in residents of the Andes (1 g/dL/1000 m), but this increment was smaller in all other regions of the world (0.6 g/dL/1000 m). While sufficient data exist for adult males and females showing that sex differences in [Hb] persist with altitude, data for infants, children, and pregnant women are incomplete preventing such analyses. Because WHO reference values were originally based on [Hb] of South American people, we conclude that individual reference values have to be defined for ethnic groups to reliably diagnose anemia and erythrocytosis in high-altitude residents. Future studies need to test their applicability for children of different ages and pregnant women.

Keywords: anemia; excessive erythrocytosis; ethnicity; newborns; infants; pregnancy

Introduction

The decreased barometric pressure at high altitude results in reduced oxygen partial pressure and oxygen saturation of hemoglobin (Hb) in arterial blood.[1] Hypoxemia stimulates ventilation, increases cardiac output, alters the distribution of blood flow, and enhances oxygen extraction from capillary blood to improve tissue oxygen supply.[2] Arterial oxygen content is increased by a decrease in plasma volume that occurs within days upon ascent to high altitude.[3] In addition, a slow increase in total Hb occurs.[4,5] Despite those adjustments, tissue oxygen supply remains insufficient, as impressively indicated by decreased birth weight in high-altitude residents[6] and reduced maximal oxygen uptake in adults.[7]

Hypoxia stimulates erythropoiesis by complex molecular mechanisms (for review, see Ref. 8).

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Briefly, hypoxia and reduced iron availability inactivate prolyl hydroxylases (PHDs, especially PHD2) in renal peritubular fibroblasts causing stabilization of the α-subunit of hypoxia-inducible factor-2 alpha (HIF-2α). HIF-2α dimerizes with HIF-1β. The heterodimer binds to the hypoxia-responsive element of the *EPO* gene to stimulate transcription and to increase erythropoietin (Epo) synthesis. Epo promotes red blood cell maturation and proliferation in the bone marrow, a process that requires iron. Its availability is assured by the hormone erythroferrone and platelet-derived growth factor BB. These factors suppress the expression of hepcidin in the liver so that hepcidin cannot induce degradation of the iron exporter ferroportin in duodenal enterocytes and in macrophages allowing for increased iron absorption and release from stores. Iron bound to transferrin is delivered to the bone marrow and used for heme synthesis.[8,9]

Stimulation of erythropoiesis elevates the concentration of Hb ([Hb]). This process requires weeks to months to reach a steady state. Early reports indicate that the increase in [Hb] in sojourners to altitude is small at altitudes up to 3000 m but increases more at higher altitudes.[4] A similar pattern of changes in [Hb] has also been observed in high-altitude residents.[10]

Comparison of [Hb] in high-altitude natives and long-term residents reveals the variation in [Hb]. For example, Tibetan people living at high altitude have a much lower [Hb] than Han Chinese upon moving to the Tibetan highlands.[11] Moreover, at similar altitude, the [Hb] of Tibetan and Ethiopian highlanders is lower than that of Andean highlanders.[12,13] The difference in [Hb] among high-altitude natives may have a genetic basis. In Tibetan people, a gain-of-function mutation in the *EGLN1* gene encoding for PDH2 results in reduced HIF-2α levels, less Epo synthesis, and decreased [Hb].[11,14] These facts make the definition of "normal" [Hb] in high-altitude residents difficult. Dependency of [Hb] on age and sex, pregnancy, socioeconomic, and nutritional status (with special focus on iron supplies) adds complexity. However, the knowledge of [Hb] change with altitude is of great clinical significance because [Hb] is the first line of evidence for diagnosis of anemia. The World Health Organization (WHO) suggests factors for correcting [Hb] with regard to altitude.[10] The WHO also provides correction factors for [Hb] differences among children, nonpregnant and pregnant women, and men. In terms of ethnicity, only the difference between Caucasian people and people with African extraction from the United States had been officially considered so far, where the latter have a [Hb] ∼1 g/dL lower than the former.[10,15] Factors can be combined to adjust [Hb] for the detection of abnormalities and program surveys. Importantly, the currently used adjustment factors for altitude are based on [Hb] from children living at altitudes between 1200 and 3000 m by applying a curvilinear fit.[16] [Hb] of children of this age is lower than that of adults. Because of age-related differences between boys and girls,[15] it is unclear whether these factors actually apply for adults as well. Correction factors for altitudes above 3000 m were obtained from the literature on adult high-altitude natives.[4] There is convincing evidence that these correction factors for altitude do not apply for ethnically different natives living at high altitude in different regions of the world.

The present study aimed at analyzing [Hb] with increasing altitude, with age, sex, pregnancy, and ethnicity and/or country and region of residence as variables. The results are expected to allow for testing the validity of the correction factors suggested by the WHO.[10] We performed a literature search on the physiology of life at high altitude and extracted [Hb] for meta-analysis. Results show increases in [Hb], but with a distinctly higher response in South American people compared with all others. Subgrouping by age was impossible because of insufficient data. This points to the need for further exploration of [Hb], at best worldwide, to fully characterize its changes with altitude and the variability of this change depending on ethnicity.

Methods

We aimed at analyzing the distribution of [Hb] concentration for infants, children, and adult males and females, as well pregnant women with regard to altitude in as many regions of the world as possible based on results published on the physiology of adaptation to moderate and high altitude. Unfortunately, the actual classification of data did not permit such detailed analysis (see below and Supplementary Information, online only). A literature search on high-altitude medicine and physiology was performed in June 2017 in PubMed of the

Table 1. Flowchart of data identification

1623 data sources extracted
1513 data sources excluded because:
375 not relevant[a]
304 sojourners <1 year[b]
63 normobaric hypoxia
665 sexes combined or not reported
49 age not well defined[c]
26 mentioned smokers and nonsmokers
22 no measure of variation[d]
3 unconventional methods of measuring [Hb]
6 only 1 subject
110 Data sources included[e]

[a]Disease and treatment studies without control group, case reports, measurements on animals and cells, mathematical models, reviews, or educational materials.
[b]Also includes studies on high-altitude training, intermittent hypoxia, and measurements after return from a trekking/climbing expedition.
[c]No age or age-range is provided; children and adults are combined.
[d]No SD or 95% confidence interval; SEM without "*n*."
[e]Many data sources contained several sets of data, for example, different age groups, different ethnicities, and men and women (see Table 2).

