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RESEARCH ARTICLE

High-altitude adaptations mitigate risk for hypertension and diabetes-associated anemia

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Abstract

Background: Human populations native to high altitude exhibit numerous genetic adaptations to hypobaric hypoxia. Among Tibetan plateau peoples, these include increased vasodilation and uncoupling of erythropoiesis from hypoxia.

Objective/Methods: We tested the hypothesis that these high-altitude adaptations reduce risk for hypertension and diabetes-associated anemia among the Mosuo, a Tibetan-descended population in the mountains of Southwest China that is experiencing rapid economic change and increased chronic disease risk.

Results: Hypertension was substantially less common among Mosuo than low-altitude Han populations, and models fit to the Han predicted higher probability of hypertension than models fit to the Mosuo. Diabetes was positively associated with anemia among the Han, but not the Mosuo.

Conclusion: The Mosuo have lower risk for hypertension and diabetes-associated anemia than the Han, supporting the hypothesis that high-altitude adaptations affecting blood and circulation intersect with chronic disease processes to lower risk for these outcomes. As chronic diseases continue to grow as global health concerns, it is important to investigate how they may be affected by local genetic adaptations.

KEYWORDS

anemia, diabetes, erythropoiesis, high-altitude adaptation, hypertension

1 | INTRODUCTION

Low oxygen pressure at altitudes over ~2 km induces hypoxic stress, with cascading consequences for human performance and evolution. Populations of the Tibetan Plateau have been living at altitudes of up to ~5,400 m for thousands of years (Beall, 2007), and exhibit a suite of characteristics that appear to fully mitigate this stress: whereas sojourners to high altitude experience a ~10–20% deficit in maximal oxygen uptake, Tibetans at high altitude show no deficit (Beall, 2007).

Understanding of Tibetan Plateau populations' adaptations to high altitude is increasing rapidly, particularly with regard to their genetic bases (Beall et al., 2010; Bigham et al., 2010; Bigham & Lee, 2014; Erzurum et al., 2007; Gilbert-Kawai et al., 2017; Guo, He, & Cui, 2017; He et al., 2018; Peng et al., 2010; Simonson et al., 2010; Yi et al., 2010; Zheng, He, & Cui, 2017). Some of these adaptations overlap with mechanisms of multiple chronic diseases, meaning that chronic disease etiology, risk, and complications are likely to manifest differently in human populations genetically adapted to high altitude. This remains an under-researched aspect of high altitude adaptation, and one that is becoming increasingly urgent as the global burden of chronic disease continues to grow.

We investigated the intersection of high-altitude adaptation and chronic disease among the Mosuo ethnic group, close relatives of Tibetans (Jeong et al., 2017; Lu et al., 2012; Wen et al., 2004; Yang et al., 2004) living in the Hengduan Mountains southeast of the Tibetan Plateau, at ~2,600 m altitude. Population-genetic research suggests that the Mosuo are closely related to a group of Tibetan Plateau peoples who descended from a single ancestral Himalayan population that carried high-altitude adapted alleles at a suite of key functional genes (Arciero et al., 2018; Jeong et al., 2017; Lu et al., 2012; Wen et al., 2004; Yang et al., 2004). Cultural and historical work suggests that the Mosuo have been residing at high elevation for ~1,500 years (Shih, 1994), suggesting that ancestral variation that was advantageous at altitude would have been maintained.

Many Mosuo communities are undergoing a rapid process of market integration associated principally with increasing tourism around the Lugu Lake area of Yunnan (Blumenfield, Sum, Shenk, & Mattison, 2018; Mattison, 2010). Chronic diseases like type 2 diabetes and hypertension have increased strikingly among populations undergoing integration into markets, due to changes in diets, physical activity, and social structure (Chan et al., 2009; Kuhnlein & Receveur, 1996). The Mosuo's recent Tibetan ancestry and rapid market integration bring together high-altitude adaptation and high chronic disease risk, allowing us to observe how the two interact.

Tibetan Plateau adaptations to hypoxia enhance blood flow to tissues via high nitric oxide (NO) production, vasodilation, reduced vascular resistance, and denser capillary networks (Beall, Laskowski, & Erzurum, 2012; Bigham & Lee, 2014; Erzurum et al., 2007). This unique vascular physiology augments oxygen delivery to compensate for reduced arterial blood oxygen content (Beall, 2007; Bigham & Lee, 2014). It also seems likely to lower susceptibility to chronic hypertension (elevated arterial blood pressures), as hypertension may be attributable to underproduction of vasodilators such as NO in the endothelium, and subsequent smooth muscle cell contraction and arteriole wall thickening (Beevers, Lip, & O'Brien, 2001).

