Effect of Developmental and Ancestral High Altitude Exposure on Chest Morphology and Pulmonary Function in Andean and European/North American Natives

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ABSTRACT Chest depth, chest width, forced vital capacity (FVC), and forced expiratory volume (FEV1) were measured in 170 adult males differing by ancestral (genetic) and developmental exposure to high altitude (HA). A complete migrant study design was used to study HA natives (Aymara/Quechua ancestry, n = 88) and low altitude (LA) natives (European/North American ancestry, n = 82) at both altitude (La Paz, Bolivia, 3,600 m) and near sea level (Santa Cruz, Bolivia, 420 m). HAN and LAN migrant groups were classified as: Nth generation migrants, born and raised in a non-native environment; child migrants who migrated during the period of growth and maturation (0–18 yrs); and adult migrants who migrated after 18 years of age. Chest depth, FVC, and FEV1 measures were larger with increasing developmental exposure in both HAN migrants at LA and LAN migrants at HA. Developmental responses were similar between HAN and LAN groups. FVC and FEV1 measures were larger in HANs vs LANs born and raised at HA to suggest a genetic effect, but were similar in HANs and LANs born and raised at LA. The similarity of HAN and LAN groups at LA suggests that the genetic potential for larger lung volumes at HA depends upon developmental exposure to HA. Additional data for females (HANs at HA, n = 20, and LAN adult migrants to HA, n = 17) show similar differences as those shown between male HAN and LAN groups. Am. J. Hum. Biol. 11:383–395, 1999.

It is well established that high altitude native (HAN) populations residing in the Andes and Himalayas have larger chests dimensions and lung volumes relative to body size compared to populations residing at low altitude (LA) (Hurtado, 1932, 1964; Frisancho, 1969, 1997; Mueller, 1978; Greksa et al., 1986, 1988; Pawson, 1977; Stinson, 1985; Droma et al., 1991; Sun et al., 1990). Based on a number of human and animal studies, it has become clear that much of the inter-population difference in this respect can be explained by a developmental response to HA during the period of growth and development, i.e., lung phenotypes in HAN populations are at least partly an acquired characteristic (Frisancho et al., 1973; Mueller et al., 1980). However, the extent to which such phenotype differences represent a genetic adaptation to HA is not well defined.

The classic approach to partition developmental (acquired) from ancestral (genetic) components of phenotype difference is to compare populations with a different ancestral background and migration status in a given environment, according to the migrant study design first described by Harrison (1966). With respect to HA studies, a

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complete migrant design calls for the study of HANs and LA natives (LANs, no ancestral exposure to HA) in both their native environment and as migrants to a non-native environment (HA or LA). Modified versions of this approach have been used previously to compare lung volumes and chest dimensions of Andean groups to those of migrant groups of Europeans and North Americans to HA (Frisancho, 1973, 1997; Stinson, 1985; Greksa, 1986, 1988). Admixture problems may have confounded the ability to partition genetic effects in some of these studies, and it should be realized that in all of these studies only a part of the complete migrant design was utilized, i.e., groups were studied at HA only. The use of a complete migrant design offers some distinct advantages. First, a complete design provides a suitable reference group for HAN populations at HA because it includes a population of HANs born, raised, and tested at LA. This is an important consideration as the magnitude of the adaptive response in lung volumes at HA is often assessed relative to a predicted value for a sea level reference population, which may or may not be appropriate for comparison with HANs. Second, the complete design makes it possible to test the interaction of developmental and ancestral exposure effects. From the point of view of developmental adaptation, it is possible to assess whether a differential developmental response exists between HANs and LANs without having to compare growth curves. From the point of view of genetic adaptation, it is possible to assess whether genetic effects depend upon a prior developmental exposure to high altitude.

In this study, a complete migrant design was used to investigate HAN (Aymara/Quechua natives) vs LAN (European/North American natives) phenotype differences in chest width, chest depth, forced vital capacity (FVC), and forced expiratory volume in one second (FEV1). Groups of HANs and LANs were tested in their native environment, La Paz, Bolivia (3,600 m) and Santa Cruz, Bolivia (420 m), respectively, and as migrants to a non-native environment. Additional data were collected for HAN females at HA and for LAN females who had migrated to HA as adults, in order to establish the general similarity of the HAN vs LAN phenotype difference between males and females.

METHODS

Subjects and study design

The study protocol was approved by the Cornell University Human Subjects Committee and the Human Subjects Committee of the *Instituto Boliviano de Biología de Altura* (IBBA), in La Paz, Bolivia. Non-smoking males (n = 170) and females (n = 37) between 18 and 35 years were recruited by newspaper advertisement, as well as through contact with health professionals, university administrators, and community leaders. All subjects were in good health and gave consent after being informed of the risks and benefits associated with the study.

A complete migrant study design was employed with 8 distinct subject groups. Groups were studied in two environments, high altitude (HA, La Paz, Bolivia, 3,600 m) and low altitude (LA, Santa Cruz, Bolivia, 420 m), and were defined based on ancestral exposure to HA and migration status. Subjects with an ancestral exposure to HA were termed "high altitude natives" (HANs, Aymara and/or Quechua ancestry), and subjects with no ancestral exposure to HA were termed "low altitude natives" (LANs, European and/or North American ancestry). HANs and LANs in their native environment were defined as a reference group. Three distinct groups of migrants were defined for both HANs and LANs. Adult migrants were born and raised in their native environment and migrated as adults (>18 yrs age) to the non-native environment. Adult migrants had at least 2 months of acclimatization time to the non-native environment prior to the study (ranging to a maximum of more than 5 years exposure in a few subjects). Thus, these subjects were studied at a time after ventilatory and hematological adaptation to HA (Huang et al., 1984). Child migrants were subjects born in their native environment who had migrated to the non-native environment during the period of growth and maturation (between 0–18 yrs). N^{th} generation migrants were defined as subjects born and raised in a non-native environment as either 1st generation migrants, or as the children or grandchildren of previous migrants. Descriptions of the study groups are given below. Additional data were collected for HAN female subjects in their native environment and for LAN female adult migrants to HA.

