

Effects of Altitude *versus* Economic Status on Birth Weight and Body Shape at Birth

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ABSTRACT

The compelling evidence linking small size at birth with later cardiovascular disease has renewed and amplified a clinical and scientific interest in the determinants of fetal growth. Although the effects of maternal nutrition on fetal growth have been extensively studied, comparatively little is known about the effects of maternofetal hypoxia. This study tested the hypothesis that in highland regions, high altitude rather than maternal economic status is associated with reduced and altered fetal growth by investigating the effects of high altitude *versus* economic status on birth weight and body shape at birth in Bolivia. Bolivia is geographically and socioeconomically unique. It contains several highland (>3500 m above sea level) and lowland (<500 m) cities that are inhabited by very economically divergent populations. Birth weight, body length, and head circumference were compared between a high- ($n = 100$) and low- ($n = 100$) income region of La Paz (3649 m; largest high-altitude city) and a high- ($n = 100$) and low- ($n = 100$) income region of Santa

Cruz (437 m; largest low-altitude city). In addition, the frequency distribution across the continuum of birth weights was plotted for babies born from high- and low-income families in La Paz and Santa Cruz. Mean birth weights were lower in babies from La Paz than in babies from Santa Cruz in both high- and low-income groups. The cumulative frequency curve across all compiled birth weights was shifted to the left in babies from La Paz compared with those from Santa Cruz, regardless of economic status. The frequency of low birth weight (<2500 g) was higher in babies from La Paz than from Santa Cruz in both high- and low-income groups. In addition, at high altitude but not at low altitude, high income was associated with an increase in the head circumference:birth weight ratio. These findings suggest that high altitude rather than economic status is associated with low birth weight and altered body shape at birth in babies from Bolivia. (*Pediatr Res* 49: 490–494, 2001)

Epidemiologic studies of populations in England and Wales have shown an association between small body size at birth and increased risk of cardiovascular disease in adulthood (1, 2). These findings have been replicated in the United States (3), Sweden (4), Finland (5), The Netherlands (6), Croatia (7), India (8), and Japan (6). Studies of birth weights of relatives (9, 10), together with evidence from animal cross-breeding experiments (11–13), have led to the conclusion that the predominant influence on fetal growth is the intrauterine environment rather than the fetal genotype. These observations have led to “the fetal origins hypothesis,” which proposes that cardiovascular disease and type II diabetes originate through adaptations that the fetus makes when it is undernourished. These adaptations, which include slowing of growth, permanently change the structure and function of the body (14). Hence, it is not

surprising that these contentions have renewed and amplified a clinical and physiologic interest in which conditions during pregnancy lead to fetal growth retardation.

Although it is accepted that the most common challenges limiting fetal growth are reduced nutrient and oxygen delivery to the fetal circulation (15), the partial contributions of each of these substrates to fetal growth impairment remain to be determined. Several studies have shown that poor maternal nutrition is associated with reduced birth weight in humans (16–19), rats (20–22), and sheep (23, 24) and that the extent of the reduction depends on the severity, duration, and timing of the challenge (23, 24). Relatively less information is available about the effects on body size at birth of maternofetal hypoxia, independent of changes in maternal nutritive state.

In human populations, maternofetal hypoxia occurs most commonly during the hypobaric hypoxia of pregnancy at high altitude (25). Several investigators have reported reduced birth weight with increasing altitude (26–33). However, because most high-altitude populations are also impoverished (32), the extent to which this reduction is governed by maternal economic status or high altitude remains uncertain.

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This study tested the hypothesis that high altitude rather than maternal economic status is associated with reduced and altered fetal growth by comparing the birth weights and body shape at birth of babies in wealthy and impoverished communities in the highest (La Paz, 3649 m above sea level) and lowest (Santa Cruz, 437 m) most populated cities of Bolivia.

Some of these data have been previously presented as an abstract (34).

METHODS

Bolivia. This South American country is geographically and socioeconomically unique. Whereas the Andean Cordillera runs through the west of the country, eastern parts of the country encompass rain forest regions that span into the Brazilian Amazon. Consequently, Bolivia is divided into several highland (>3500 m above sea level) and lowland (<500 m) regions, which stand highest to lowest as one travels from the west to the east of the country.