Previous research into Tibetans' risk for hypertension, however, is ambiguous and poorly suited to test this hypothesis. Blood pressures generally increase with altitude due to hypoxic stress; this has been observed among sojourners (Calbet, 2003; Luks, 2009), those raised at altitude (Aryal, Weatherall, Bhatta, & Mann, 2018; Norboo et al., 2015), and Tibetans (Aryal, Weatherall, Bhatta, & Mann, 2016; Mingji, Onakpoya, Perera, Ward, & Heneghan, 2015). Both lower rates of hypertension (Norboo et al., 2015) and higher rates of hypertension (Sun, 1986) have been reported among Tibetans, compared to Han or other ethnic groups at similar altitudes—this likely reflects differences in subsistence, diet, and lifestyle that confound direct comparisons between Tibetan Plateau and lowland populations residing at altitude. We resolve this by comparing Mosuo risk for hypertension to that predicted from models fit to Han with similar overall lifestyle characteristics.

Tibetan Plateau adaptations to high altitude also include a blunted erythropoietic response to hypoxia: in the presence of physiological changes to enhance oxygen delivery to tissues in the presence of reduced arterial blood oxygen content, natural selection favored changes to the hypoxia-inducible factor (HIF) pathway that uncoupled erythropoiesis from hypoxia sensing, allowing Tibetans to avoid erythrocytosis and blood hyperviscosity (Beall et al., 2010; Bigham et al., 2010; Peng et al., 2010; Simonson et al., 2010; Yi et al., 2010). Thus, whereas elevated blood hemoglobin concentration (Hb) is typical of lowland-native sojourners to high altitude, Tibetan Plateau populations exhibit only moderately elevated Hb (Beall, 2007; Bigham & Lee, 2014). This blunted erythropoiesis may lower risk for anemia associated with chronic disease, particularly diabetes.

Diabetes is defined by persistent elevated blood glucose, and caused by impaired production of, or sensitivity to, the hormone insulin, which promotes tissue absorption of glucose. Although not consistently emphasized in discussions of diabetes complications, anemia is very common among people with both type 1 and type 2 diabetes (El-Achkar et al., 2005; Goldhaber, Ness-Abramof, & Ellis, 2009; Thomas et al., 2004; Thomas, MacIsaac, Tsalamandris, Power, & Jerums, 2003). Multiple pathways may link diabetes and anemia, including inflammation, autoimmunity, and micronutrient deficiency. However, one pathway unique to diabetes has repeatedly been implicated: the impaired ability to correct insipient anemia via the homeostatic kidney erythropoietin (EPO) response. HIF-pathway hypoxia sensing in normally-functioning kidneys maintains oxygen homeostasis by increasing EPO production by peritubular fibroblasts in response to hypoxia and vasoconstriction (Fisher, 2003; McGill & Bell, 2006). Diabetic kidney damage to the peritubular fibroblasts can result in fibrosis (McGill & Bell, 2006), leading to failed EPO elevation among diabetics (McGill & Bell, 2006; Thomas, 2006). This failure is likely attributable to impaired sensitivity to hypoxia, rather than EPO secretory capacity (Bosman et al., 2002; Fisher, 2003; Thomas, 2006). Because erythropoiesis in the Tibetan-type adaptation to high altitude is already decoupled from the hypoxia-sensing

TABLE 1 Study hypotheses

	Physiology	Benefit at altitude	Impact on chronic disease
H1	Vasodilation; denser capillary networks	Increased oxygen delivery to tissues	Lower risk for hypertension
H2	Blunted erythropoietic response to hypoxia	Decreased blood viscosity	Lower risk for anemia among diabetics

HIF pathway, risk for diabetes-associated anemia may be lower among Tibetan-descended populations.