HAN-HA (males = 24, females = 20). HANs studied in their native environment (HA) were rural Aymara Indians living on the Bolivian *altiplano* in the village of Pucarani, 10 miles from the Southern shore of Lake Titicaca. These subjects were primarily agropastoral laborers, raising food crops and tending to small flocks of domesticated animals. Aymara Indians are descendents of Amerindian groups who have had a sustained habitation in the Andes region of at least 10,000 years (Cardich, 1994). Nonetheless, it must be made clear that current Andean populations have seen at least some admixture with European populations in the time since the Spanish conquest (Chakraborty et al., 1989).

LAN-AM (males = 27, females = 17). LAN adult migrants to HA were expatriate European and North American professionals living and working in La Paz, Bolivia.

LAN-CM (n = 10). LAN child migrants to HA were recruited from the private university system in La Paz, Bolivia, and as such were generally from the upper socioeconomic class. These subjects were generally the children of families from Europe or North America who had migrated to La Paz for business and/or diplomatic associations with the Bolivian community.

LAN-BHA (n = 20). LAN N^{th} generation migrants born and raised at HA came from established North American and/or European migrant communities in La Paz. These subjects were also recruited from the private university system. Subject history interviews were used to establish no admixture with indigenous populations. Most of the subjects were the children or grand children of previous migrants, but some subjects could trace their ancestry at HA back 2 or more generations. Thus, historic HA exposure varied in this group.

LAN-LA (n = 25). LANs tested in their native environment (LA) were upper class Brazilians of European ancestry who were attending medical school in Santa Cruz.

HAN-AM (n = 24). HAN adult migrants to LA were Aymara and/or Quechua Indians. Many of these migrants were urban rather than rural residents of the *altiplano* prior to their migration. These subjects were generally young men in search of work and they occupied the lowest position on the Bolivian socioeconomic scale.

HAN-CM (n = 22). HAN child migrants to LA were the children of earlier *altiplano* migrants to LA. In this respect they differed from the HAN-AM group in that they were not a transient group, but rather came from established neighborhoods in Santa Cruz. Most *altiplano* migrant communities in Santa Cruz can be characterized as impoverished.

HAN-BLA (n = 18). HAN N^{th} generation migrants born and raised at LA were similar to the HAN-CM group. Migration from the *altiplano* to Santa Cruz Bolivia is a relatively recent phenomenon, and most subjects were the children or grandchildren of earlier migrants. For this reason, significant admixture with lowland populations was considered unlikely.

Anthropometry, hematology, and pulmonary function

Subjects were measured using standard anthropometric techniques (Weiner and Lourie, 1981) by the same investigator. Height, weight, chest width (transverse chest diameter), chest depth (anterior-posterior chest diameter), percent body fat (%body fat), and fat free mass (FFM) are reported. The %body fat and FFM were estimated from skinfolds (subscapular, suprailiac, biceps, and triceps) according to equations of Durnin and Womersley (1974). Hemoglobin concentration (Hb) was measured by a Hemocue blood hemoglobin analyzer (Angelholm, Sweden) from capillary blood obtained by finger prick. Pulmonary function was assessed with a Collins 9 liter survey spirometer (Warren Collins, Braintree, MA). Each subject performed a maximal inspiration, followed immediately by a forced maximal expiration while in a seated position. From this procedure, the forced vital capacity (FVC) and forced expiratory volume made in 1 second (FEV1) were determined based on the best of at least two efforts. FVC and FEV1 measures were corrected for BTPS. As an index of general chest morphology (shape), the ratio of chest depth to chest width was computed.

Analysis and statistics

Anthropometric and hematological variables were tested for group differences by ANOVA. Pulmonary function and chest dimensions were tested by ANCOVA as these measures are generally related to both stature (height) and body weight, as well as age. In this particular sample, where the age range of subjects was narrow, subject age was not significantly related to any study

TABLE 1. Anthropometric characteristics of European/North American low altitude native (LAN) groups, including LANs tested at LA (LAN-LA), LAN adult migrants to HA (LAN-AM), LAN child migrants to HA (LAN-CM), and LANs born and raised at HA (LAN-BHA). Values are given as least square means (standard error) from analysis of variance. Statistical significance is given vs a reference group (LAN-LA)

	Reference group (at 420 m)	LAN Migrants to high altitude (3,600 meters)		
	LANs tested at LA (LAN-LA)	LAN adult migrants (LAN-AM) MALES	LAN child migrants (LAN-CM)	LANs born and raised at HA (LAN-BHA)
n	25	27	10	20
Age (years)	22.4 (0.7)	26.8* (0.9)	22.1 (1.5)	24.2 (1.3)
Hb (g/dl)	15.2 (0.2)	17.6* (0.2)	17.6* (0.2)	17.8* (0.3)
Height (cm)	175.0 (1.4)	175.8 (1.3)	180.0 (1.7)	175.2 (1.8)
Weight (Kg)	68.3 (1.4)	70.3 (1.4)	74.1 (4.6)	68.5 (2.4)
Body fat (%)	20.2 (1.0)	19.6 (0.8)	19.2 (1.6)	20.0 (1.2)
Fat free mass (Kg)	54.3 (0.9)	56.4 (1.0)	59.5* (3.0)	54.4 (1.4)

(*) Significantly different from REFERENCE group, $P < 0.05$.

measurement. Thus, covariance analysis was used to test for group differences in pulmonary function and chest dimensions, adjusting for stature, consistent with an approach used previously by Greksa (1986). The covariance approach allows for an unbiased expression of group differences, and avoids the bias inherent in the ratio standard approach, i.e., pulmonary function measures divided by some component of body size (see Tanner, 1949; Nevill, 1992). Separate covariance models were used to test for differences between male groups (for the combined sample of males), and for differences between females and their counterpart male groups within the study.

