ORIGINAL ARTICLE

High-altitude ancestry protects against hypoxia-associated reductions in fetal growth

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Objective: The chronic hypoxia of high-altitude (⩾2500 m) residence has been shown to decrease birth weight in all populations studied to date. However, multigenerational high-altitude populations appear protected relative to newcomer groups. This study aimed to determine whether such protection exists independently of other factors known to influence fetal growth and whether admixed populations (ie, people having both high- and low-altitude ancestry) show an intermediate level of protection.
Design: 3551 medical records from consecutive deliveries to Andean, European or Mestizo (ie, admixed) women at low, intermediate or high altitudes in Bolivia were evaluated for maternal characteristics influencing fetal growth as measured by birth weight and the frequency of small for gestational age births (SGA or ⩽10th percentile birth weight for gestational age and sex). Two-way analysis of variance and χ^2 tests were used to compare maternal and infant characteristics. The effects of ancestry or altitude on SGA and birth weight were assessed using logistic or linear regression models, respectively.
Results: Altitude decreased birth weight and increased SGA in all ancestry groups. Andean infants weighed more and were less often SGA than Mestizo or European infants at high altitude (13%, 16% and 33% respectively, $p<0.01$). After accounting for the influences of maternal hypertensive complications of pregnancy, parity, body weight, and number of prenatal visits, European relative to Andean ancestry increased the frequency of SGA at high altitude nearly fivefold.
Conclusions: Andean relative to European ancestry protects against altitude-associated reductions in fetal growth. The intermediate protection seen in the admixed (Mestizo) group is consistent with the influence of genetic or other Andean-specific protective characteristics.

The chronic hypoxia of high altitude residence (⩾2500 m) decreases birth weight[1 2] primarily due to slowed fetal growth rather than greater prematurity.[3–5] Birth weight declines with altitude in all populations studied to date. However, multigenerational high-altitude populations (ie, Andeans, Tibetans) are protected relative to newcomer groups (ie, Europeans, Han ''Chinese'')[6–8] suggesting that hypoxia is responsible for the reductions in fetal growth. Differences in healthcare access, socioeconomic status, number of prenatal visits, parity, maternal height or hypertensive complications do not explain the degree to which birth weight decreases with altitude.[1 9] Although multiple factors could be responsible for the differences among high-altitude populations in the magnitude of hypoxia-associated reduction in birth weight, being born and raised at high altitude does not seem responsible, suggesting that the protective effect of high-altitude ancestry on birth weight at altitude is genetic in nature.[10 11]

Previous reports documenting a protective effect of high-altitude ancestry on fetal growth have been limited by small sample size and/or a lack of information concerning other risk factors for low birth weight (eg, socioeconomic status, maternal stature).[8 12] Furthermore, no study, to our knowledge, has asked whether admixed groups (ie, high-altitude and low-altitude ancestry) show an intermediate level of protection. We therefore asked whether Andean ancestry acted independently to protect against decreased fetal growth with altitude, and whether such protection was intermediate in infants of mixed Andean-European parentage (Mestizos).

Identifying population differences in susceptibility to hypoxia-associated reduction in fetal growth is of clinical importance in that small size at birth increases perinatal morbidity and mortality,[13 14] and the risk for cardiovascular disease in adulthood.[15] In countries such as Bolivia, where infant mortality is high,[7 16] knowledge of the source of mortality risk is essential for designing effective treatment and prevention strategies.

METHODS

The Colorado Multiple Institutional Review Board and the ethical oversight group for the Bolivian organisations (Colegio Médico) approved all the study procedures.

Study design

We examined the medical records for 3551 consecutive, singleton deliveries at low (416 m, Santa Cruz), intermediate (2500 m, Cochabamba) or high altitude (3200–4100 m, La Paz or Oruro) in Bolivia. These cities are the largest urban areas at their respective altitudes and are served by the same healthcare system for the insured public (the Caja Nacional de Salud (CNS); ''public'') and also by private facilities catering to the middle and upper classes (''private'').

We collected records of births between 1 January and 31 May 1998 in public hospitals and 1 January 1996 and 31 May 1999 in private clinics. Exclusion criteria were fewer than two prenatal visits; no birth weight, gestational age or infant sex data; or the presence of pre-existing risk factors known to influence birth weight (ie, maternal chronic hypertension or diabetes).