We tested the predictions that Tibetan-type high-altitude adaptations lower risk for hypertension and diabetes-associated anemia among the Mosuo. We collected data among the Mosuo in Yunnan province, and accessed data from the China Health and Nutrition Survey (CHNS) for two Han comparison groups: (a) all Han included in the CHNS data; and (b) a sub-sample of the first comparison group limited to Han from rural Hunan, which is southern and inland, like the Mosuo homeland in Yunnan and Sichuan, but lower in altitude (~100–800 m), and offers a larger sample of Han in CHNS than other nearby provinces. Because rates of hypertension may differ across ethnic groups due to disparate lifestyles, we compared models of hypertension from the Mosuo and rural Hunan Han samples, who are broadly comparable in terms of diet and subsistence, to test the hypothesis that Mosuo have overall lower risk for hypertension, given the same risk factors. For the diabetes-associated anemia outcome, we compared models of anemia across the three samples to test the hypothesis that diabetes is a risk factor for anemia among the Han, but not the Mosuo (Table 1).

2 | MATERIALS AND METHODS

2.1 | Study setting and design

Risk factors for hypertension and associations between diabetes and anemia among Han Chinese were assessed using data from the China Health and Nutrition Survey (http://www.cpc.unc.edu/projects/china). CHNS used random cluster sampling to generate a representative sample of residents of participating Chinese provinces; in 2009 (the year for which biomarker data were available), this included 217 communities from 9 provinces (Guangxi, Guizhou, Heilongjiang, Henan, Hubei, Hunan, Jiangsu, Liaoning, Shandong).

Risk factors for hypertension and associations between diabetes and anemia among the Mosuo were assessed as part of a larger survey of the Mosuo investigating the impact of rapid market integration on wealth, health, and inequality. Rapid market integration is occurring among some Mosuo communities due to increasing tourism around Lugu Lake in Yunnan Province. Communities were selected to include those with high, moderate, and low levels of participation in the tourism economy. The median altitude of residence for our study participants was 2,638 m (range, 1,515 to 3,050 m).

The demographic survey portion of the Mosuo study occurred in 2017. A sample of survey participants were subsequently invited to participate in a second round of data collection (including diabetes and anemia screenings) which was carried out in the summers of 2017 and 2018. Individual participants were not selected at random; instead, subsets of communities from the larger survey were targeted to ensure representation of communities with varying degrees of access to markets. All adult participants in those communities were invited, and all of those who volunteered were included in the subsample for this study.

2.2 | Biomarker selection

Aspects of health (inflammation, diabetes, iron deficiency, and anemia) were described among this subsample using biomarkers. Biomarkers for these health outcomes were selected to be measurable, when possible, with field-friendly point-of-care test (POCT) devices, and, when this was not possible, to be measurable in dried blood spot (DBS) specimens. Biomarkers were also selected for interpretability in a population with a high burden of infectious disease (e.g., robustness of the iron nutrition biomarker to changes in inflammation), and for practicality in population-based research (e.g., minimal diurnal variation in all biomarkers, minimal pretest preparation requirements for participants).

Diabetes was characterized with glycated hemoglobin (HbA_{1c}). HbA_{1c} has been validated against blood glucose measures as gold standards (World Health Organization, 2011b); it was selected for use in this project to meet the practical limitations of population-based research, as it does not require research participants to fast prior to participation, and is less variable over short time scales than fasting plasma glucose or oral glucose tolerance tests (Sacks, 2011). Limitations of HbA_{1c} include artificially *low* values for individuals with elevated erythrocyte turnover (e.g., due to hemolytic disease, hemoglobinopathy, or recent acute blood loss), and artificially *high* values for individuals with iron deficiency (with or without anemia) (English et al., 2015; Sacks, 2011). HbA_{1c} introduces possible misclassification of diabetes, if erythropoiesis or erythrocyte lifespan were abnormal among Mosuo participants; this is unlikely, as elevated erythropoiesis is not part of the Tibetan pattern of adaptation to high altitude (Beall, 2007; Bigham & Lee, 2014). Further, iron deficiency can result in artificially high HbA_{1c}; this increase is significant, but small enough that it is unlikely to significantly overestimate rates of diabetes (Kim, Bullard, Herman, & Beckles, 2010; Sacks, 2011). We addressed this concern via statistical control for iron deficiency.

Inflammation, a common predictor of chronic disease, was described with C-reactive protein (CRP), a stable, commonly used, and easy to measure pro-inflammatory acute phase reactant. Iron deficiency was described with soluble transferrin receptor (sTfR), which, unlike many other biomarkers of iron status, is unaffected by inflammation and the acute phase response, enhancing its interpretability in settings with a high infectious disease burden, and is measurable in DBS (McDade & Shell-Duncan, 2002; World Health Organization, 2014). Anemia was described with Hb (World Health Organization, 2011a).