National Library of Medicine of the United States, using "hemoglobin," "hematocrit," "oxygen transport," and "high altitude" or "highlanders" as keywords. This resulted in 1553 hits. We surveyed an additional 70 publications quoted in other work on high-altitude physiology that had not appeared in the above-mentioned search. Our search did not include other summarized data and national surveys. [Hb] was extracted from 110 publications. Several studies contained data on more than one group, such as men and women or different altitudes. [Hb] has been measured spectrophotometrically and by the use of various automated systems. Exclusion criteria are listed in Table 1.

Inclusion and exclusion criteria of data

Only those data were included in our analysis where authors stated explicitly to have studied healthy individuals, which is an inevitable criterion to estimate "physiological" responses to high altitude. This decision excluded publications, where [Hb] was very low and with a likelihood of anemia without further definition of its cause. We also excluded publications explicitly mentioning that the study group included smokers. However, there were insufficient numbers of publications to form a separate subgroup on smokers. In 2005, Leon-Velarde *et al.* suggested that a cutoff of 21 g/dL for men and 19 g/dL for women defines high-altitude residents suffering from chronic mountain sickness (CMS).[17] Based on this report, some studies published after 2005 stated to have omitted individuals with [Hb] above those thresholds. Thus, we cannot exclude that in studies before the appearance of this publication subjects possibly suffering from CMS had been included in studies.

Grouping

We further aimed to form subgroups with narrow age ranges of children and juveniles because the [Hb] increases until the maturity is reached.[15] However, this was impossible because the age of the subjects recruited in published studies was inconsistent and/or incomplete. In addition, data were excluded if [Hb] values for adult males and females, pregnant or nonpregnant, were not reported separately.

We further attempted to subgroup ethnicities, regions, and/or countries of the world based on reported differences in [Hb]. Reports describe "Andean, Tibetan or Ethiopian patterns of adaptation"[18] and genetic mutations associated with [Hb] in Tibetan people.[11,14]

For calculations, we assigned uncorrected [Hb] values to the nearest altitude provided in the publication. Groups of 1000-m ranges starting at sea level were formed. Several publications reported the altitude where the study had been performed (in a hospital or a city) without mentioning the exact altitude of residence of the subjects. If ranges of altitudes of residence were provided for a mean value of [Hb], then the mean altitude was used in our analysis.

Mean [Hb] and the range of validity for the defined subgroups (newborn, juveniles, adult men and women, and pregnancy) with regard to ranges of altitude for various regions of the world are presented in Table 2. Details on the grouping variables used for the classification of altitude ranges, age groups, and of ethnicity/region/country are listed in Table S1 (online only). The countries included in the analysis are summarized in Table S2 (online only).

Statistical analysis

The meta-analysis was based on mean values of [Hb] (not adjusted for altitude) and corresponding

Table 2. Hemoglobin concentration at different altitudes above sea level, in relation to age, sex, and region/country/ethnicity

Gender/age/ pregnancy status	0–999 m			1000–1999 m			2000–2999 m			3000–3999 m			4000–4999 m			≥5000 m		
	Mean	95%-CrI	N/ds/ refs	Mean	95%-CrI	N/ds/ refs	Mean	95%-CrI	N/ds/ refs	Mean	95%-CrI	N/ds/ refs	Mean	95%-CrI	N/ds/ refs	Mean	95%-CrI	N/ds/ refs
The United States of America																		
Newborn										***17.2***	*nc*	*44/ 1/1*						
M-juvenile	**12.8**	11.0–14.5	2248/ 8/5															
F-juvenile	**12.6**	11.2–13.9	2113/ 8/5															
M-adult	**14.7**	13.3–16.0	7440/ 18/15	**15.6**	13.3–17.9	1296/ 7/16	**16.1**	14.1–19.0	34/ 4/17	**16.4**	14.7–18.2	63/ 5/18	***17.5***	*nc*	*4/ 1/17*			
F-adult	**13.0**	11.7–14.3	6900/ 17/45	**13.4**	0.0–26.8	129/ 3/46	***16.0***	*nc*	*6/ 1/17*	**15.0**	−0.4–30.8	50/ 3/47						
F-pregnant										***12.6***	*9.5–15.7*	*10/ 1/65*						
Central/South America-rest																		
Newborn										**19.0**	nc	53/ 1/75						
M-juvenile																		
F-juvenile	***13.1***	*nc*	*138/ 1/11*							***15.7***	*nc*	*470/ 2/12*	***16.1***	*nc*	*96/ 2/13*	***17.6***	*nc*	*42/ 1/13*
M-adult	**14.9**	11.9–18.0	730/ 6/S19	**15.3**	7.7–22.9	589/ 2/20	**16.6**	13.3–19.8	607/ 8/21	**17.9**	13.8–22.0	1803/ 13/22	**19.5**	16.2–22.8	2395/ 17/23	***20.3***	*nc*	*80/ 2/24*
F-adult	***13.7***	*nc*	*142/ 2/48*	***14.1***	*nc*	*201/ 2/49*	**14.8**	13.7–15.9	378/ 7/50	**15.4**	11.0–19.8	562/ 8/51	**17.0**	14.4–19.6	1459/ 9/52	***18.2***	*nc*	*78/ 2/24*
F-pregnant	***11.3***	*nc*	*8449/ 2/66*							**13.7**	12.7–14.8	24833/ 5/67	***14.1***	*nc*	*2305/ 2/68*			
South America-Quechua																		
Newborn																		
M-juvenile													***15.4***	*nc*	*30/ 1/6*			
F-juvenile																		
M-adult										***17.8***	*nc*	*106/ 2/25*	**16.4**	14.5–18.2	122/ 7/6			
F-adult																		
F-pregnant																		
Africa-rest																		
Newborn																		
M-juvenile																		
F-juvenile																		
M-adult	**14.3**	12.4–16.2	475/ 5/26	**15.4**	14.0–16.9	623/ 6/27	***16.1***	*nc*	*10/ 1/28*									
F-adult	**12.9**	12.1–13.7	811/ 6/53	**13.7**	12.0–15.5	959/ 6/54												
F-pregnant				**11.9**	1.0–22.8	3736/ 3/69	***12.7***	*nc*	*100/ 1/69*									
Africa-Ethiopia																		
Newborn																		
M-juvenile																		
F-juvenile																		
M-adult				**15.4**	11.7–19.1	256/ 8/29				**17.1**	14.7–19.5	573/ 9/30						
F-adult				**14.3**	11.8–16.8	109/ 6/55	**14.2**	9.8–18.7	597/ 4/56	**15.6**	13.3–18.0	389/ 8/57						
F-pregnant																		
Asia-rest																		
Newborn	**16.0**	13.8–18.2	2664/ 5/2	***17.0***	*nc*	*45/ 1/3*	***18.7***	*nc*	*574/ 2/2*									
M-juvenile																		
F-juvenile																		
M-adult	**14.7**	12.1–17.3	369/ 4/31	**16.2**	9.2–23.3	1868/ 4/32	***16.7***	*nc*	*114/ 1/33*	***16.0***	*nc*	*94/ 1/33*						
F-adult	***12.1***	*nc*	*288/ 1/58*	**13.3**	10.3–16.3	1557/ 4/59												
F-pregnant	***10.4***	*nc*	*80/ 2/70*	***12.3***	*nc*	*323/ 2/71*	***12.9***	*nc*	*20/ 1/72*									