Abbreviations: LMP, last menstrual period; SGA, small for gestational age

Study variables and definitions

We recorded infants' birth weight, gestational age, sex, length, head circumference and any fetal or newborn complications. For each mother, maternal and paternal surnames, altitude of residence, age at last menstrual period (LMP), parity, health history, education, occupational status (manual labour *v* salaried worker or professional), number of prenatal visits, weight at term, maximum blood pressure, number of blood pressure values ⩾140/90 mm Hg, proteinuria, delivery type, and pregnancy or labour/delivery complications were recorded. For the father, maternal and paternal surnames, age, education, and occupation were noted.

Infant ancestry was classified using parental surnames, a method validated by comparison with gene markers.[17] According to naming traditions in Bolivia, infants have four surnames (two maternal and two paternal). Infants were considered ''Andean'' if three or more surnames were of Aymara or Quechua origin, ''Foreign'' if three or more surnames were non-Hispanic or the parents were of non-Bolivian nationality, and ''Mestizo'' for all others. As ~90% of ''Foreign'' infants were of European origin, this category is identified as ''European'' here.

Gestational age was reported as weeks from the LMP except when values differed by two or more weeks from clinical estimates, in which case the latter was used. Pre-term was defined as gestational age <37 weeks. Small for gestational age (SGA) was defined as a birth weight ⩽10th percentile for a given gestational age and sex based on data that have been validated with perinatal mortality criteria[18] in the USA. Owing to the lack of birth weight for gestational age charts in Bolivia we could not use a population-specific reference. Ponderal index was calculated as 100× birth weight (g)/crown–heel length $(cm)^3$. Prenatal mortality was calculated as (gravidity) – (parity + number of non-spontaneous abortions). Newborn respiratory complications were defined as any condition requiring oxygen treatment at birth or during the first few days of life: diagnosis of respiratory distress, apnoea, respiratory depression, pulmonary hypertension, or hyaline membrane disease, or newborn hypoxia as a discharge diagnosis.

Maternal pregnancy-induced hypertensive complications were defined as two or more blood pressure readings ⩾140 mm Hg (systolic) or ⩾90 mm Hg (diastolic) at least 6 h apart or a ⩾30mm Hg or ⩾15 mm Hg rise above levels at the first prenatal visit in an otherwise normotensive woman (<20 weeks or postpartum). Pre-eclampsia was defined as the presence of hypertension and proteinuria (qualitative reading of ⩾1+ or 300 mg/l 24-h collection) during pregnancy, gestational hypertension as hypertension without proteinuria, and pre-eclampsia/gestational hypertension when the absence of proteinuria determinations did not allow their distinction. Bleeding during pregnancy, premature membrane rupture, oligohydramnios or polyhydramnios, and placental abruption were noted.

Table 1 Maternal characteristics at low (416 m), intermediate (2500 m) and high (3200–4100 m) altitude*