2.3 | Anthropometry

At the time of participation in the demographic survey of the Mosuo, each participant's height was measured with a stadiometer (Seca 213) and weight with a digital scale (Tanita BF522W).

2.4 | Point of care testing

At the time of participation in the demographic survey of the Mosuo, blood pressures were estimated in duplicate using a portable upper arm blood pressure monitor (Omron HEM-BP785N), with the participant in a seated position after a period of rest. Coefficients of variation (CVs) for systolic and diastolic blood pressures were 3.5 and 5.4%, respectively. At the time of screening for diabetes and anemia, capillary whole blood was collected via finger stick with a sterile safety lancet. Blood specimens were immediately evaluated for HbA_{1c} with the A1CNOW POCT (PTS Diagnostics) and Hb with a hemoglobinometer (HemoCue 201+).

2.5 | Laboratory evaluation of biomarkers

After POCT, additional drops of whole blood were allowed to fall freely onto a filter paper card (Whatman #903) for DBS specimens. DBS were allowed to dry for up to 24 hr and were then frozen. Specimens were transported to the MOE Key Laboratory for Contemporary Anthropology at Fudan University and evaluated for CRP (BioCheck BC-1119) and soluble transferrin receptor (sTfR; Ramco TFC-94) using commercially available kits modified for use with DBS specimens: One 1/8 in. disc of DBS specimen was removed with a hole punch, combined with the specimen dilution buffer provided with each kit (125 μl for sTfR; 150 μl for CRP), and allowed to soak overnight at 4°C. The resulting eluent was assayed without further dilution; dilution was calculated as 1.5 μl serum equivalent (Mei, Alexander, Adam, & Hannon, 2001) per volume of dilution buffer. Specimens with unquantifiably high values were re-evaluated at higher dilutions as needed. Inter-assay CVs for sTfR were 14.1% at high and 11.7% at low concentrations; intra-assay CVs were 9.2% for CRP and 4.3% for sTfR. (Controls to assess inter-assay variability were not provided by BioCheck.)

2.6 | CHNS data access

CHNS data sets ("Biomarkers," "Physical exam," and "Survey") were downloaded from the study website. Data sets were merged by individual id (IDIND) and data from the 2009 wave (the year for which biomarker information is available) were retained.

2.7 | Data analysis

Systolic and diastolic pressures were averaged across two estimates; when only one measurement of blood pressures was made, the single estimate was used. Blood pressures categories were defined as normal (average systolic <120 mmHg and average diastolic <80 mmHg), elevated (120 ≤ systolic <130 mmHg and diastolic <80 mmHg), Stage 1 hypertension (130 ≤ systolic <140 mmHg *or* 80 mmHg ≤ diastolic <90 mmHg), and Stage 2 hypertension (systolic ≥140 mmHg *or* diastolic ≥90 mmHg); for binary comparisons, hypertension was considered absent for normal or elevated blood pressures and present for Stage 1 and Stage 2 hypertension (Whelton et al., 2017). Diabetes was defined as a reported physician's diagnosis of diabetes or HbA_{1c} ≥ 6.5% (World Health Organization, 2011b); no distinction was made between types 1 and 2 diabetes. Anemia was defined according to WHO standards (World Health Organization, 2011a) both with (as Hb < 13.3 g/dl for women and Hb < 14.3 g/dl for men) and without (as Hb < 12 g/dl for women and Hb < 13 g/dl for men) adjustment of 1.3 g/dl for elevation of 2,500 m. (The unadjusted reference is likely more appropriate for the Mosuo, as high-altitude adapted Tibetans have been found to have only slightly elevated Hb compared to those at sea level.) Iron deficiency was defined differently in CHNS and the Mosuo data sets: Unlike most biomarkers, sTfR measurement methods can generate tremendously different values (World Health Organization, 2014), and cut points are specific to analysis method. sTfR in CHNS was evaluated with nephelometry (Siemens BNP), rather than enzyme immunoassay, as was used among the Mosuo. Thus, iron deficiency was defined as sTfR >1.76 mg/L in CHNS and sTfR ≥8.3 mg/L among the Mosuo. sTfR was also evaluated as a continuous variable, as was CRP. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$, and BMI was evaluated as a continuous variable.