Continued

Table 2. ***Continued***

Gender/age/ pregnancy status	0–999 m			1000–1999 m			2000–2999 m			3000–3999 m			4000–4999 m			≥5000 m		
	Mean	95%-CrI	N/ds/ refs	Mean	95%-CrI	N/ds/ refs	Mean	95%-CrI	N/ds/ refs	Mean	95%-CrI	N/ds/ refs	Mean	95%-CrI	N/ds/ refs	Mean	95%-CrI	N/ds/ refs
Han Chinese people																		
Newborn										***18.6***	*12.5–24.7*	*15/ 1/4*						
M-juvenile							***13.7***	*nc*	*144/ 1/7*	**14.5**	12.1–16.8	515/ 12/8	**15.2**	11.7–18.8	54/ 5/9	***17.1***	*nc*	*6/ 1/7*
F-juvenile							***13.7***	*nc*	*108/ 1/7*	**14.1**	11.5–16.6	350/ 12/8	***15.4***	*nc*	*18/ 1/7*	***15.6***	*nc*	*5/ 1/7*
M-adult	**15.5**	14.0–17.1	2185/ 11/34				**15.7**	11.0–20.5	1320/ 3/35	**17.5**	14.5–20.5	926/ 15/36	**18.9**	16.6–21.2	1328/ 7/37	**19.6**	nc	30/ 2/7
F-adult	**13.4**	12.7–14.0	2609/ 8/60				***14.3***	*nc*	*335/ 2/7*	**15.0**	12.9–17.0	639/ 13/61	***16.5***	*nc*	*227/ 2/7*	***19.6***	*nc*	*30/ 2/7*
F-pregnant										***14.0***	*nc*	*68/ 2/73*						
Tibetan																		
Newborn										***16.7***	*nc*	*15/ 1/4*						
M-juvenile							***13.4***	*nc*	*42/ 1/7*	**13.9**	11.3–16.5	976/ 13/10	**14.9**	13.2–16.6	342/ 7/8	***14.6***	*nc*	*12/ 1/7*
F-juvenile							***13.4***	*nc*	*58/ 1/7*	**13.7**	11.3–16.1	950/ 13/10	***14.2***	*nc*	*227/ 2/14*	***14.5***	*nc*	*10/ 1/7*
M-adult	***14.2***	*nc*	*14/ 1/38*				**14.8**	10.7–19.0	635/ 4/35	**16.3**	14.4–18.2	1298/ 20/39	**16.8**	14.8–18.5	770/ 17/40	**16.2**	11.8–20.6	74/ 3/41
F-adult							***12.9***	*nc*	*326/ 2/7*	**14.4**	12.8–16.1	1339/ 25/62	**15.4**	12.7–18.2	809/ 14/63	**15.2**	9.1–21.2	101/ 3/41
F-pregnant										**12.5**	11.2–13.9	2243/ 3/74						
Sherpa																		
Newborn																		
M-juvenile																		
F-juvenile																		
M-adult				***14.2***	*nc*	*14/ 1/42*				**16.9**	15.6–18.3	198/ 4/43	***17.0***	*nc*	*28/ 1/44*			
F-adult										***14.8***	*nc*	*211/ 2/64*				***15.3***	*nc*	*23/ 1/44*
F-pregnant																		

NOTE: Mean values (mean) of the Hb concentration (g/dL) and 95% credible intervals (95% CrI) were calculated from reported mean values, number of individuals (*n*) in the number of datasets (ds), and standard deviations as reported in the respective set of publications ("refs;" see below). Values for Hb are rounded to one decimal. Note that one reference may contain more than one dataset. Numbers shown in italics and in gray-shaded fields indicate that only one or two datasets were available. In this case, the mean values of the one or two studies are shown, and the 95% CrI field contains "nc" indicating that from these datasets no convergent range can be calculated, and that the mean value is thus not reliable. In general, a wide 95% CrI indicates high uncertainty of the estimate of the mean. Altitudes (or mean values when ranges were provided in the publication) were sorted into the respective categories. Values on newborns were obtained immediately after delivery. The group "juveniles" covers the age range between 1 and 15 years, adults are subjects older than 15 years of age. Abbreviations: F, female; M, male.

