UNIVERSIDAD DE INVESTIGACIÓN DE TECNOLOGÍA EXPERIMENTAL YACHAY

School of Biological Sciences and Engineering

TITTLE: "RETROSPECTIVE COHORT STUDY OF RISK FACTORS FOR DEVELOPING ACUTE MOUNTAIN SICKNESS AND HIGH-ALTITUDE PULMONARY EDEMA IN THE ECUADORIAN ANDES"

Trabajo de integración curricular presentado como requisito para la obtención del título de Biólogo

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Dedication

This work is wholeheartedly dedicated to my beloved parents, who patiently instructed and sowed me the curiosity to learn more. That curiosity influenced the decisions on my professional profile leading me to choose the university, Yachay Tech, my career in basic sciences and the topic for undergraduate work. In addition, they always gave me strength and unconditional support at the times when I thought of giving up or was confused.

Karen Elizabeth Sánchez Blacio

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El presente trabajo lo dedico de todo corazón a mis amados padres, quienes pacientemente me formaron y sembraron en mí la curiosidad por aprender más. Aquella curiosidad influyó en las decisiones sobre mi perfil profesional llevándome a elegir la universidad, Yachay Tech, mi carrera en ciencias puras y el tema de trabajo de titulación. Además, ellos siempre me brindaron fortaleza y apoyo incondicional en los momentos en que pensé rendirme o estaba confundida.

Karen Elizabeth Sánchez Blacio

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Karen Elizabeth Sánchez Blacio

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Karen Elizabeth Sánchez Blacio

Abstract

The Andes divide Ecuador in low (sea-level, Coast) and high altitude (HA defined as >2,500 m.a.s.l., *Sierra*) regions. Whereas many Ecuadorians live at HA, others have to overcome slopes over 4,000 m.a.s.l to commute from Coast to *Sierra*. Because of the hypobaric pressure starting at HA and the rapid ascent, many are exposed to HA-induced illnesses (HAI). Acute HAI includes benign Acute Mountain Sickness (AMS) and life-threatening High-Altitude Pulmonary Edema (HAPE), which are caused by the physiological intolerance to hypoxia (low O_2 partial pressure). The goal of this retrospective study was to evaluate AMS and HAPE risk factors. In the archives of a Zumbahua's Hospital (Ecuador), sited at 3,600 m.a.s.l, we found two cohorts of patients having either HAPE or AMS after sojourning at 4,000 m.a.s.l. Both cohorts were compared for the following predictive variables: demographics (sex, ethnics, age, body mass index), environmental (residence altitude and recent sea-level stay), health (vital signs), and hemogram. Cramér's values, simple logistic regression (SLR), and multiple logistic regression (MLR) analyses revealed significant associations and odds ratios. It was found that indigenous residents of the *Sierra* were HAPE-prone, whilst *mestizos* living in the Coast only had AMS. Among indigenous group residing at HA, HAPE prevalence significantly increased after a recent stay at the sea-level, a phenomenon called *re-entry HAPE*. Interestingly, enhanced HGB emerged as a risk factor for HAPE, but not for AMS. Women were more resilient to HAPE than men because of their sex-dependent lower HGB concentration. Based on the differential risk factors, AMS and HAPE neither could have the same etiology nor are in the same HAI continuum. Using an epidemiological retrospective analysis on HAIs in the Ecuadorian population, a role for HGB is inferred in the etiology of HAPE.

Keywords:

HAPE, AMS, hypoxia, hemoglobin, high-altitude illness, epidemiology.

Resumen

Los Andes dividen al Ecuador en regiones de baja (nivel del mar, Costa) y de gran altitud (HA definida como > 2,500 m.s.n.m., Sierra). Mientras que muchos ecuatorianos viven a HA, otros tienen que atravesar pendientes de más de 4,000 m.s.n.m. para viajar de la Costa a la Sierra. Debido a la presión hipobárica que comienza a HA y al rápido ascenso, muchos están expuestos a enfermedades inducidas por la HA (HAIs). Las HAIs agudas incluyen la enfermedad benigna aguda de montaña (AMS) y el potencialmente mortal edema pulmonar de gran altitud (HAPE), ambas patologías causadas por la intolerancia fisiológica a la hipoxia (baja presión parcial de O2). El objetivo de este estudio retrospectivo fue evaluar los factores de riesgo para AMS y HAPE. En los archivos un Hospital de Zumbahua (Ecuador), ubicado a 3.600 m.s.n.m., encontramos dos cohortes de pacientes que padecieron HAPE o AMS después de una estadía a 4.000 m.s.n.m. Ambas cohortes se compararon para las siguientes variables predictivas: demográficas (sexo, etnia, edad, índice de masa corporal), ambientales (altitud de residencia y estadía reciente al nivel del mar), salud (signos vitales) y hemograma. Los análisis de valores de Cramér, regresión logística simple (SLR) y regresión logística múltiple (MLR) revelaron asociaciones significativas y odds ratios. Se encontró que los residentes indígenas de la Sierra eran propensos a HAPE, mientras que los mestizos que vivían en la costa solo padecían AMS. Entre los grupos indígenas que residen a HA, la prevalencia de HAPE aumentó significativamente después de una estadía reciente al nivel del mar, un fenómeno llamado *HAPE de reingreso*. Curiosamente, el incremento de HGB surgió como un factor de riesgo para HAPE, pero no para AMS. Las mujeres fueron más resistentes al HAPE que los hombres debido a su menor concentración de HGB dependiente del sexo. En base a los factores de riesgo diferenciales, AMS y HAPE no tendrían la misma etiología, ni serían la misma HAI progresiva. Usando un análisis epidemiológico retrospectivo sobre las HAIs en la población ecuatoriana, se infiere un papel para la HGB en la etiología del HAPE.