Variable	Group	Low	Intermediate	High	p Altitude
Maternal age (years)	All	28.5 (0.2), 810‡	28.4 (0.2, 953‡	29.5 (0.1), 1760¶	<0.01
	Andean	26.1 (1.1), 30	29.8 (1.4), 25	28.2 (0.4), 250	NS†
	Mestizo	28.4 (0.2), 716‡	28.3 (0.2), 893‡	29.6 (0.1), 1425¶	< 0.01
	European	31.3 (0.9), 39	29.3 (1.0), 27	31.9 (0.7), 64	NS†
	p Ancestry	<0.01	NS	<0.01	
Parity (no.)	All	2.4 (0.1), 811‡	2.3 (0.1), 807‡	2.3 (0.0), 1755¶	NS
	Andean	2.5 (0.0), 31	3.7 (0.4), 25	2.9 (0.1), 250	NS
	Mestizo	2.3 (0.0), 719‡	2.3 (0.1), 758‡	2.2 (0.0), 1422¶	NS
	European	3.2 (0.3), 36‡	2.0 (0.5), 15¶	2.1 (0.2), 62¶	<0.01
	p Ancestry	<0.01	<0.01	<0.01	
Maternal weight at term (kg)	All	71 (0), 712‡	67 (0), 442‡	68 (0), 1713¶	<0.01
	Andean	68 (2), 28	64 (2), 17	66 (0), 245	NS
	Mestizo	70 (0), 632‡	67 (1), 413¶	68 (0), 1390¶	<0.01
	European	71 (2), 35	–	71 (2), 58	NS
	p Ancestry	NS	NS	<0.01	
First prenatal visit (weeks)	All	19 (0), 768‡	22 (0), 557¶	17 (0), 1626§	<0.01
	Andean	23 (1), 31‡	26 (2), 19‡	20 (0), 248¶	<0.01
	Mestizo	19 (0), 682‡	22 (0), 524¶	16 (0), 1309§	<0.01
	European	15 (2), 33	9 (1(6)	12) (1(52)	NS
	p Ancestry	<0.01	<0.01	<0.01	
Preeclampsia or gestational hypertension (%)	All	11 (9 to 13), 814‡	8 (6 to 10), 965¶	17 (15 to 19), 1772§	<0.01
	Andean	10 (3 to 25), 31	4 (7 to 20), 25	20 (16 to 25), 250	NS†
	Mestizo	11 (9 to 14), 719‡	8 (7 to 10), 899¶	16 (14 to 18), 1437§	<0.01
	European	5 (1 to 17), 39	4 (1 to 18), 27	11 (5 to 21), 64	NS
	p Ancestry	NS	NS	NS	
Caesarean section (%)	All	58 (54 to 61), 790‡	48 (45 to 51), 923¶	40 (38 to 43), 1754§	<0.01
	Andean	29 (16 to 47), 31	8 (2 to 26), 24	16 (12 to 21), 248	NS†
	Mestizo	57 (54 to 61), 701‡	48 (45 to 52), 860¶	44 (42 to 47), 1421¶§	<0.01
	European	78 (63 to 89), 37‡	69 (50 to 84), 26‡	48 (37 to 60), 64¶	<0.05
	p Ancestry	<0.01	<0.01	<0.01	
Private clinic (%)	All	41 (37 to 44), 814‡	48 (45 to 51), 965¶	43 (40 to 45), 1771‡§	<0.01
	Andean	0 (0 to 11), 31‡	24 (12 to 43), 25¶	2 (1 to 5), 250‡§	<0.01
	Mestizo	38 (34 to 41), 719	48 (45 to 51), 899	47 (45 to 50), 1436	NS
	European	95 (83 to 99), 39	100 (88 to 100), 27	100 (94 to 100), 64	NS†
	p Ancestry	<0.01	<0.01	<0.01	
Prenatal mortality (deaths/1000 births)	All	16 (9 to 25)‡	4 (2 to 10)¶	23 (15 to 34)‡	<0.05
	Andean	0 (0 to 4)‡	0 (0 to 4)‡	27 (19 to 39)¶	<0.01
	Mestizo	17 (11 to 27)‡	5 (2 to 12)¶	22 (15 to 33)‡	NS
	European	9 (5 to 17)‡	0 (0 to 4)¶	27 (19 to 39)§	<0.01
	p Ancestry	<0.01	<0.01	NS	

NS, non-significant.
*Data are mean (SEM or 95% CI), sample size for each variable.
†0.05<p<0.10.
‡¶§Significant differences from post-hoc comparisons between altitude groups.
Totals for ''All'' may not equal ancestry group totals because—for example, mothers of infants with fewer than three surnames (and hence who could not be assigned an ancestry group) are included in ''All''.

Statistical analysis
Data are reported as the mean (SEM or 95% CI) for proportions. For continuous variables, normality was tested using the Kolmogorov–Smirnov method. We made comparisons across altitude or ancestry groups using analysis of variance for continuous variables and χ^2 tests for categorical variables. Post-hoc tests were conducted using Scheffé's method. We used regression models to assess the influence of maternal pregnancy-induced hypertensive complications (pre-eclampsia, gestational hypertension and pre-eclampsia/gestational hypertension), ancestry, parity, maternal weight at term and number of prenatal visits on the frequency of SGA (logistic) and birth weight (linear). We carried out the analyses using SAS or SPSS. Significance was reported when the p value was <0.05 and trends were reported where $0.05<p<0.10$.

RESULTS
Maternal characteristics
The Andean women were younger at low and high altitudes, but of higher parity than the Europeans or Mestizos at intermediate or high altitudes (table 1). Maternal weight at term was slightly lower in Andean or Mestizo than in European women at high altitude. The Andeans began prenatal care later (table 1), were less educated and were more often engaged in manual labour than the Mestizo or European women (data not shown).