Refs: 1;[6] 2;[37] 3;[50] 4;[38] 5;[15] 6;[42] 7;[41] 8;[40,41,51] 9;[40,41] 10;[40,41,51,52] 11;[53] 12;[53,54] 13;[55] 14;[41,51] 15;[15,56–59] 16;[56–60] 17;[57] 18;[48,57] 19;[4,33,61–64] 20;[33,61] 21;[33,61,65–69] 22;[4,12,33,70–74] 23;[4,33,55,63,64,75–79] 24;[55] 25;[27,80] 26;[81–83] 27;[82,84–86] 28;[87] 29;[88–91] 30;[13,88–91] 31;[92–94] 32;[92,95,96] 33;[93] 34;[28,97–101] 35;[41,97] 36;[40,41,98,99,101–105] 37;[40,41,97,106–108] 38;[28] 39;[40,41,74,98,99,102–105,109–112] 40;[11,40,41,97,106,111,113–115] 41;[41,116] 42;[117] 43;[27,118–121] 44;[115] 45;[15,56,57,122] 46;[56,57] 47;[6,57] 48;[61,66] 49;[61] 50;[61,65,67,69,123] 51;[12,43,74,124–128] 52;[55,75,76,125,126,129] 53;[81–83,130] 54;[82,84,85,130,131] 55;[89–91] 56;[132] 57;[89–91,133] 58;[92] 59;[92,95,96] 60;[98–100] 61;[40,41,98,99,102,105,134] 62;[40,41,74,98,99,102,105,109,110,112,134,135] 63;[11,40,41,109,113,114] 64;[118,121] 65;[6] 66;[68,136] 67;[136] 68;[136,137] 69;[138] 70;[139,140] 71;[139,141] 72;[140] 73;[134,142] 74;[135,142,143] 75.[39]

standard errors. If publications reported medians and interquartile ranges, mean and standard errors were calculated using a dedicated statistical algorithm.[19,20]

Individual study results were combined within prespecified subgroups that were defined with regard to categories of ethnicity, altitude, sex, and age (see Table S1, online only). Within those subgroups, a pooled mean effect along with a 95% equal-tailed credible interval was derived by fitting a Bayesian random-effects model to the data. In a Bayesian meta-analysis, prior information is combined with observed data to obtain a posterior distribution of the effect of interest, as we are

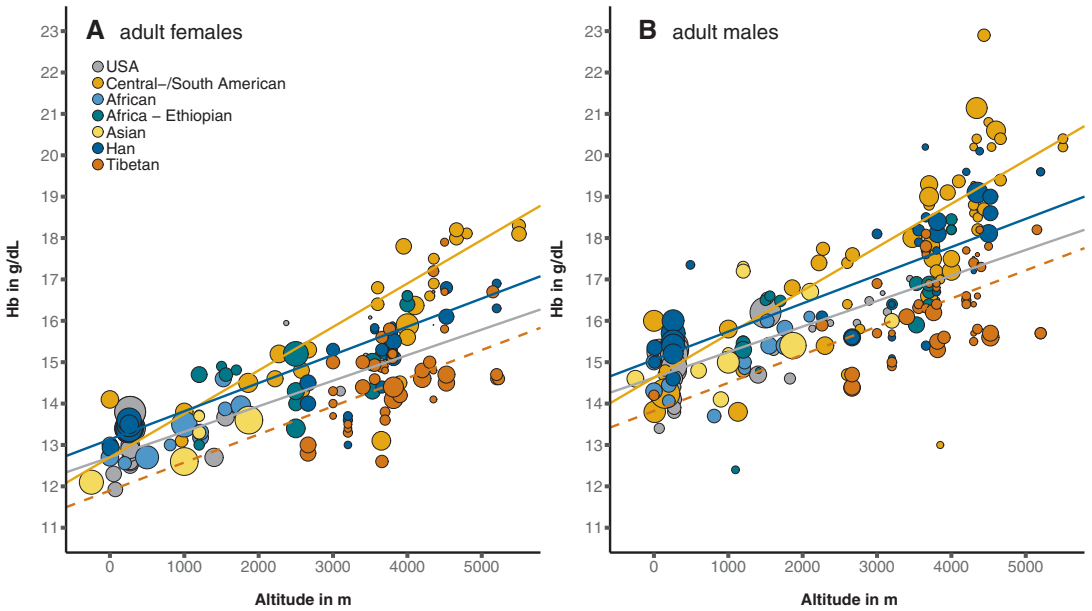

Figure 1. Meta-regression analysis of changes in the hemoglobin concentration with altitude of residence in adult females (A) and males (B). Data are grouped by ethnicity or region/country. Each point indicates the mean value of a dataset reported in the literature (see references to Table 2). The size of each dot reflects its precision and thus its influence on the regression. Lines are shown where significant (full lines) or a trend ($P < 0.1$; dashed line) of differences to the reference group (the U.S. females; gray line) existed in intercept or slope (see details in Table 3).

mainly interested in an initial summary of available data and the underlying distribution of the population's [Hb].[21] Given the data, the resulting 95% credible interval includes the true population value of Hb with probability of 95%. Due to limited preliminary information, flat (improper) uniform priors on the mean effect and the between-study heterogeneity were used.

Heterogeneity was explored by the I^2-statistic, calculated with the highest posterior probability of the between studies variance. A sensitivity analysis was conducted by excluding all studies before 1980 (chosen arbitrarily) to account for possible heterogeneity in methods and design introduced by early investigations.

To investigate the influence of the altitude on [Hb], we performed a meta-regression based on a random-effects model, with altitude (continuous scale), sex (female/male), ethnicity/region/country (the United States, Central/South America, Africa, Africa-Ethiopia, Asia (Tibet excluded), Tibetan Han Chinese, and Tibetan people), and the interaction of altitude and ethnicity/region as covariates. We randomly chose native women from the United States as a reference population. Because of insufficient data, only data of adults were taken into account in the meta-regression approach. The South American Quechua and Himalayan Sherpa people are excluded for the same reason.