Statistical testing for the genetic and developmental effects of HA exposure was by ANCOVA with male subjects only, adjusting for stature. The genetic effects model was a two factor ANCOVA with ancestral HA exposure group (HAN vs LAN) and developmental exposure (none or full) as main effects. This model holds the effect of developmental exposure constant (within a given environment) by comparing HAN and LAN subject groups who were born, raised, and tested at either HA or LA (i.e., the HAN-HA, LAN-BHA, LAN-LA, and HAN-BLA subject groups). The developmental effects model was a two factor ANCOVA with developmental HA exposure tested as the main effect. Three levels of developmental exposure were defined as: 1) no developmental exposure; 2) partial developmental exposure; and 3) full developmental exposure, depending on migration status. This model holc the effect of genetic exposure constant b testing the main effect across HAN m grants to LA (HAN-AM, HAN-CM, HAN BLA) and LAN migrants to HA (LAN-AM LAN-CM, LAN-BHA). In all ANCOVA mo els interactions between the main effec were tested. Statistical significance wa held at the $P < 0.05$ level. All statistics we performed using the GLM procedure of th Systat Statistical Software, version 5 (Evanston, IL).

RESULTS

Subject characteristics

Group means for anthropometry and h matology are given in Tables 1 and 2 f LAN and HAN subject groups, respectivel Data presented in these tables show lea square mean values from ANOVA for th combined sample of all male study group with a focus on the comparison of LAN ar HAN migrant groups to their appropria reference group. Reference groups were d fined as the LAN or HAN study group bo and raised in their native environmen LAN migrant groups at HA were similar the LAN reference group at LA except for higher Hb level, consistent with a full h matological adaptation to HA (Dirren et a 1994). HAN migrant groups to LA had greater %body fat compared to the HAN r erence group and a lower Hb (consiste with a deacclimatization effect at LA). Co parisons of HANs vs LANs are not explicit shown in these tables, however it is qui

TABLE 2. Anthropometric characteristics of Aymara/Quechua high altitude native (HAN) groups, including HANs tested at HA (HAN-HA), HAN adult migrants to LA (HAN-AM), HAN child migrants to LA (HAN-CM), and HANs born and raised at LA (HAN-BLA). Values are given as least square means (standard error) from analysis of variance. Statistical significance is given vs a reference group (HAN-HA)

	Reference group (at 3,600 m)	HAN Migrant groups to low altitude (420 meters)		
	HANs tested at HA (HAN-HA) MALES	HAN adult migrants (HAN-AM)	HAN-child migrants (HAN-CM)	HANs-born and raised at LA (HAN-BLA)
n	24	24	22	18
Age (years)	23.6	26.0*	21.7	20.2
	(0.9)	(1.3)	(0.8)	(0.7)
Hb (g/dl)	17.5	14.8*	14.5*	14.6*
	(0.2)	(0.3)	(0.2)	(0.3)
Height (cm)	162.7	161.1	163.2	165.8
	(1.6)	(1.2)	(1.2)	(1.6)
Weight (Kg)	56.7	59.4	60.2	63.4*
	(1.0)	(1.3)	(1.9)	(2.1)
Body fat (%)	15.3	20.1*	17.9*	19.1*
	(0.9)	(1.1)	(1.2)	(1.1)
Fat free mass (Kg)	47.9	47.3	49.1	50.9
	(0.8)	(0.9)	(1.1)	(1.1)

(*) Significantly different from REFERENCE group, $P < 0.05$.

clear that HANs were smaller (body weight and stature) and leaner (%body fat) compared to LANs. Comparisons of HAN and LAN female groups to their appropriate counterpart male groups within the study are given in Table 3. HAN and LAN female groups were different from their counterpart male groups in all respects (except age), including Hb, height, weight, %body fat, and FFM. HAN vs LAN differences between females were generally similar to the differences seen between males, except HAN and LAN females had the same %body fat.

Pulmonary function and chest dimension measures

As an overview, absolute and adjusted mean values for pulmonary function and chest dimensions are given in Tables 4 and 5 for the male LAN and HAN subject groups, respectively. Comparisons between migrant groups and their appropriate reference groups, or between HANs and LANS, are not explicitly described here as the more relevant comparisons are given below as the results of ANCOVA testing for genetic and developmental effects. Comparisons of HAN and LAN female groups to their appropriate counterpart male groups within the study are given in Table 6. FVC, FEV1, chest depth, and chest width, adjusted for stature, were lower in both LAN and HAN female groups compared to their counterpart male groups. However, ratios of FEV1 to FVC and chest depth to chest width were similar between males and females.

Genetic effects on pulmonary function and chest dimensions

Figure 1 shows the least square mean group values of measures where a genetic effect was detected by ANCOVA, adjusting for stature. No genetic effect was detected for either the chest depth or width, or for the ratio between chest depth and chest width. Genetic effects were detected for both the FVC and the FEV1. In both cases the genetic effect was detected as an interaction between ancestral group (HAN vs LAN) and developmental exposure (none or full) in the 2-factor ANCOVA model employed.