Altitude increased the prevalence of pregnancy-induced hypertensive complications (table 1) as well as oligohydramnios or polyhydramnios or bleeding during pregnancy (data not shown). Caesarean sections were less common among the Andean women than other groups at all altitudes (table 1) primarily because, relative to European or Mestizo women, few Andean women delivered at private clinics, where caesarean sections were done nearly twice as often as at public hospitals (64.0% (95% CI 61.6% to 66.2%) *v* 36.0% (33.7% to 38.4%), respectively, $p<0.01$).

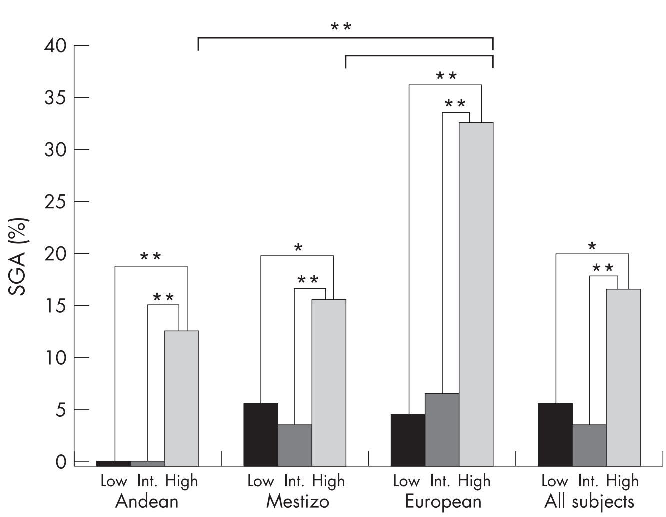

Figure 1 Among the sample of 3551 subjects (right-hand bars) in Bolivia, the frequency with which babies were small for gestational age (SGA, defined as $\leqslant$10th percentile for gestational age and sex[18]) was greater at high (3200–4100 m) than intermediate (2500 m) or low (416 m) altitude. SGA was more common at high than low or intermediate altitude in each group (within ancestry group comparisons designated with thin lines). At high but not other altitudes, SGA was less common among Andeans or Mestizos than Europeans ($p<0.01$ for each comparison, within altitude comparisons designated with bold lines). *$p<0.05$, **$p<0.01$; see table 2 for the means and CIs shown here.

Infant characteristics
SGA increased and birth weight decreased in all groups with increasing altitude (fig 1, table 2). Gestational age was slightly lower among Andean than other ancestry groups (table 2), a difference attributable to fewer Andean deliveries by caesarean section, which were done nearly a week earlier than vaginal births. The prevalence of SGA among Europeans at high altitude was more than twice that of Mestizos or Andeans; no ancestry-associated differences in frequency of SGA were present at lower altitudes (fig 1, table 2). The ponderal index was lower in the European women than in the other groups at high altitude. The proportion of female births was similar at low (49.9%), intermediate (48.2%) and high altitude (48.1%; p = NS).

Prenatal mortality was greater at higher than lower altitudes among Europeans and Andeans but not Mestizos, in whom the frequency was higher at low altitude relative to other groups (table 1). The frequency of respiratory complications increased with higher altitude in European or Mestizo infants but not in the Andeans. European infants experienced respiratory complications more often than Andeans at high altitude (table 2).

Relationship between maternal characteristics and infant birth weight
At low altitude, hypertensive complications of pregnancy increased the frequency of SGA more than twofold (table 3). At high altitude, pre-eclampsia and gestational hypertension increased the frequency of SGA approximately 1.5-fold. Greater parity and maternal weight at term were protective against SGA at high altitude (table 3). After taking the influences of pre-eclampsia or gestational hypertension and the other independent variables into account, European relative to Andean ancestry increased the frequency of SGA nearly fivefold at high altitude (table 3).

Birth weight also fell with increasing altitude in each ancestry group after adjusting birth weight for other independent variables influencing birth weight: gestational age, maternal weight at term, parity, prenatal visits, pre-eclampsia or gestational hypertension and infant sex (Andean: 3328 (29) g, 3329 (33) g and 3122 (20) g; Mestizo: 3315 (18) g, 3325 (22) g, 3119 (13) g; European: 3215 (40) g, 3200 (45) g, 2999 (37) g, respectively for low intermediate and high altitude, $p<0.001$ for all). Even after these adjustments, ancestry remained a significant determinant of birth weight at high altitude such that Europeans were 229 g and 243 g lighter than Mestizos and Andeans, respectively ($p<0.001$ for all). Ancestry did not influence birth weight at lower altitudes.