The analyses were carried out by the software R (R Core Team (2017)), a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/). For the Bayesian analysis, we used the R package bayesmeta, version 1.5.,[22] and for meta-regression the R package meta, version 4.7-2-2.[23]

Results

Table 2 summarizes [Hb] values of various subgroups at different altitudes. Figure 1 and Table 3 summarize the result of a multifactorial regression analysis on [Hb] of adult females and males only. One important observation is that data published on the physiology of acclimatization to high altitude in residents are incomplete. In Table 2, many entries are lacking indicating that corresponding data were not available. Fields shaded in gray containing a mean value indicate that analysis did not reach

Table 3. Multiple meta-regression model describing the change in the [Hb] with increasing altitude for adult females and males in dependence of ethnicity/region/country

	Beta	SE	*P* value	CI.lb	CI.ub
(A) Intercept = sea level (Hb; g/dL)					
Reference: U.S. females	12.703	0.137	0.000	12.435	12.970
Males	+1.925	0.079	0.000	1.771	2080
Additional correction of intercept for:					
South American people	−0.331	0.235	0.159	−0.792	0.130
African (not Ethiopian) people	−0.188	0.277	0.498	−0.731	0.356
Ethiopian people	+0.020	0.345	0.953	−0.656	0.696
Asian (not Han or Tibetan) people	+0.020	0.341	0.953	−0.649	0.688
Han Chinese people	+0.432	0.210	0.039	0.021	0.843
Tibetan people	−0.806	0.418	*0.054*	−1.625	0.013
(B) Slope = change with altitude (Hb; g/dL/1 km)					
Reference group	0.617	0.098	0.000	0.425	0.809
Additional correction of slope for:					
altitude∗South-American people	0.433	0.112	0.000	0.213	0.653
altitude∗African people	0.112	0.234	0.631	−0.347	0.571
altitude∗Ethiopian people	0.109	0.147	0.462	−0.180	0.397
altitude∗Asian people	0.020	0.238	0.935	−0.446	0.485
altitude∗Han-Chinese people	0.064	0.111	0.565	−0.154	0.282
altitude∗Tibetan people	0.063	0.142	0.659	−0.215	0.340

Note: As an example, the Hb for a male South American (non-Quechua) living at an altitude of 4500 m (4.5 km) can be estimated as: **Hb = 12.703 g/dL + 1.925 g/dL – 0.331 g/dL + 0.617 g/dL/km ∗ 4.5 km + 0.433 g/dL/km ∗ 4.5 km = 19.022 g/dL**, where 12.703 g/dL is the reference Hb of an adult woman living in the United States, 1.925 g/dL is the difference between men and women, –0.33 g/dL is the difference in the intercept between the U.S. and Andean population (independent of sex), 0.617 g/dL/km ∗ 4.5 km is the increase in Hb with altitude for the reference-population, and 0.433 g/dL/km ∗ 4.5 km is the additional increase in Hb with altitude in the Andean population. For comparison, the measured value is 19.5 g/dL (16.2–22.8) as shown in Table 2, suggesting adequacy of the present equation.

Calculation and comparisons were made using Hb values from adult female residents (randomly chosen) from the United States as reference (age >15 years, where the actual altitude provided in the respective publication was used for calculations). Quechuas and Sherpas were not included because of the narrow range of altitudes, where data were available. The model does not include age and pregnancy due to incomplete datasets. (A) Calculated intercept (i.e., sea-level value) and its correction for sex and ethnicity/region/country. (B) Change in Hb with altitude for the reference population (independent of sex) and the additional correction factors for individual ethnicity/region/country.

Beta, the respective value; SE, standard error; *P* value, level of statistical significance; CI.lb and CI.ub, lower and upper boundary of the confidence interval, respectively.

congruence (range = nc) because either only one publication was available or the published data were highly variable with unreasonably wide 95% intervals (95% CrI). Taken together, datasets covering wide ranges of altitudes of residence could only be obtained in nonpregnant adult females and males. Table 2 serves as a look-up table to check whether a measured [Hb] is within the normal range or not.

Because of incomplete datasets, multiple-regression analysis could only be performed on adult males and nonpregnant females. Also, data from Quechua and Sherpa people were omitted from multiple-regression analysis because they originate from narrow ranges of altitudes. The analysis of the remaining groups shows that calculated [Hb] at sea level (Table 3A) differs among residents of different ethnicity or region or country. As reference [Hb] value, we arbitrarily chose the data on healthy female U.S. residents. Based on these data, we exemplify how to calculate the predicted Hb value of a male South American highlander living at 4500 m of altitude. In contrast to the South American population, Tibetan males and females tend to have a [Hb] at sea level that is 0.8 g/dL lower than the reference ($P = 0.0534$). By contrast, the calculated sea level [Hb] for Han Chinese people was significantly higher (+0.4 g/dL; $P = 0.0389$) than [Hb] of the reference group. The model also

shows that overall, as expected, [Hb] of males is 1.9 g/dL higher than that of females ($P < 0.0001$).

Our regression analysis confirms previous results showing that [Hb] increases with altitude independent of ethnicity or region or country of the residents (Table 3B). It further shows that independent of sex, [Hb] of the reference group (North American women) increased by 0.62 g/dL per 1000 m of altitude ($P < 0.0001$). Interestingly, a higher rate of increase was found in South American residents compared with the U.S. reference group (1.05 g/dL/1000 m; $P < 0.0001$). By contrast, the increase in [Hb] with altitude in all other groups was not different from the reference.