The two most populated Bolivian cities, La Paz and Santa Cruz, are also the highest and the lowest in the country, respectively. La Paz is the highest capital city in the world, standing at 3649 m above sea level and containing 1,900,786 inhabitants (35). Santa Cruz stands at 437 m above sea level and has 1,364,389 inhabitants (35). Both La Paz and Santa Cruz are made up of striking economically divergent populations where 71% of the inhabitants in La Paz and 58% of those in Santa Cruz are highly impoverished by standards set by the Bolivian Ministry of Human Development (35). The rest of the populations in La Paz and Santa Cruz maintain a standard of living similar to that in affluent North American or European cities (35).

Maternity hospitals, birth measurements, and maternal characteristics. Records from pregnancies during 1997 and 1998 were obtained from maternity hospitals situated in wealthy (high-income) and impoverished (low-income) regions of La Paz and Santa Cruz. Informed consent was obtained, and the study was approved by the Ministry for Human Development in Bolivia. Levels of income in families from La Paz and Santa Cruz in the high- and low-income brackets were similar. The average household income in families from the high-income groups was approximately \$1500 (US) per month. The average household income in families from the low-income groups was just above the minimal national salary that was 400 bolivianos per month during the period of the study. The high-income maternity hospital in La Paz (high altitude-high income) was CEMES, a private clinic attended selectively by wealthy families. The low-income hospital in La Paz (high altitude-low income) was ENDA Hospital de La Mujer, a government-funded maternity unit situated in the region of El Alto where 90% of the low-income families of La Paz live (35). Similarly, the high-income maternity hospital in Santa Cruz (low altitude-high income) was a branch of PROSALUD, attended by the wealthier families. The low-income maternity hospital in Santa Cruz (low altitude-low income) was SID-CRUZ, a mission hospital that caters specifically to disadvantaged families.

Data describing birth weight, body (crown-heel) length, and head circumference were gathered retrospectively from 100 babies randomly chosen from the available birth books of each of the four hospitals in La Paz and Santa Cruz. All four groups of 100 babies (high altitude-high income, high altitude-low income, low altitude-high income, and low altitude-low income) contained infants born from non-smoking mothers with mixed parity and mixed ages. The level of literacy, professional occupation, and degree of assistance in their own household among the mothers from the high- and low-income groups were very different but similar between La Paz and Santa Cruz. Mothers from the high-income groups, by and large, had finished high school, whereas mothers from the low-income groups had either never attended school or had a level of literacy equivalent to primary school. Mothers from low-income groups were generally domestic helpers with a large degree of assistance in their own household. In contrast, the professional occupation of mothers from high-income groups ranged from company directors to secretarial positions, and these mothers had a comparatively low degree of assistance in their own household. Maternal age at first pregnancy also varied between income groups but was also similar between La Paz and Santa Cruz (La Paz-high income, 22.1 ± 0.5 y; Santa Cruz-high income, 22.8 ± 0.7 y; La Paz-low income, 18.1 ± 0.5 y; Santa Cruz-low income, 18.9 ± 0.9 y; mean \pm SEM). In the present study, only singleton pregnancies that reached term (>38 wk) with information about maternal health and smoking were used in the investigation. Other birth records with incomplete information about the mother or the health of the pregnancy were excluded in the analysis.

Data and statistical analyses. Values for birth weight, body length, head circumference, and head circumference:birth weight ratio are expressed as mean \pm SEM. Comparisons of any of these variables between La Paz and Santa Cruz and between high- and low-income regions were assessed using ANOVA with the *post hoc* Dunn's test or the Tukey test, as appropriate. In addition, the cumulative frequency distribution across all birth weights gathered was plotted for each of the groups of babies from La Paz and Santa Cruz. Significance for any statistical comparison was accepted when $p < 0.05$.