DISCUSSION
We have demonstrated that Andean ancestry confers protection against SGA and the reduction in birth weight seen among high-altitude residents. Such protection was evident in the raw data and after adjusting for the influences of socioeconomic and maternal characteristics on birth weight. Consistent with our hypothesis, mixed Andean-European parentage had an intermediate level of protection. We therefore conclude that some Andean-specific factor(s), possibly genetic, acquired with multigenerational high-altitude residence, protects against altitude-associated reductions in fetal growth.

The retrospective nature of our study limited our ability to distinguish between early-onset and late-onset or symmetrical and asymmetrical SGA. However, prospective longitudinal studies including fetal growth and vascular measurements are in progress. These will help to define whether the patterns of fetal growth restriction with altitude differ among population groups and whether the increased number of SGA babies reflects true restriction of fetal growth or greater numbers of

Table 2 Infant characteristics at low (416 m), intermediate (2500 m) and high (3600–4100 m) altitude*

Variable	Group	Low	Intermediate	High	p Altitude
Birth weight (g)	All	3365 (18), 780‡	3306 (16), 944¶	3101 (12), 1739§	<0.01
	Andean	3497 (88), 31‡	3338 (100), 24¶	3202 (31), 250¶	<0.01
	Mestizo	3368 (19), 693‡	3317 (17), 880¶	3090 (13), 1480§	<0.01
	European	3261 (80), 35‡	3045 (93), 26¶	2957 (64), 61¶	<0.01
	p Ancestry	NS	<0.05	<0.01	
Small for gestational age (%)	All	6 (4 to 8), 801‡	4 (3 to 5), 965‡	17 (15 to 18), 1772¶	<0.01
	Andean	0 (0 to 18), 18	0 (0 to 13), 25	13 (9 to 18), 250	<0.05
	Mestizo	6 (4 to 8), 719‡	4 (3 to 5), 899‡	16 (9 to 18), 1437¶	<0.01
	European	5 (1 to 17), 39‡	7 (2 to 23), 27‡	33 (23 to 45), 64¶	<0.01
	p Ancestry	NS	NS	<0.01	
Gestational age (weeks)	All	38.9 (0.0), 778‡	38.9 (0.0), 770‡	38.8 (0.0), 1748¶	NS
	Andean	39.9 (0.3), 30	39.1 (0.4), 22	39.4 (0.1), 250	NS
	Mestizo	38.9 (0.0), 688‡	38.9 (0.0), 718‡	38.7 (0.1), 1415¶	<0.05
	European	38.7 (0.0), 37	38.0 (0.0), 16	38.6 (0.0), 63	NS
	p Ancestry	<0.01	NS	<0.01	
Ponderal index	All	2.6 (0.0), 769‡	2.7 (0.0), 901‡	2.7 (0.0), 1711¶	<0.05
	Andean	2.7 (0.0), 31	2.6 (0.0), 24	2.7 (0.0), 246	NS
	Mestizo	2.7 (0.0), 684	2.7 (0.0), 838	2.7 (0.0), 1386	NS
	European	2.5 (0.0), 35‡	2.6 (0.0), 25‡	2.5 (0.0), 60¶	NS
	p Ancestry	NS	NS	<0.01	
Newborn respiratory complications (%)	All	1 (1 to 2), 804‡	0 (0 to 1), 963‡	5 (4 to 6), 1771¶	<0.01
	Andean	6 (1 to 26), 18	0 (0 to 13), 25	2 (1 to 5), 250	NS
	Mestizo	1 (1 to 2), 722‡	0 (0 to 1), 897¶	5 (4 to 7), 1433§	<0.01
	European	0 (0 to 9), 39‡	0 (0 to 12), 27‡	12 (6 to 23), 64¶	<0.05
	p Ancestry	NS	NS	<0.01	

NS, non-significant.
*Data are mean (SEM or 95% CI), sample size for each variable.
†0.05<p<0.10.
‡¶ §Significant differences from post-hoc comparisons between altitude groups.
Totals for "All" may not equal ancestry group totals since, for example, mothers of infants with less than three surnames (and hence who could not be assigned an ancestry group) are included in "All".