Discussion

Our meta-analysis demonstrates an increased [Hb] in male and female high-altitude residents across all age ranges independent of ethnicity and countries of residence. However, the high-altitude residents from the Andes are exceptional in that they show a significantly more pronounced increase in [Hb] compared with all other populations of the world. This finding points to different adaptation strategies related to oxygen transport among different ethnicities. The observed heterogeneity implies that one single set of correction factors for [Hb] at altitude as suggested by the WHO for the diagnosis of anemia cannot be applied worldwide. Our data analysis further revealed that research on high-altitude acclimatization so far focused mainly on adult women and men, whereas research on newborns, children of different age, pregnancy, but also on pathophysiologic conditions, such as smoking and cardiovascular and respiratory diseases, is sparse. As a result of our literature survey, we generated look-up tables (Table 2) for judging whether a measured [Hb] is within the normal range. In these tables, we also indicated where information is lacking and where future studies are required to fill these gaps.

[Hb] at high altitude differs among ethnicities/countries

A slow increase in erythrocyte count during a sojourn at high altitude of mostly Caucasian lowlanders has been first described by Viault[24] over a century ago. It was later noticed that also native highlanders of the Andes have elevated [Hb] (summarized by Ref. 4). However, heterogeneity has been reported among Andean highlanders indicating that when living, for example, at 3600 m, Quechua people had a lower [Hb] (15.8 g/dL) than Aymara (18.2 g/dL). Interestingly, there was no difference between these populations at sea level.[4,25] Later, it has been reported that also [Hb] of natives of the Tibetan plateau,[11,26] Himalayan sherpas,[27] and residents of the Ethiopian highlands was lower than most of the Andean population.[13] Our meta-analysis is in line with these results (Table 2) and indicates significantly higher [Hb] in non-Quechua Andean adult women and men living at altitudes >3000 m than residents of similar altitude ranges from most other countries/regions around the world.

This difference points toward varying set-points for adjusting [Hb] in different ethnicities residing at moderate to high altitudes. Interestingly, such differences have also been detected at sea level, where people of South and West African ancestry have a lower [Hb] than Caucasian people. This difference is evident at all ages, in children and adult of both sexes.[15] Such differences are not apparent in other ethnicities, with the exception of Tibetan people, who show lower [Hb] than Han Chinese people at low altitude.[28] Our results obtained from multiple regression analysis (Table 3) support this notion.

The molecular basis for the lower [Hb] in Tibetan people is at least in part explained by polymorphisms in genes affecting the oxygen sensing process, the expression of hypoxia-related genes, and Hb synthesis. High-frequency missense mutations were described in the *EGLN1* gene encoding PHD2, the oxygen sensor. These genetic variants exhibit a lower K(m) value for oxygen, suggesting increased HIF degradation under hypoxic conditions. This mutation originated approximately 8000 years ago and seems to protect Tibetan people from excessive erythrocytosis at high altitude.[29] In addition, genome-wide analyses revealed a positive selection of haplotypes in the *EPAS1*, *EGLN1*, and *PPAR1* genes encoding HIF-2α, HIF-prolyl-hydroxylase 2, and peroxisome proliferator−activated receptor α, respectively, which were associated with decreased [Hb] in Tibetan people.[11,30] Of note, we have observed that this oxygen sensing mechanism precisely senses altitude differences of 300 m even in low to moderate altitudes (M.G., data unpublished, in preparation).

Taken together, the pronounced differences in [Hb] among high-altitude residents from different countries around the world point toward alterations in the response to hypoxia among ethnicities. This differential response also reflects on the need for establishing normal [Hb] values in high-altitude residents according to their ethnicity to be able to correctly diagnose anemia and erythrocytosis.

Degree of increase in [Hb] with altitude

Our multiple regression analysis revealed that the magnitude of increase in [Hb] varied considerably among ethnicities/countries (Fig. 1). A greater increase in [Hb] with altitude was detected in most South American natives (ΔHb = 1.05 g/dL/1000 m) compared with all others (ΔHb = 0.62 g/dL/1000 m; see Table 3). Unfortunately, we were unable to calculate such slopes for Quechua and Sherpa people because they inhabit only narrow ranges of altitudes. Figure 1 also shows that in those regions with the lower ΔHb the regression lines approximately run parallel and slopes were not significantly different (Table 3B). However, the offsets, which represent a calculated [Hb] at sea level, were different (Table 3A). This finding indicates that oxygen sensitivity of the erythropoietic system is comparable in the populations with similar ΔHb, whereas an increased oxygen sensitivity of the erythropoietic system may account for the greater ΔHb in the Andean population. Additional explanations may include differences in the hypoxic ventilatory response of the Andean residents, who show elevated end-tidal CO_2 compared with Tibetan high-altitude residents and corresponding lower arterial SO_2.[31] The decreased oxygen sensitivity of respiratory control results in decreased arterial oxygen content, which then drives erythropoiesis.

We chose to analyze the data with a linear model because grouped data do not allow for more complex curve fitting. The increase in [Hb] with altitude has also been modeled using nonlinear functions, which appears appropriate based on the sigmoidal shape of the oxygen dissociation curve resulting in a disproportionate decrease in arterial oxygen saturation at altitudes over 2000 meters. However, nonlinear functions only appear appropriate when arterial oxygen saturation and thus oxygen content is the only factor affecting [Hb]. A polynomial fit of higher orders published by the Center for Disease Control is used for adjusting [Hb] in program surveys; it is based on data covering altitudes ranging from sea level to 3000 meters.[16] Winslow and Monge[32] applied another polynomial fit for data analysis of Chilean workers, where the highest study point was at 4600 meters.[33] Yet, another approach used the shape of the oxygen dissociation curve and was based on data obtained in Ecuadorian children living up to 3400 meters.[34] In 1945, Hurtado *et al.*[4] estimated correction values from the published literature obtained at locations up to 5350 meters. The linear approach applied in the present study appears to give a very good fit for women of all different ethnicities/regions (Fig. 1A). Interestingly, a deviation from linearity appears to exist in South American men. It is possible that this disproportionate ΔHb is contributed by samples obtained from miners,[4,33,35] who intermittently work at altitudes higher than their altitude of residence and who are often exposed to dust and badly ventilated mining tunnels. Both of these conditions increase the severity of hypoxia resulting in more pronounced erythropoiesis. Another reason for elevated [Hb] is CMS that is associated with polycythemia.[32] Unfortunately, most publications do not state clearly whether individuals suffering from CMS had been omitted. It was only in 2005 that a cutoff [Hb] of 21 g/dL in men and 19 g/dL in women has been defined above which an individuals' [Hb] might indicate CMS.[17] Therefore, beyond 2005, most studies state that individuals with a [Hb] above this threshold had been omitted, assuming that they suffered from CMS but often without clinical verification of this diagnosis. This may not have been the case in studies before 2005, which would result in elevated mean [Hb] in those studies.