Developmental effects on pulmonary function and chest dimensions

Figure 2 shows the least square mean group values of measures for which a developmental effect was detected by ANCOVA, adjusting for stature. A significant developmental effect was shown in both HAN and LAN migrant groups for the FVC and FEV1. That is, HAN adult migrants at LA had larger pulmonary function measures than HAN child migrants and HANs born and raised at LA, while LAN migrants born and raised at HA had larger pulmonary function measures than LAN child migrants and LAN adult migrants. A similar developmen-

*TABLE 3. Anthropometric characteristics of female subject groups vs their corresponding male subject groups within the study. Values are given as least square mean values (standard error) from analysis of variance between the subject groups shown**

	LAN adult migrants to HA (3,600 m) (LAN-AM)		HANs tested at HA (3,600 m) (HAN-HA)	
	A. Males	B. Females	C. Males	D. Females
n	27	17	24	20
Age (years)	$26.8^{C,D}$ (0.9)	25.7 (0.9)	23.6 (0.9)	23.4 (1.1)
Hb (g/dl)	$17.6^{B,D}$ (0.2)	$15.4^{C,D}$ (0.3)	17.5^{D} (0.2)	16.5 (0.3)
Height (cm)	$175.8^{B,C,D}$ (1.3)	165.4^{D} (2.2)	162.7^{D} (1.6)	149.7 (1.3)
Weight (kg)	$70.3^{B,C,D}$ (1.4)	60.8^{D} (2.4)	56.7^{D} (1.0)	49.4 (1.1)
Body fat (%)	$19.6^{B,C,D}$ (0.8)	33.3^{C} (1.7)	15.3^{D} (0.9)	30.0 (1.1)
Fat free mass (Kg)	$56.4^{B,C,D}$ (1.0)	$40.1^{C,D}$ (1.1)	47.9^{D} (0.8)	34.4 (0.6)

*B, Significantly different from LAN adult migrant FEMALE group, $P < 0.05$; C, significantly different from HAN-HA MALE group, $P < 0.05$; D, significantly different from HAN-HA FEMALE group, $P < 0.05$.

TABLE 4. Stature adjusted mean values (standard error) of chest dimension and pulmonary function in European/North American low altitude native (LAN) groups, including LANs tested at LA (LAN-LA), LAN adult migrants to HA (LAN-AM), LAN child migrants to HA (LAN-CM), and LANs born and raised at HA (LAN-BHA). Statistical significance is given vs a reference group (LAN-LA)

	Reference group (at 420 m)		LAN migrant groups to high altitude (3,600 m)					
	LANs born and raised at LA (LAN-LA)		LAN adult migrants (LAN-AM) MALES		LAN child migrants (LAN-CM)		LAN born and raised at HA (LAN-BHA)	
	Mean	Adjusted mean (SE)	Mean	Adjusted mean (SE)	Mean	Adjusted mean (SE)	Mean	Adjusted mean (SE)
n	25		27		10		20	
FVC	5327	4840 (121)	5560	5062 (118)	6077	5282* (192)	5830	5334* (133)
FEV1	4550	4116 (115)	4881	4402 (113)	5258	4550* (183)	5049	4607* (127)
FEV1/FVC	85.7	n.a.	87.3	n.a.	86.6	n.a.	86.9	n.a.
Chest depth (anterior-posterior), cm	196	195 (4)	203	202 (4)	208	206 (6)	216	215* (4)
Chest width (lateral), cm	287	282 (4)	295	291 (3)	295	287 (6)	290	285 (4)
Chest depth/chest width	68.5	n.a.	69.0	n.a.	70.6	n.a.	74.7*	n.a.

(*) Significantly different from REFERENCE group, $P < 0.05$.

tal effect in both groups was detected for the chest depth, but not the chest width. The chest depth developmental effect is expressed in the ratio of chest depth to chest width given in Figure 2. The developmental response to HA exposure was similar between HAN and LAN groups, i.e., there were no detectable interaction effects between ancestral group and developmental exposure by ANCOVA.

HAN and LAN child migrant groups provided another means of testing for developmental effects as these samples were comprised of individuals covering a range of different developmental exposures to HA from birth to adulthood. Figure 3 shows a significant positive relationship ($r = 0.325$, $P = 0.049$) for the regression of the residuals of FVC (adjusted for stature) on the number of years of HA exposure in the combined

TABLE 5. Stature adjusted mean values (standard error) of chest dimension and pulmonary function in Aymara/Quechua high altitude native (HAN) groups, including HANs tested at HA (HAN-HA), HAN adult migrants to LA (HAN-AM), HAN child migrants to LA (HAN-CM), and HANs born and raised at LA (HAN-BLA). Statistical significance is given vs a reference group (HAN-HA)

	Reference group: HANs born and raised at HA (HAN-HA) MALES		HAN Migrant groups to low altitude (420 M): HAN adult migrants (HAN-AM)		HAN child migrants (HAN-CM)		HAN born and raised at LA (HAN-BLA)	
	Mean	Adjusted mean (SE)	Mean	Adjusted mean (SE)	Mean	Adjusted mean (SE)	Mean	Adjusted mean (SE)
n	24		24		22		18	
FVC	5386	5649 (117)	5035	5397 (119)	4904	5139* (121)	4601	4679* (132)
FEV1	4707	4941 (111)	4214	4537 (113)	4224	4433* (115)	4112	4181* (126)
FEV1/FVC	87.3	n.a.	84.0	n.a.	86.3	n.a.	89.4	n.a.
Chest depth (anterior-posterior), cm	201	202 (4)	206	207 (4)	194	195 (4)	194	194 (4)
Chest width (lateral), cm	289	291 (3)	284	288 (4)	285	287 (4)	286	287 (4)
Chest depth/chest width	69.7	n.a.	72.5	n.a.	68.3	n.a.	67.8	n.a.