For optimal comparisons to the Mosuo sample, we limited analysis of the CHNS data set to ethnic Han individuals age 16 years or older. We calculated age-standardized and sex-standardized prevalence of hypertension and diabetes for all three samples (Mosuo, all Han, rural Hunan Han) by applying Mosuo and rural Hunan Han prevalence in age strata to the Han population's age structure, stratified by sex.

Predictors of hypertension and associations between diabetes and anemia were described with logistic regression using R 3.5.1 (R Foundation for Statistical Computing). Models were constructed separately for the Mosuo and the CHNS data sets. Associations between hypertension and known risk factors (age, sex, diabetes, BMI, CRP, smoking) were modeled for all three samples. Predicted probabilities for the Mosuo sample were calculated from both the rural Hunan Han model and the Mosuo model and compared. Associations between diabetes and anemia were modeled for all three samples. Known anemia risk factors including smoking, sex, age, sTfR, CRP, and BMI, which were also likely to be associated with diabetes or HbA_{1c} test results, were included as control variables. Participant's province was controlled in all models of the larger CHNS Han sample and field season (2018 vs. 2017) was controlled in all models of the Mosuo sample. Limited access to health care and limited communication in the healthcare setting among the Mosuo made it difficult for participants to accurately describe their current medications and comorbid conditions, so we excluded these additional potential confounders from our analyses.

TABLE 2 Sample characteristics for all Han, rural Hunan Han, and Mosuo (M) ≥16 years old

	All Han	Rural Hunan Han	Mosuo	All Han	Rural Hunan Han	Mosuo
	Counts			**Percentages**		
Anemia (Hb < 12 g/dl for females; Hb < 13 g/dl for males)	1,027	109	37	13.7	17.6	10.05
Anemia adjusted for altitude (Hb < 13.3 g/dl for females and Hb < 14.3 g/dl for males)			108			29.35
Diabetes (HbA_{1c} ≥ 6.5% or reported diagnosis)	661	34	63	8.81	5.48	17.12
Hypertension (diastolic bp > 80 or systolic bp > 130)	3,926	272	121	60.0	54.1	39.0
Iron deficiency (sTfR ≥1.76 mg/l for CHNS; sTfR ≥8.3 mg/l for Mosuo)	1,446	110	78	19.3	17.7	21.20
Current smoker	2,011	177	86	26.8	28.5	23.37
Female sex	3,998	321	247	53.3	51.8	67.12
	Median			**Range**		
Age (years)	50	49	49	16, 98	16, 94	16, 84
C-reactive protein (mg/l)	1	1	0.79	0, 500	0, 51.0	0, 29.3
Soluble transferrin receptor (mg/l)	1.34	1.27	6.13	0.131, 14.2	0.207, 5.89	2.93, 16.8
Body mass index	23.13	22.04	23.7	13.5, 42.7	15.3, 36.3	15.4, 36.1
N for diabetes sample (N for hypertension sample)	7,504 (6,548)	620 (503)	368 (310)			

TABLE 3 Age-standardized prevalence (per 1,000) of hypertension for Mosuo, rural Hunan Han, and all Han ≥16 years of age

	Mosuo			Rural Hunan Han			All Han	
	Crude	Standardized[a]	95% CI	Crude	Standardized[a]	95% CI	Crude	95% CI
Females	360.3	345.7	273.8, 449.3	515.4	526.6	441.0, 625.9	541.1	511.9, 571.5
Males	264.5	267.1	182.6, 378.0	562.0	560.6	469.8, 664.7	636.1	602.3, 671.2

[a]Prevalence were standardized to the age structure observed among all Han participants in CHNS.

TABLE 4 Prevalence (%) of hypertension by age and sex among Mosuo, rural Hunan Han, and all Han

	Mosuo		Rural Hunan Han[a]		All Han[a]	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*
Age < 20 years	0.0	0.0	37.5	0.0	30.0	14.1
Age 20–29 years	11.1	0.0	23.1	12.9	43.6	19.6
Age 30–39 years	19.0	7.9	37.8	28.9	55.3	34.8
Age 40–49 years	22.5	46.8	64.7	38.7	68.0	51.5
Age 50–59 years	27.8	41.3	66.7	71.4	70.5	65.8
Age 60–69 years	47.8	73.3	54.8	83.3	73.8	75.0
Age 70–79 years	40.0	36.4	83.3	90.9	78.4	80.5

[a]The prevalence of hypertension documented in other large samples of the Chinese population (e.g., Gao et al., 2013; Wang et al., 2014) are consistent with these rates, considering they employed a higher threshold for hypertension than we used (Whelton et al., 2017).