RESULTS

Birth measurements. Mean birth weight was significantly lower in babies from La Paz than in babies from Santa Cruz in both high- and low-income groups (Fig. 1A). Even babies born from impoverished families in the low-income groups of Santa Cruz had considerably greater mean birth weight than babies born from high-income families in La Paz. Babies from low-income families in Santa Cruz had lower mean birth weight than those from high-income families in Santa Cruz. Furthermore, babies from high-income families in La Paz had lower mean birth weight than those from low-income families in La Paz.

Both low income and altitude were associated with a decrease in body length (Fig. 1B). Head circumference was greater in babies born from high-income families in La Paz than those born from low-income families in La Paz (Fig. 1C).

The head circumference:birth weight ratio was greater in babies from La Paz than from Santa Cruz, regardless of income status. In addition, at high altitude but not at low altitude, high income was associated with an increase in the head circumference:birth weight ratio (Fig. 1D).

Plots of the cumulative frequency distribution across all birth weights gathered showed a shift to the left in the curve of babies from high altitude compared with from low altitude, regardless of economic status (Fig. 2). The cumulative frequency distribution of babies from La Paz showed that the curve for babies from high-income groups appeared shifted to the left relative to the curve for babies from low-income groups. The cumulative frequency distribution of babies from Santa Cruz showed that the curve for babies from low-income groups appeared shifted to the left relative to the curve of babies from high-income groups (Fig. 2). The percentage of babies with low birth weight was greater in babies from La Paz than those from Santa Cruz in both high- and low-income groups (Table 1).

DISCUSSION

This study used epidemiologic data to test the hypothesis that high altitude rather than maternal economic status is associated with fetal growth retardation and altered fetal growth patterns during gestation in highland regions. Our results support this hypothesis because birth weights in La Paz (high-altitude city) were lower than in Santa Cruz (low-altitude city) in both high- and low-income groups. Interestingly, even babies from the strikingly impoverished low-altitude population of Santa Cruz were heavier than babies from high-income groups of La Paz. Furthermore, the frequency distribution across all birth weights gathered showed a shift to the left in the curve of babies from La Paz compared with babies from Santa Cruz, regardless of maternal economic status. Hence, the percentage of babies with low birth weights was also greater in babies from La Paz than from Santa Cruz in both high- and low-income groups.

The rationale behind this study depends on the assumption that maternal economic status is associated with maternal nutritive state. Although sparse knowledge is available on the contribution of economic status to maternal nutritive state during pregnancy at either low or high altitude, independent studies have reported the unremarkable finding that individuals from low socioeconomic status are under-nourished and that those from high socioeconomic status are well-nourished in Andean countries (36, 37).

The data in the present study support previous findings that reported reduced birth weight at altitude in Colorado (27, 38, 39), Peru (40, 41), and the Himalayas (42, 43). The persistence of low birth weight in babies from La Paz despite this being Bolivia's capital city, coupled with an elevated incidence of reduced birth weight in Colorado reported in other studies (27, 38, 39), lends further support to the hypothesis that high altitude without undernutrition contributes to decreased birth weight in high-altitude populations. Another observation by Howard *et al.* (44) is of particular significance because it relates to mothers who gave birth to infants with reduced birth

weight at the elevated region of Lake County in Colorado but who had previously borne children of normal weight in lowland regions outside of Lake County.

The mechanism mediating a decrease in the rate of fetal growth and altered body shape at birth at high altitude is unclear. Although many factors may distinguish the population of La Paz and Santa Cruz, one possibility is that the hypoxia of pregnancy at altitude may lead to altered fetal growth and reduced birth weight in high-altitude populations. That the highland mother and fetus are hypoxic relative to lowland pregnancies has been determined in previous investigations (25, 32, 45, 46). Furthermore, experiments in pregnant animals