(*) Significantly different from REFERENCE group, $P < 0.05$.

*TABLE 6. Stature adjusted pulmonary function and chest dimension measures in female subject groups vs their corresponding male subject groups within the study. Values are given as least square mean values (standard error) from analysis of variance between the subject groups shown**

	LAN adult migrants to HA (3,600 m) (LAN-AM): A. MALES		B. FEMALES		HANs tested at HA (3,600 m) (HAN-HA): C. MALES		D. FEMALES	
	Mean	Adjusted mean (SE)	Mean	Adjusted mean (SE)	Mean	Adjusted mean (SE)	Mean	Adjusted mean (SE)
n	27		17		24		20	
FVC	5560	$4862^{B,C}$ (120)	4018	$3948^{C,D}$ (114)	5386	5485^{D} (96)	3569	4505 (146)
FEV1	4881	$4193^{B,C}$ (131)	3669	3604^{C} (124)	4707	4799 (105)	3055	3928 (159)
FEV1/FVC	87.3	n.a.	91.5^{D}	n.a.	87.3	n.a.	85.7	n.a.
Chest depth (anterior-posterior), cm	203	$207^{B,D}$ (4)	183	184^{C} (4)	201	200 (4)	181	177 (5)
Chest width (lateral), cm	295	287^{B} (4)	265	264^{C} (3)	289	290^{D} (3)	265	275 (4)
Chest depth/chest width	69.0	n.a.	69.3	n.a.	69.7	n.a.	68.5	n.a.

*B, Significantly different from LAN adult migrant FEMALE group, $P < 0.05$; C, significantly different from HAN-HA MALE group, $P < 0.05$; D, significantly different from HAN-HA FEMALE group, $P < 0.05$.

sample of HAN and LAN child migrants. A formal test for a HAN vs LAN difference in the slope of this relationship was also conducted to show that the relationship was only significant in the HAN child migrant group, and not in the LAN child migrant group. However, it should be emphasized that there were only 12 subjects in the LAN-CM group. For this reason, Figure 3 shows data for the combined sample of HAN and