2.8 | Results

Characteristics of the samples are shown in Table 2. As predicted, although hypertension was common among all groups, it was substantially less common among the Mosuo than either comparison group of Han (Tables 3 and 4). Diabetes was also common among all groups, with a higher prevalence among the Mosuo (Table S1).

We compared predicted probabilities of hypertension from logistic regression models to assess whether Mosuo had different risk for hypertension given their values for known hypertension risk factors.

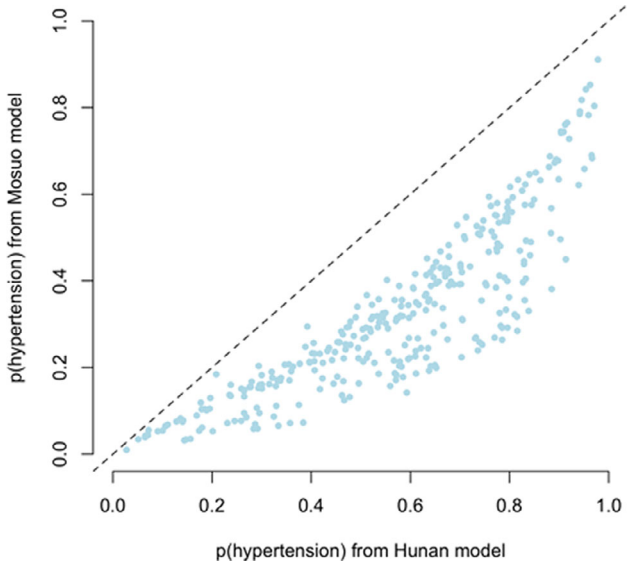

FIGURE 1 Predicted probabilities of hypertension among the Mosuo. Logistic regression models for the outcome hypertension were estimated for rural Hunan Han and Mosuo samples (Tables S1 and S2). Each model was then used to predict probabilities of hypertension among the Mosuo sample. The model fit to Hunan Han predicted substantially higher p(hypertension) for all Mosuo participants than the model fit to the Mosuo, suggesting that the Mosuo sample would experience substantially higher rates of hypertension, given their age, sex, and other risk factors, than were actually observed, if they were similar to the Han in susceptibility to hypertension

TABLE 5 Logistic regression models of associations between diabetes and anemia

	OR	ß	95% CI		*p*
Model 1[a]: All Han					
Diabetes	1.291	0.256	−0.004	0.507	.049
Model 2: Rural Hunan Han					
Diabetes	2.226	0.800	−0.083	1.644	.067
Model 3[b]: Mosuo (anemia definition adjusted for altitude)					
Diabetes	0.949	−0.0521	−0.818	0.686	.891
Model 4[b]: Mosuo (anemia definition unadjusted for altitude)					
Diabetes	1.341	0.293	−0.792	1.284	.575

Note: All models controlled for age, sex, BMI, C-reactive protein, soluble transferrin receptor, and smoking.
[a]Also controlled for province.
[b]Also controlled for field season. See Tables S3 and S4 for full models.

Logistic regression models of hypertension (Tables S2 and S3) predicted substantially lower probabilities of hypertension when fit to the Mosuo sample than the rural Hunan Han sample (Figure 1). Comparison of these probabilities suggests that the Mosuo's observed risk factors (age, sex, BMI, CRP, and smoking) should have resulted in a higher prevalence of hypertension than we observed if they were indeed similar to Hunan Han in hypertension risk. Specifically, the predicted probabilities of hypertension differed by 0.246 (95% CI: 0.214, 0.278) between models. The mean p(hypertension) for Mosuo from the model fit to Mosuo was 0.328; the mean p(hypertension) for Mosuo from the model fit to rural Hunan Han was 0.574 ($t = -14.911$; $df = 628.19$; $p < .0001$).

As predicted, diabetes was positively associated with anemia among the Han (OR = 1.291, ß = .256, 95% CI = −0.004, 0.507 for all Han; OR = 2.226, ß = .800, 95% CI = −0.083, 1.644 for rural Hunan Han), but not among the Mosuo (OR = 1.341, ß = .293, 95% CI = −0.792, 1.284; Tables 5, S4, and S5). Comparison of the regression coefficients (Figure 2) and predicted probabilities of anemia (Figure 3) show that Mosuo were distinct in that diabetes was not associated with anemia.