Children. Our analysis fails to provide reference ranges for the diagnosis of anemia in both children and pregnant women because data are scarce in the literature (Table 2). These groups are particularly prone to an increased risk when anemic. At birth, [Hb] is high. It then decreases during the next few months and then increases again to reach stable values in females at the age of approximately 13–15 years and in males between 17 and 20 years. At this age, the [Hb] of males is approximately 2 g/dL higher compared with females.[15,36] [Hb] of children of African origin living in the United States is approximately 1 g/dL lower than that of Caucasian

people.[15] It is currently not well understood whether the magnitude of change in [Hb] related to altitude is the same in children and adults in different regions of the world. In Saudi Arabia, [Hb] tended to be elevated in newborns at 2700 m relative to those born at low altitude.[37] Niermeyer and colleagues found that [Hb] in Tibetan newborns was lower compared with Han Chinese newborns.[38] There was no difference in [Hb] in Puno (3840 m) between newborn indigenous Aymaras, Hispanic, and mixed origin people.[39] [Hb] increased linearly in Quechua boys by approximately 2.7 g/dL between the age of 6 and 21 years, which is in the same range as found in Caucasian boys[15] and similar to the age-related increase of Tibetan and Han Chinese children.[40,41] [Hb] of children living in the Andes has been shown to be approximately 0.5–1.0 g/dL higher than Han Chinese children at comparable altitude.[42] Together, these results indicate differences in children's [Hb] between ethnical groups that appear to be similar to those observed in adults (Table 2 and Fig. 1). Furthermore, the age-related increase in [Hb] persists in children native to high altitude.

Pregnancy. Plasma volume expansion during pregnancy reduces [Hb], and this "dilution" might be interpreted as anemia. Thus, correction factors have been suggested,[16] but these factors apply to low altitude only. However, there are some indications that changes are similar in European people and Andean natives living in La Paz, Bolivia, at 3600 meters.[43,44]

Diagnosing anemia. Because of the increase in [Hb] with altitude and the differences in this increase among regions/ethnicities, it is a challenge to determine whether a measured [Hb] of a high-altitude resident shall be considered as clinically "normal" or not. The mean values and ranges of [Hb] listed in Table 2 will support this diagnosis. Measured [Hb] outside the indicated ranges has to be considered abnormally low or high for the respective altitude. However, the utility of Table 2 is limited by the quality and availability of data in the literature. A large number of imprecise (gray-shaded) or even missing values, in particular for newborns, children, and pregnant women, are indicated in Table 2.

Another possibility to detect anemia in high-altitude residents is the application of cutoff values for age, sex, and pregnancy suggested by the WHO for low altitude[10] and the use of correction values for the altitude of residence. Care must be taken into account for the differences observed between regions (ethnicity), as we report here. Based on our analyses, we strongly recommend using the ΔHb/1000 m values and the formulas provided in Table 3A and B to adjust the low altitude anemia threshold for altitude[10] as shown in Table 4A, at least for adult women and men. The adjustment factors previously reported by the WHO were determined from Hb values analyzed exclusively in South American high-altitude natives and thus are not widely applicable to other high-altitude regions of the world. These frequently used correction factors define wrong cutoff values resulting in false diagnosis. For illustration, a Tibetan or an Ethiopian native with a normal [Hb] for his/her ethnicity and altitude of residence will be considered anemic after applying the South America-derived WHO correction factor.

It is important to note that particularly in South American Aymaras living at moderate altitudes application of a linear increase in [Hb] may result in higher numbers of individuals diagnosed with anemia compared with those cut-off values suggested by WHO, where an exponential fit is applied. Most probably, however, this is not the case for South American Quechuas who in general show lower [Hb] compared with Aymaras. It is unclear, whether similar heterogeneities as seen in South America exist in other regions of the world, too. This illustrates the urgent need of studying [Hb] of individual ethnicities worldwide, even within regions, in more detail. Inappropriate cut-off levels for [Hb] may result in unreasonably high percentages of anemia causing unnecessary supplementation with iron and other treatments.

Diagnosing erythrocytosis. At low altitude, values above a [Hb] of 18.5 g/dL for adult men and 16.5 g/dL for adult women have been defined as cutoff values for the detection of excessive erythrocytosis and polycythemia,[45,46] aiming mainly at the detection of polycythemia vera, but values have never been objectively verified.[47] Changes of cutoff values with altitude and differences among ethnicities have not been considered so far indicating that those values need to be defined. One possible approach is the correction of these values

Table 4. Cutoff values for the [Hb] (g/dL) to diagnose anemia (A) and erythrocytosis (B) in adult, nonpregnant women living at different high altitude regions