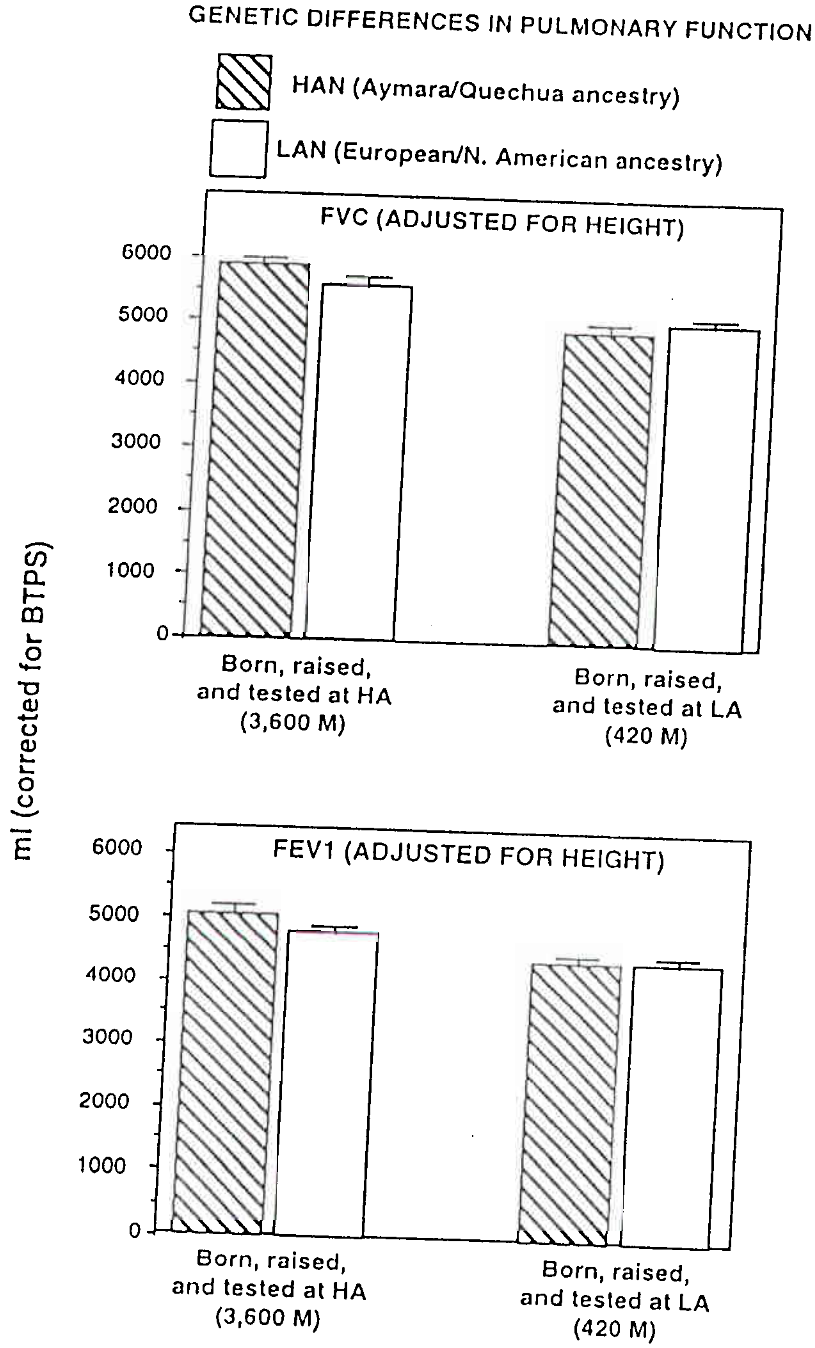

Fig. 1. Results of ANCOVA modeling for ancestral (genetic) high altitude exposure effects. This model compares: at HA, HANs and LANs born and raised at HA; and at LA, HANs and LANs born and raised at LA. For both the FVC and FEV1 a significant genetic effect was detected as the interaction between ancestral group (HAN vs LAN) and developmental exposure to HA, $P < 0.05$. That is, HANs and LANs born, raised, and tested at LA had the similar measures of lung volume, while HANs at HA had larger measures of lung volume than LANs born and raised at HA.

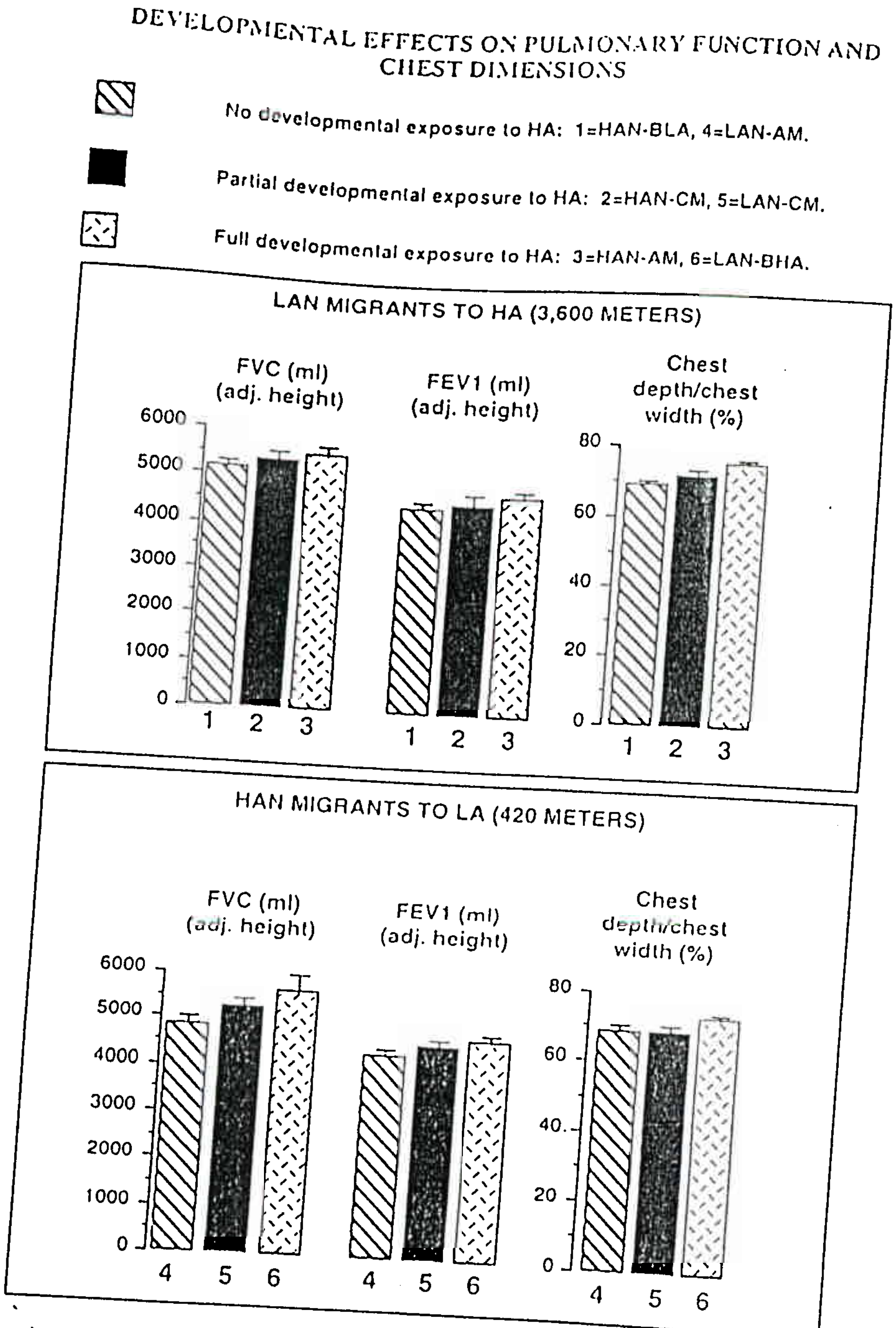

Fig. 2. Results of ANCOVA modeling for developmental high altitude exposure effects. This model tests for the effect of developmental exposure across HAN and LAN migrant groups to LA and HA, respectively. In each case, depending on migration status, migrant groups differ from one another with respect to their developmental exposure status (ranging from no exposure, to partial and full exposure). In both HANs and LANs, FVC, FEV1, and the ratio of chest depth to chest width, increased with increasing developmental exposure to HA, $P < 0.05$. No interaction effects between ancestral group (HAN vs LAN) and developmental exposure were detected. That is, HAN and LAN migrant groups showed similar developmental responses with increasing developmental HA exposure.