3 | DISCUSSION

The low rates of hypertension and diabetes-associated anemia we observed are notable, given that Mosuo are undergoing rapid market integration, with concomitant increasing risk for hypertension, diabetes, and other chronic diseases. We postulate that Tibetan Plateau adaptations to high altitude that increase blood flow and uncouple erythropoiesis regulation from hypoxia, enhancing oxygen delivery to tissues without dramatic increases in red blood cell production, protect Mosuo against hypertension and diabetes-associated anemia in an increasingly diabetogenic and obesogenic environment.

Our study design is subject to some limitations: The sampling strategy limits generalizability, as the Mosuo sample was not selected at random from among the entire Mosuo population, so, although we do not suspect any systematic biasing in the sample given the recruitment strategy, the fairly high rates of diabetes we observed (substantially higher than among Tibetans [Wang et al., 2017], for example) must nonetheless be interpreted with caution. In addition, relying on CHNS data to characterize hypertension risk factors and associations between diabetes and anemia among the Han precluded a comparison of our Mosuo sample to Han living at a comparable altitude (~2,600 m), nor do we have a sample of Mosuo living at low altitude. It is thus possible that the lower rates of hypertension and diabetes-associated anemia we observed among the Mosuo are attributable to lifelong residence at high altitude (e.g., developmental adaptations to hypoxia), rather than to Tibetan-type genetic adaptations to altitude. However, genetic adaptations to altitude among Tibetan Plateau populations predict our findings in ways that developmental adaptations, such as increased lung volume and alveolar area, do not (Frisancho, 1977; Garruto et al., 2003).

The Mosuo's relatively low risk for hypertension suggests that Tibetan Plateau adaptations, such as enhanced vasodilation and dense capillary networks, may work not only to increase oxygen delivery to tissues, but also to mitigate the hypertensive effects of high-altitude hypoxia. It is unlikely that this observation could be attributed to better care for hypertension among the Mosuo (e.g., via medication), for whom access to medical care remains limited. This pattern of lower

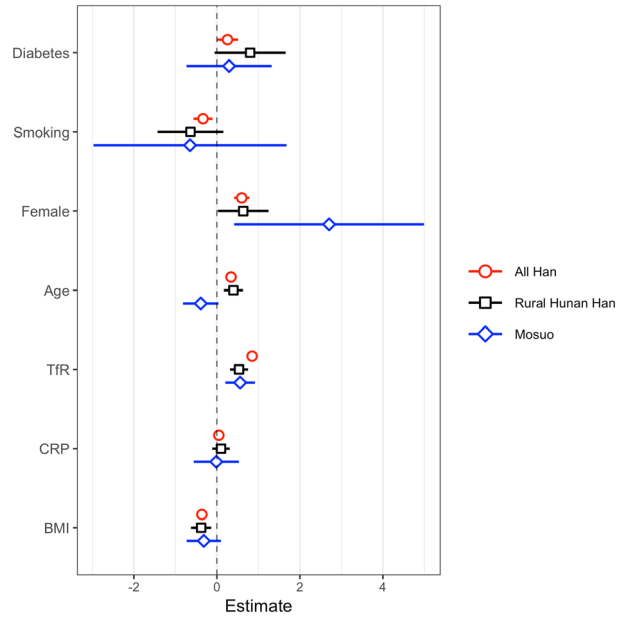

FIGURE 2 Comparison of coefficients from logistic regression models of anemia (unadjusted for altitude; Tables S3 and S4) and selected exposure variables: diabetes, smoking, female sex, age (in years), soluble transferrin receptor concentration (sTfR), C-reactive protein concentration (CRP), and body mass index (BMI) among all Han, rural Hunan Han, and Mosuo samples