infants who are constitutionally small. The absence of routine measurement of proteinuria limited our ability to differentiate between gestational hypertension and pre-eclampsia. Despite including some of the best medical facilities in Bolivia, only 2% of normotensive and 12% of hypertensive women in Santa Cruz were screened for proteinuria and in La Paz, there were no measurements available for proteinuria for 38% of normotensive and 30% of hypertensive women. Thus, to assess the influence of pregnancy-induced hypertension on fetal growth, we considered pre-eclampsia, gestational hypertension and pre-eclampsia/gestational hypertension as a single variable.

Table 3 Relationship between maternal characteristics and small for gestational age (SGA) deliveries at low (416 m) and high (3600–4100 m) altitude

Dependent variable: SGA Independent variable	Estimated coefficient (β)	Odds ratio (95% CI)	p Value
Low altitude			
PE or GH (yes)	0.81	2.26 (1.03 to 4.93)	<0.05
Ancestry	–	–	NS
Andean (reference)	–	–	NS
Mestizo	–	–	NS
European	–	–	NS
Parity (no. births)	–	–	NS
Maternal weight at term (kg)	–	–	NS
Prenatal care (no. visits)	–	–	NS
High altitude			
PE or GH (yes)	0.38	1.46 (1.05 to 2.05)	<0.05
Ancestry	–	–	<0.001
Andean (reference)	–	–	–
Mestizo	0.30	1.35 (0.89 to 2.05)	NS
European	1.60	4.94 (2.35 to 10.38)	<0.001
Parity (no. births)	–0.20	0.82 (0.73 to 0.92)	<0.01
Maternal weight at term (kg)	–0.05	0.95 (0.93 to 0.97)	<0.001
Prenatal care (no. visits)	–	–	NS

PE, pre-eclampsia; GH, gestational hypertension.

Pregnancy-induced hypertension was defined as two or more blood pressure readings ⩾140 mm Hg (systolic) or ⩾90 mm Hg (diastolic) and/or a rise in blood pressure (see Methods), despite current recommendations to omit the latter.[19] We decided to use this comparatively liberal definition because Bolivia uses these criteria and, in our sample, even mild pregnancy-induced hypertension was associated with adverse outcomes such as preterm delivery, prenatal mortality, SGA and newborn respiratory complications.

As the public facilities included in our analyses belonged to the largest organisation in Bolivia providing healthcare to the insured public (CNS), our sample included women from a range of socioeconomic backgrounds. Further, women attending CNS facilities generally receive prenatal care sufficient to diagnose pregnancy complications. Such women also generally deliver in hospitals, where medical records could be obtained. To obtain sufficient ancestry variation, we also collected records from private facilities, where wealthier, often foreign ancestry, groups receive care. Although mixing public and private facilities may introduce some variability in diagnostic criteria, doctors often work at both kinds of facility, a practice that affords some uniformity of care between sites. Thus, our study design maximised the extent to which comparisons could be made across various facilities.

All of the women whose medical records were included in this study had prenatal care and delivered in hospitals, although in Bolivia only 43% of births are attended by healthcare workers and even fewer receive prenatal care.[20] Our study design permitted us to assess the influence of population ancestry on fetal growth and pregnancy complications. However, it probably underestimated the true prevalence of these disorders in Bolivia. Likewise, given that a large proportion of women do not deliver in hospitals, our results may overestimate the proportion of all births by caesarean section. However, similar to the percentages of caesarean deliveries reported here, the 2005 World Health Organization

What is already known on this topic

- The chronic hypoxia of high-altitude residence (⩾2500 m) potently decreases birth weight in all populations studied to date.
- Multigenerational high-altitude ancestry (eg, Tibetan or Andean) appears to protect against the reduction in birth weight and neonatal mortality associated with high-altitude residence.