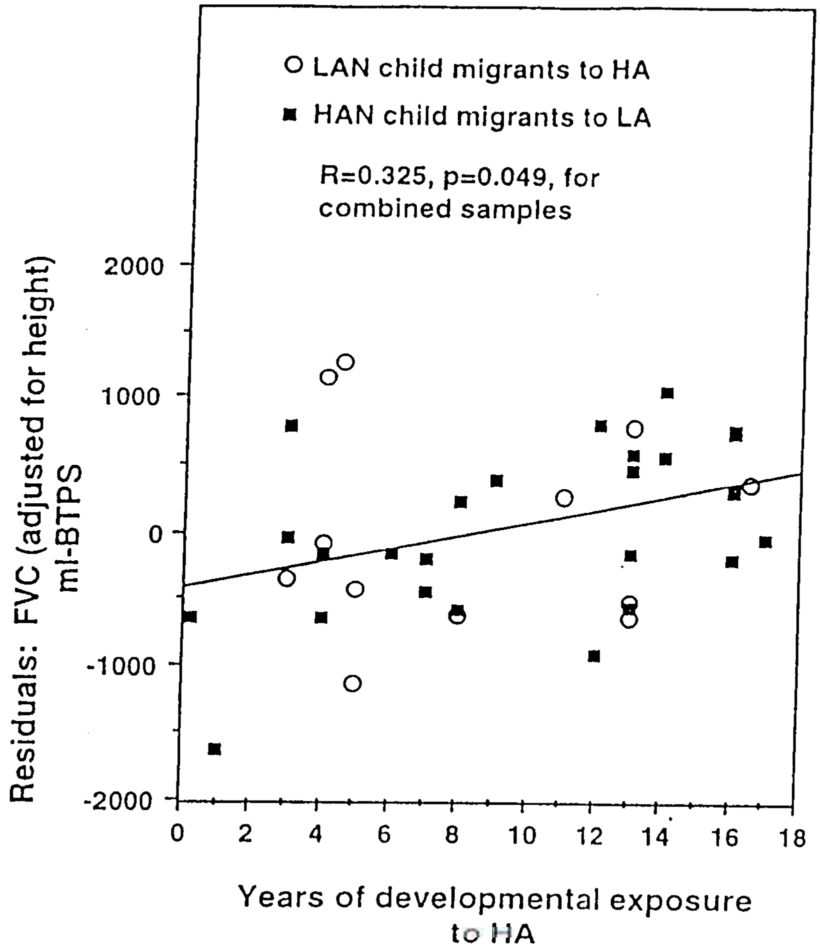

Fig. 3. A developmental response in FVC is evident in the positive relationship between the residuals of FVC adjusted for stature (ml·BTPS) and the length of HA exposure (yrs) for the combined sample of HAN and LAN child migrant groups.

LAN child migrants where the overall relationship is significant. Similar regressions were run for the FEV1 and for measures of chest dimension, but no significant relationships with years of developmental exposure to HA were detected.

DISCUSSION

A complete migrant study design was used to partition the chest morphology and pulmonary function phenotype difference between Andean HANs and European/North American LANs into developmental and/or ancestral (genetic) components according to an approach first described by Harrison (1966), and later modified by Abelson (1974) and Haas (1980). Analysis of adaptive difference between groups based on this approach depends upon the proper designation of individuals into defined study groups, and on the ability to control for non-adaptive (confounding) variability between groups. With respect to the former, there is no question that there has been significant admixture between European and Andean populations (Chakraborty et al., 1989). For the HANs, only subjects who appeared to be of Indian ancestry, and who described themselves as being either Quechua and/or Aymara were admitted into the study. Importantly, all HAN populations studied were considered to be equally Indian, given the relatively recent migration phenomenon from the Bolivian *altiplano* to the Bolivian lowlands. Admixture was not an issue for LAN subjects as they were clearly defined based on family history interviews. With respect to the potential for confounding, the HAN subjects were of a lower socioeconomic status (SES) compared to the European/North American LAN subjects. However, the potential for confounding based on a stunting effect of chronic poor nutrition is of concern only if body size decreases disproportionately to lung size. The available evidence indicates that this is not the case (Greksa, 1985; Mueller et al., 1980). Although specific data to show the proportionality between FVC and stature are not presented, these two variables were linearly related in this study, both within and across groups. The overall SES within an ancestral group was constant, with the possible exception of a lower SES in the HAN-AM group at LA whose members were mostly transient workers. This is an important consideration in assessing the effect of developmental HA exposure, as comparisons to test this effect were made within an ancestral group.

It should be noted that a small environmental effect (HA vs LA) was detected for measures of FVC and FEV1. That is, FVC and FEV1 measures were slightly higher at HA, independent of ancestral or developmental HA exposure considerations. It is likely that the altitude effect is explained in part by the lower air density at HA (Forte et al., 1997), and it should be emphasized that this effect has no impact on covariance models used to test for developmental and/or genetic HA exposure effects. Taking the altitude effect into account, lung volumes adjusted for stature are similar in adult migrant groups compared to their respective reference groups. This is an important consideration for model validity as the reference and adult migrant groups are conceptually the same population, differing only by the altitude at which they were tested.

Given the general validity of the study approach, the results are consistent with previous findings. That is, Andean HANs at HA show a different chest morphology (deeper chests) and larger measures of pulmonary function (FVC and FEV1 normalized to body size) compared to LAN populations. Although data are reported for only two groups of female subjects (HAN-HA and LAN-AM), the general HAN vs LAN phenotype difference is similar between males and females, as reported previously (Frisancho et al., 1997; Greksa, 1986, 1988; Stinson, 1985).