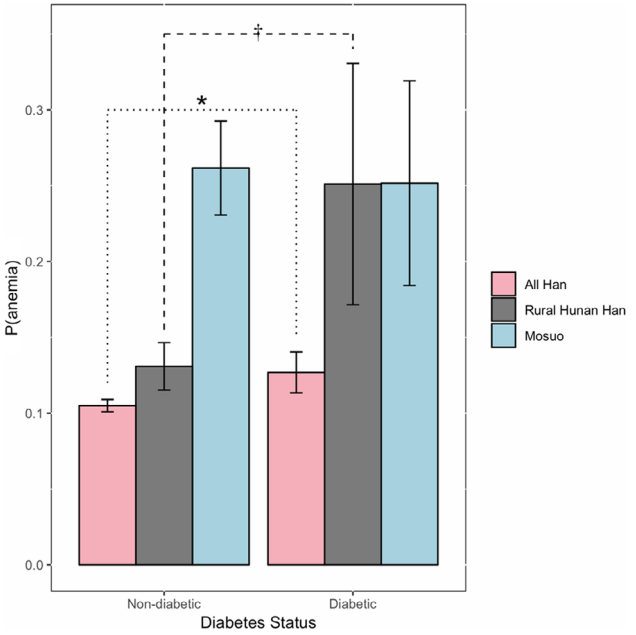

FIGURE 3 Predicted probabilities of anemia (unadjusted for altitude; Tables S3 and S4) given diabetes status among all Han, rural Hunan Han, and Mosuo samples (*denotes significant difference at $\alpha = .05$; † denotes significant difference at $\alpha = .10$)

risk for hypertension was obscured in previous research among Tibetans (Aryal et al., 2016; Mingji et al., 2015; Norboo et al., 2015; Sun, 1986), which was conducted at generally higher elevations and could not adequately control for differences in lifestyle between Tibetans and comparison groups. Our work suggests that lower risk for hypertension may be an additional feature of Tibetan Plateau adaptations to high altitude.

The Mosuo's low risk for diabetes-associated anemia—despite high rates of diabetes—is consistent with evidence that EPO regulation differs in fundamental ways between Himalayan populations and the Han, bolstering the emerging understanding that blunted erythropoietic responses, due to changes in the HIF pathway, characterize Tibetan Plateau adaptations to high altitude (Beall et al., 2010; Bigham & Lee, 2014).

Our findings also suggest that chronic diseases may provide an important source of information for human high-altitude adaptation research. For example, although the high-altitude adaptations that are best understood involve systems that deliver oxygen to tissues, it is likely that aspects of metabolism are involved in adaptation to high altitude as well—possibly as a means to conserve the scarce resource of oxygen, or to divert it differently during exertion (Bigham & Lee, 2014). Genes involved in metabolism were among those identified as under selective pressure in Himalayan high-altitude populations (Arciero et al., 2018; Bigham & Lee, 2014). This raises the possibility that unique characteristics of diabetes epidemiology, progression, or complications could be identified in high-altitude-adapted populations, which could provide clues to ways in which positive selection on metabolism-related genes (Arciero et al., 2018; Horscroft et al., 2017) may have enhanced high-altitude function.

The study of interactions between high-altitude adaptations and chronic diseases is likely to become increasingly important as market integration affects more such populations globally. Our evidence suggests that Tibetan Plateau adaptations *lower* risk for hypertension and diabetes-associated anemia; however, the possibility also exists for these adaptations to *increase* risk or complicate other chronic diseases. Further, differences in adaptations to hypoxic stress across high-altitude regions may dramatically affect high-altitude adapted populations' experience of chronic disease. Our findings likely do not apply to high-altitude-adapted populations of the Andean Plateau or Ethiopian Highlands, whose adaptations differ in key ways (Beall, 2006); though, intriguingly, at least some Andean natives have strikingly low blood pressure (Toselli, Tarazona-Santos, & Pettener, 2001). As chronic diseases like hypertension and diabetes continue to grow as global health concerns, it is thus important to investigate how risk for chronic disease may be affected by highly localized genetic adaptation to the environment.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

S.M.M., M.K.S., and T.B. secured funding for the project. K.W., M.S., and S.M.M. designed the study. M.S. and C.Y.S. collected the data under supervision of K.W. and S.M.M., M.S. performed laboratory analyses under the supervision of H.L. and K.W., P.M.M., M.S., and K.W. analyzed the data. K.W., M.S., P.M.M., and S.M.M. drafted the manuscript. All authors reviewed and edited the final manuscript.

DATA AVAILABILITY STATEMENT

Data and materials availability: CHNS data may be accessed via the University of North Carolina at Chapel Hill website. Anonymized Mosuo data and R code will be archived on GitHub following completion of planned analyses.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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