What this study adds

- The protection afforded by high-altitude ancestry against hypoxia-associated reductions in birth weight is *independent* of other factors known to influence fetal growth.
- People of admixed Andean-European ancestry (''Mestizos'') show an intermediate level of protection against altitude-associated reductions in fetal growth, suggesting an influence of genetic factors on hypoxia-associated reductions in fetal growth.

survey on maternal and child health in eight Latin American countries reported median caesarean delivery rates of 33% overall and 51% in private hospitals.[21]

Our results agree with previous reports documenting the reduction of birth weight with altitude above 2000 m,[22 23] as well as those demonstrating the protective effect of high-altitude ancestry on birth weight at altitude. In Bolivia (3600 m) Haas reported that infants born to women of European ancestry were 120 g lighter than those born to Aymara women,[24] a smaller difference than that we report here (245 g). Our results are similar to Haas' if we compare the birth weights of European and Mestizo infants in the current study (133 g), suggesting that some of Haas' group classified as Aymara may have been whom we termed ''Mestizo''.

As multiple factors influence fetal growth, we considered the extent to which maternal stature or socioeconomic status may have contributed to our observations. In Bolivia malnutrition remains an important public health issue, particularly in lower economic strata and indigenous populations residing in highland and rural areas.[25–28] Thus Andean infants would be expected to be lighter than Europeans; however, our data suggest the opposite. After accounting for variation in maternal weight at term, infant sex and gestational age, Andean infants were 245 g heavier than European infants at high altitude, whereas the difference between Mestizo and European infants increased from 133 g to 213 g. Haas reported that after accounting for gestational age, parity, maternal stature, iron status and haemoglobin levels the difference in birth weight between Aymara and European infants at 3600 m increased from 120 g to 191 g.[24] Further, although maternal height is positively associated with birth weight and birth length,[29] Andean women deliver infants of heavier birth weight at altitude than European women, despite their smaller stature.[24 30] Thus the protective effect of high-altitude ancestry is probably not the result of maternal stature or nutritional factors, suggesting that the protective effect of high-altitude ancestry on fetal growth also exists independently of socioeconomic status. Despite having lower educational attainment and higher participation in manual labour, Andean women delivered SGA infants less often SGA than other groups suggesting that the protection afforded by high-altitude ancestry may be an adaptive response.

Infants of a geographically and genetically distinct high-altitude ancestry group (ie, Tibetans) are also protected from decreasing birth weight with altitude. We have previously reported that Tibetans weigh more than Han infants born at 3600 m,[31] and experience only a third of the altitude-associated reduction in birth weight compared with Han infants living across the same 2700–3800 m altitude gradient in the Tibetan Autonomous Region of southwestern China.[7] Specifically, we found that Tibetan infants weighed 310 g more than Han infants at 2700–3000 m and 530 g more at 3000–3800 m[8] suggesting that birth weight difference between these groups at altitude is due to variable to hypoxia, rather than intrinsic variation in birth weight at any altitude. The Tibetan and Han infants were of similar weight when born at lower altitudes.[6 7]

Interestingly, Lhasa, Tibet, and La Paz, Bolivia, are both located at approximately 3600 m, allowing direct birth weight comparisons between these populations. Tibetan and Andean birth weights were similar (3280 g and 3202 g, respectively) but the Han birth weights were considerably less than the European birth weights reported here (2645 g and 2957 g, respectively). This may be due to the comparative recency of the Han migration to the Tibetan Plateau (~60 years) whereas European-derived populations have resided in the South American highlands for up to 400 years. Although it is not known how many generations of high-altitude residence are required to observe a protective effect for preserving fetal growth neither lifelong[10 32] nor one to two generations of high-altitude residence[8] appear sufficient.

In summary, this report indicates that Andean ancestry protects against hypoxia-associated reductions in fetal growth. Given that recent studies have shown ancestry-associated variability in maternal vascular adaptation to pregnancy[7] and that susceptibility to SGA and its risk factors may be attributed to genetic effects[33–35] our results raise the possibility that the ancestry-dependent influences on fetal growth reported here may be genetic in nature. As reduced fetal growth increases the risk of infant mortality,[13 14] genes protecting fetal growth presumably would be selected for, or maintained, over generations of high-altitude residence. The preservation of ancestry-associated differences after accounting for available socioeconomic and maternal characteristics and the intermediate level of protection seen in people of admixed Andean-European ancestry further supports the idea that involvement of genetic factors. Direct study is needed to define the mechanisms by which such effects are exerted and correspondingly, whether other factors are responsible. Although comprising a small portion of the world's population, high-altitude residents are uniquely positioned to define the genetic, physiological or other characteristics influencing fetal growth, and thus to improve our ability to diagnose more accurately and ultimately prevent these conditions.

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