Developmental adaptation

A strong developmental response was detected across migrant groups by ANCOVA showing larger measures of relative chest depth, FVC, and FEV1 with increasing developmental exposure to HA (Fig. 2). The effect was detected both in LAN migrant groups to HA, and in HAN migrant groups to LA. Additionally, a strong developmental effect was evident within the HAN and LAN child migrant groups showing that FVC is larger in LAN-CMs who migrate to HA earlier during growth and development, and in HAN-CMs who migrate to LA later during growth and development (Fig. 3). These results are consistent with previous studies where a developmental effect with HA exposure has been shown for one or more of the following measures: chest depth, chest width, FVC, FEV1, total lung volume (TLV), and/or residual lung volume (RV) (Greksa, 1988; Frisancho et al., 1973, 1997, Mueller, 1980; Boyce et al., 1974). It has been suggested that this developmental response to HA exposure reflects underlying structural changes in the pulmonary system which work to facilitate oxygen transport (Frisancho, 1981). The work of Dempsey (1971) indicates that this may be the case as individuals with a developmental exposure to HA have a smaller alveolar-arterial oxygen difference during exercise. However, a direct link between developmental lung growth and oxygen transport capacity to support this hypothesis has not been firmly established in the literature.

One advantage of the complete migrant design is that the developmental response to HA exposure can be compared between HAN and LAN migrant populations, i.e., interaction effects between developmental and ancestral HA exposure can be tested. In this sense, the developmental response itself can be viewed as a genetic characteristic of a given population group. Although HAN migrants tended to show a larger increase in FVC with increasing developmental exposure compared to LAN migrants, this effect did not reach statistical significance. The issue of differential developmental responses between HANs and LANs has been addressed previously by Greksa et al. (1986, 1988), who showed similar chest growth relative to stature between HAN Aymara and European adolescents (9–18 yrs) born and raised at HA. While Greksa's approach of comparing cross-sectional growth data between HANs and LANs is different from the approach presented here, results between the studies are consistent. That is, the relative effect of developmental HA exposure on chest growth and pulmonary function (from at least adolescence to adulthood) appears to be independent of ancestral exposure to HA. This fact does not preclude the possibility of an earlier developmental response difference between HANs and LANs (prenatal to early adolescence), nor does it preclude the possibility of a genetic effect expressed as an absolute difference in lung volume between HANs and LANs at any given stage of development.

Genetic adaptation

Effects were detected in the genetic ANCOVA models to explain the larger FVC and FEV1 in HANs compared to LANs born and raised at HA. This is consistent with previous findings where HANs compared to European/North American LANs born and raised at HA were shown to have larger chest dimensions relative to stature (Stinson, 1985; Greksa, 1986) and larger RVs, and TLVs relative to body surface area (Frisancho, 1997). However, it should be immediately noted that the genetic effect in this study was detected as an interaction between ancestral exposure (HAN vs LAN) and developmental exposure (full vs none) by ANCOVA. That is, pulmonary function differences were only apparent between HANs and LANs born, raised, and tested at HA, but not between groups born, raised, and tested at LA (Fig. 1).

The general similarity of HAN vs LAN lung volumes at LA implies that the genetic potential for a greater lung volume in HANs is dependent upon exposure to HA during the period of growth and development. This is an intriguing hypothesis, but it is clearly not supported by the developmental results presented here. If developmental exposure is necessary before genetic differences between HANs and LANs become apparent, then HANs vs LANs should show a different developmental course in lung growth with HA exposure. As previously discussed, no conclusive developmental response difference was detected between HANs and LANs. However, this possibility cannot be excluded. It may be that HANs have a different course of lung development during the prenatal period or during the first few years of life. The age range of developmental HA exposure in the child migrant groups of this study was not sufficient to test for such an effect. Similarly, Greksa et al., (1986) report data only for children between 9–18 yrs of age where growth patterns are already established. Resolution of this issue will require longitudinal growth data comparisons between HANs and LANs during the earliest years of life (Greksa et al., 1988).

Genetic effects were detected only for pulmonary function measures (FVC and FEV1), but not for measures of chest dimensions, especially chest depth (morphology), which was strongly affected by developmental exposure. The inability to detect a genetic effect for chest morphology, i.e., the classic barrel chest of the Andean HAN, is not consistent with previous results reported for Andean HANs (Greksa, 1986; Stinson, 1985). This may be because natural selection operates only weakly on chest morphology compared to measures of pulmonary function which hold functional correlation with the lung diffusion capacity (see Cerney et al., 1973; Degraff et al., 1970; Dempsey et al., 1971; Guleria et al., 1971). In fact, significant relationships between relative chest depth and the adjusted FVC (residuals of FVC adjusted for stature), either across or within groups were not detected. While this negative result is not explicitly presented in this paper, it suggests that chest morphology (shape) has little functional significance related to oxygen transport.

In summary, effects were detected by covariance modeling to suggest both developmental and ancestral (genetic) components of the larger FVC and FEV1 seen in Andean HANs. Chest morphology (relative chest depth) is affected by developmental HA exposure, but there was no difference between HANs and LANs born and raised at HA or LA to suggest a genetic effect of HA exposure for this measure. For all measures showing a developmental HA exposure effect, the developmental response with increasing HA exposure was similar between HANs and LANs. This finding is at odds with the result of the genetic covariance model, where genetic effects appear as an interaction between developmental and ancestral HA exposure in the model. This suggests that the expression of genetic potential on lung volumes requires developmental exposure to HA.

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