Altitude (m)	South American people	Tibetan people	Han Chinese people	All others	WHO altitude formula
(A) Suggested cutoff values for diagnosing anemia in women in g/dL (for men add 1 g/dL)					
0	12.0	11.2	12.4	12.0	**12.0**
1000	13.1	11.8	13.0	12.6	**12.1**
1500	13.6	12.1	13.3	12.9	**12.4**
2000	14.1	12.4	13.6	13.2	**12.7**
2500	14.6	12.7	13.9	13.5	**13.2**
3000	15.2	13.1	14.3	13.9	**13.8**
3500	15.7	13.4	14.6	14.2	**14.6**
4000	16.2	13.7	14.9	14.5	**15.4**
4500	16.7	14.0	15.2	14.8	**16.4**
5000	17.3	14.3	15.5	15.1	**17.5**
(B) Suggested cutoff values for diagnosing erythrocytosis in women (for men add 2 g/dL)					
0	16.5	15.7	16.9	16.5	16.5
1000	17.6	16.3	17.5	17.1	16.6
1500	18.1	16.6	17.8	17.4	16.9
2000	18.6	16.9	18.1	17.7	17.2
2500	19.1	17.2	18.4	18.0	17.7
3000	19.7	17.6	18.9	18.4	18.3
3500	20.2	17.9	19.1	18.7	19.1
4000	20.7	18.2	19.4	19.0	19.9
4500	21.2	18.5	19.7	19.3	20.9
5000	21.8	18.8	20.0	19.6	**22.0**

Note: Values are based on the model presented in Table 2 in comparison to the adjustments suggested by the WHO.[10,46] The table shows only values for those groups (ethnicity/country/region), where statistically significant differences (or a clear trend) existed in the calculated [Hb] at sea level and its increase with high altitude (Table 3). According to the recommendations by the WHO, the cutoff for anemia in adult women at sea level is defined as 12 g/dL and for polycythemia as 16.5 g/dL.[46] Ethnicity/region–related differences in low-altitude Hb values are adjusted according to Table 3A, and altitude-related changes are calculated from the respective slope (Table 3B) and according to the formula suggested by WHO.[10] Values can be applied by choosing the nearest altitude or by extrapolation between altitude ranges. Cutoff values can be adjusted for age, pregnancy, and smoking as suggested.[10]

based on the results of the multiple regression model presented here. To this end, the WHO cutoff values for [Hb] must be corrected with the intercepts (sea-level values) for the different ethnicities as presented in Table 3A, resulting in ethnicity-specific sea-level cutoff values. In a second step, the ethnicity-specific increase in [Hb] with altitude shown in Table 3B should be applied to calculate cutoff values for specific altitudes. In Table 4B, we exemplified such a calculation and compare the results with adjustments for altitude as suggested by the WHO.[10] Obviously, the currently used WHO correction results in much higher cutoff values for altitudes above 4000 m than those after applying our linear approach (Table 4B). It is important to note that cutoff values at altitudes above 3000–4000 m reach Hb values higher than those suggested for the detection of CMS.[17] This indicates that at those altitudes, more specific clinical tests are required to distinguish, for example, polycythemia vera and other forms of excessive erythrocytosis mostly deriving from CMS.

Smokers. [Hb] is elevated by up to 1 g/dL in smokers, where the degree of increase depends on the number of cigarettes/cigars per day.[16] Thus, smoking is another source contributing to abnormally high [Hb] at high altitude resulting in difficulties in reliable detection of both anemia and polycythemia. Studies on high-altitude physiology typically exclude smokers. Thus, we were unable to account for this subgroup, which would have been of importance because carboxyHb formation decreases arterial oxygen loading and causes hypoxemia, which stimulates erythropoiesis. This suggests that effects on [Hb] of hypoxia by altitude

and smoking may be additive. In fact, it has been shown that the elevation in [Hb] in response to smoking is comparable at low and intermediate altitudes.[48,49]

Conclusion

[Hb] is generally elevated in high-altitude residents, but the degree of required [Hb] adjustment under physiological conditions varies among different regions of the world. This clearly indicates that differences exist between ethnicities and points to different strategies of adjustment of oxygen transport in blood. Accordingly, these variations render the diagnosis of anemia in high-altitude residents a difficult task. Moreover, the standard correction factor for [Hb] suggested by WHO is not valid for its worldwide use. Therefore, we established look-up tables and correction factors to account for these differences between ethnicities. Due to gaps in available literature data on high-altitude physiology, we only can provide information on adult women and men, whereas data on newborns, children, and pregnant women are incomplete. We suggest using threshold [Hb] for the detection of anemia established for low altitude and to apply region/ethnicity–specific regression lines (Table 3) to extrapolate to the altitude of residence to diagnose anemia in patients in high-altitude clinics as shown in Table 4. Using a single correction factor worldwide is certainly not appropriate. Importantly, it was outside the scope of this analysis to establish additional correction factors, such as for pregnancy, African origin, and smokers at various altitudes that are frequently applied for adjustment of [Hb] in program surveys.[10] Future studies have to be designed to fill all these gaps.

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We apologize to all those authors whose original or review articles could not be cited due to space limitation. Moreover, due to the keywords used for the search, we might have missed important contributions. Thus, if the reader feels that some important publications were not considered, we kindly ask to provide us with the suggested paper(s) so that we can update this analysis in a future study.

Statement

Part of this manuscript was presented at the World Health Organization (WHO) technical consultation "Use and Interpretation of Haemoglobin Concentrations for Assessing Anaemia Status in Individuals and Populations," held in Geneva, Switzerland on November 29–30 and December 1, 2017. This paper is being published individually but will be consolidated with other manuscripts as a special issue of *Annals of the New York Academy of Sciences*, the coordinators of which were Drs. Maria Nieves Garcia-Casal and Sant-Rayn Pasricha. The special issue is the responsibility of the editorial staff of *Annals of the New York Academy of Sciences*, who delegated to the coordinators preliminary supervision of both technical conformity to the publishing requirements of *Annals of the New York Academy of Sciences* and general oversight of the scientific merit of each article. The workshop was supported by WHO, the Centers for Disease Control and Prevention (CDC); the United States Agency for International Development (USAID), and the Bill & Melinda Gates Foundation. The authors alone are responsible for the views expressed in this paper; they do not necessarily represent the views, decisions, or policies of the WHO. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors, publisher, or editorial staff of *Annals of the New York Academy of Sciences*.

Supporting information

Additional supporting information may be found in the online version of this article.

Table S1. Summary of categories used for the present statistical evaluation.

Table S2. Countries included in the evaluation of Hb concentration at increasing altitudes.

Competing interests

The authors declare no competing interests.

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