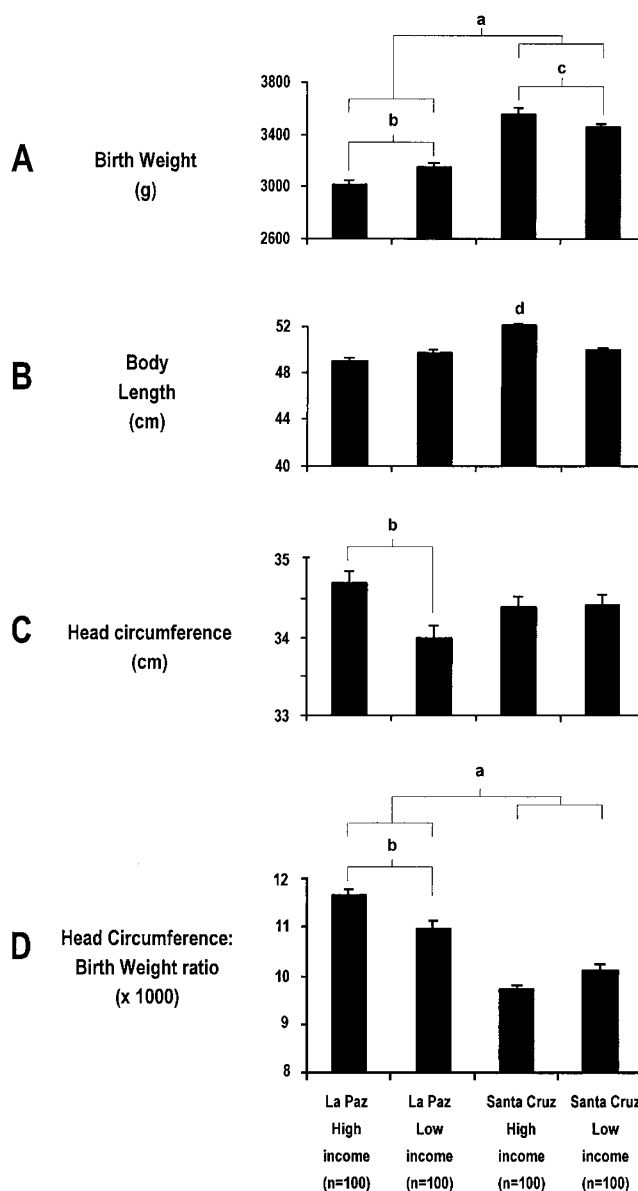


Figure 1. Birth weights and measurements in Bolivian babies. Values are mean \pm SEM of 100 babies taken from economically divergent populations in La Paz (3649 m above sea level) and Santa Cruz (437 m above sea level). Significant differences are ^a $p < 0.05$, La Paz vs Santa Cruz; ^b $p < 0.05$, La Paz-high income vs La Paz-low income; ^c $p < 0.05$, Santa Cruz-high income vs Santa Cruz-low income; ^d $p < 0.05$, Santa Cruz-high income vs all. ANOVA plus Dunn's or Tukey test.

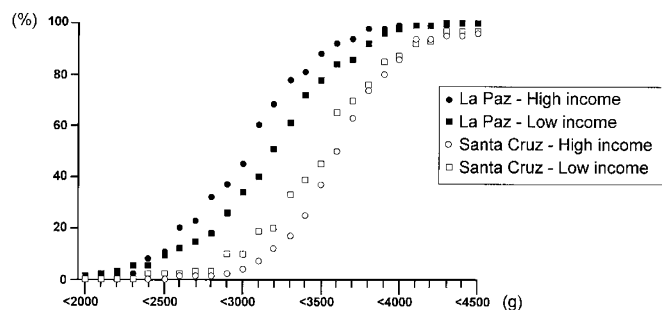


Figure 2. Cumulative frequency distribution across all birth weights gathered for babies from high- and low-income groups in La Paz and Santa Cruz.

echo the contention that chronic hypoxia without undernutrition during pregnancy can lead to growth retardation *in utero* (47–53).

Additional results in the present study showed that altitude was associated with an increase in the head circumference:birth weight ratio in both high- and low-income groups. Because an increase in this ratio is associated with stroke in adulthood (54), these findings suggest that babies born at high altitude may be more susceptible to this disease. Increased head circumference:body weight ratio may also reflect disproportionate or asymmetric growth retardation that spares brain growth at the expense of the fetal trunk (55). In the human, such fetal adaptations to adverse intrauterine conditions have been suggested to take place if the challenge to the intrauterine environment occurs during the third trimester of gestation (2). Interestingly, Haas *et al.* (30) reported that the low birth weight measured in Peruvian infants at altitude resulted mainly from reduced adipose deposition and decreased lower limb growth, processes that are known to occur in the last third of gestation in the human. In addition, McCullough *et al.* (38) and Unger *et al.* (39) reported that the greatest reduction in fetal growth rate in human pregnancies in Colorado occurred after 32 wk of gestation. Thus, it can be inferred from past and present observations that fetal growth retardation at high altitude may occur primarily in late gestation and may reflect maternoplacental insufficiency to meet the fetal oxygen demands at this time. Potential mechanisms may include a reduction in the transplacental oxygen partial pressure gradient (56) and/or depressed uteroplacental vasodilators (57, 58) leading to reduced uterine blood flow (32, 59), all of which have been reported in high-altitude pregnancy. It is possible that this unmatched fetal oxygen demand may trigger the release of fetoplacental hormones and factors that control tissue accretion and differentiation in the fetus during late gestation, such as insulin, thyroxine, cortisol, and IGF (60, 61). Pregnancy at high altitude may also alter the fetal plasma concentrations of binding proteins and the sensitivity of fetal tissues to these hormones and/or factors. The sparse available data suggest that up-regulation of IGF-binding proteins by chronic hypoxia may provide a mechanism operating in the human fetus to restrict IGF-mediated growth *in utero* (62, 63). In addition, human fetal growth may be regulated directly by the availability of oxygen. Hence, a direct effect of reduced oxygen tension on mitotic rate cannot be ruled out (43, 64).

Table 1. Percentage of babies with low birth weight from high- and low-income groups in La Paz and Santa Cruz

	Percentage of babies				
	<2800 g	<2700 g	<2600 g	<2500 g	<2400 g
● La Paz—high income	32	23	20	11	8
■ La Paz—low income	18	15	12	9	5
○ Santa Cruz—high income	1	1	1	0	0
□ Santa Cruz—low income	3	3	2	2	2

Of further interest are the findings of the present study that show a greater incidence of reduced birth weights across all ranges of birth weights gathered in babies from high-income compared with low-income groups in La Paz. In addition, at high altitude but not at low altitude, high income was associated with an increase in the head circumference:birth weight ratio. This is reminiscent of the more complete observations of Zamudio *et al.* (43) and Haas *et al.* (65) who suggested that fetal growth retardation at altitude is correlated to the duration of high-altitude residence, independent of maternal nutrition: the longest resident population experiencing the least decline and the shortest resident groups demonstrating the most reduction in birth weight. Accordingly, reductions in birth weight at elevations greater than 3000 m above sea level are greatest in North Americans, intermediate in South Americans, and least in Tibetans (43). Thus, women from high-altitude resident ancestry like the Tibetans (43) and the Aymaras (65) give birth to heavier babies than women from low-altitude resident ancestry like Han women in China and women from European or mestizo ancestry in South America. In the present study, the low socioeconomic group of La Paz contained a high percentage (92%) of women from Amerindian origin with Aymara patronymics and matronymics (32). In contrast, the high socioeconomic group of La Paz contained a high European admixture (62%). In addition, the attenuated increase in head circumference:body weight ratio in babies from low-income groups compared with those from high income in La Paz in the present study may represent a reduced drive to redistribute the fetal cardiac output toward the brain away from the peripheral circulations in Aymaran fetuses. These observations provide some evidence in support of the presence of protective mechanisms against altitude-associated fetal growth retardation in Bolivians from prolonged high-altitude resident ancestry. The physiology behind this protection and whether these mechanisms are at the maternal and/or placental and/or fetal level remain unknown. However, recently Beall *et al.* (66) identified a major gene that enhances arterial oxygen saturation in sedentary Tibetan natives. Moore (67) suggested that uterine blood flow was greater in Tibetan women than in acclimatized Han newcomers during pregnancy. Other studies have shown that the placenta at high altitude is more vascularized and has a greater diffusion capacity than at low altitude (68, 69).

In conclusion, our findings suggest that high altitude, independent of maternal economic status, is associated with low birth weight and altered body shape at birth in babies from highland regions of Bolivia.

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