Palabras Clave:

HAPE, AMS, hipoxia, hemoglobina, enfermedad de gran altura, epidemiología.

TABLE OF CONTENT

INTRODUCTION AND JUSTIFICATION

The term high-altitude illness or HAI (also known as *Mountain Sickness*) is commonly used to describe a series of cerebral and pulmonary syndromes that can develop shortly after rapid ascent at 2,500 m.a.s.l. and over (defined as HA; Hackett & Roach, 2001; Barry & Pollard, 2003; Basnyat & Murdoch, 2003; Imray, Booth, Wright, & Bradwell, 2011). HAI occurs when the human body is exposed to rapid changes in atmospheric pressure that cause a significant reduction of the partial pressure of O_2 (Hackett & Roach, 2001; Barry and Pollard, 2003; Imray et al. 2010; Imray, Wright, Subudhi, & Roach, 2011; Whayne, 2014). It usually occurs after rapid ascent to mountains of more than 2,500 m.a.s.l., where there is only a 75% of the O_2 available at the sea-level. Under hypobaric conditions, there is a poor diffusion of O_2 from the alveolar air into the blood and the percentage of O_2 carried by hemoglobin (HGB) drops below 90% (hypoxemia; Ge et al., 1997). Since appropriate O_2 delivery to tissues is vital for organ function, especially the brain, the human body reacts by a series of homeostatic mechanisms to compensate the O_2 desaturation in blood. This process, called *acclimatization*, can spend from hours to days, and even weeks (Siebenmann, Robach, & Lundby, 1985; Chawla & Saxena, 2014). An *acclimatization* failure leads to HAIs (West, 2004; Grimminger et al, 2017).

HAI symptoms vary across individuals from benign, self-limiting forms including the Acute Mountain Sickness (AMS), High-Altitude Headache (HAH), High-Altitude Sleepiness (HAS), and subtle cognitive impairments to more serious clinical manifestations like the High-Altitude Cerebral Edema (HACE), the High-Altitude Pulmonary Hypertension (HAPH), and subsequent High-Altitude Pulmonary Edema (HAPE; Barry & Pollard, 2003; Bloch, Buenzli, Latshang, & Ulrich, 2015; Dehnert, Berger, Mairbäurl, & Bärtsch, 2007; Grimminger et al, 2017; Hackett & Roach, 2001; Hornbein, 1992; Imray et al., 2010; Imray et al., 2011; Luks, Swenson, & Bärtsch, 2017; Maloney & Broeckel, 2005; Marmura & Hernández, 2015; Rabold, 1989; West, 2004; Wilson, Newman, & Imray, 2009). Regarding chronic forms of HAI, between 1.3% and 33% of the highlanders develop the Chronic Mountain Sickness (CMS). Described by Dr. Carlos Monge in the Peruvian Andes in 1925, CMS symptoms include the hallmark extreme polyglobulia, severe right ventricular hypertrophy, low systemic blood pressure, excess pulmonary hypertension, arterial O_2 desaturation, and hypoventilation (Whayne, 2014). AMS and HAPE constituted the goals of this study. AMS consists of a series of symptoms including dizziness, nausea or vomiting, headache, fatigue, and trouble sleeping after ascending to HA (Imray et al., 2010). HAPE, however, is a fatal life-threatening condition

caused by a rapid accumulation of extracellular fluid flooding the pulmonary alveoli (Dehnert et al., 2007; Imray et al., 2010; Imray et al., 2011; Lobenhoffer, Zink, & Brendel, 1982; Maloney & Broeckel, 2005; Paul, Gangwar, Bhargava, Khurana, & Ahmad, 2018).

It is estimated that more than 35 million of inhabitants live in the Andes and that countless others sojourner for work, travel, and sport (Moore, 2001; Pasha & Newman, 2010; Moore, 2017). Native dwellers of the Andes are not as well adapted as the Tibetans to HA due to genetic and environmental differences (Beall, 2006; Bigham, 2016; Bigham & Lee, 2014; Hainsworth & Drinkhill, 2007; Jacovas et al., 2018; Moore, 2017; Simonson et al., 2015; Simonson, McClain, Jorde, & Prchal, 2012; Painschab et al., 2015; Peng et al., 2011; Simonson et al., 2015; Crawford et al., 2017). Epidemiological studies on HAIs have been conducted especially in Peru and Bolivia; in Ecuador a very few despite its ethnic diversity, that is unique in the Andes (Instituto Nacional de Estadística y Censos, n.d.; Naeije, Mélot, & Lejeune, 1986; Painschab et al, 2015; Serrano Dueñas, 1998; Zubieta-Castillo, Zubieta-Calleja, & Zubieta-Calleja, 2006).

PROBLEM STATEMENT

The Andean ridge (4,000-6,300 m.a.s.l.) forms a passageway of highlands (the *Sierra* or Andean *altiplano*) sited at 2.500-4,000 m.a.s.l. which separates most of the Ecuadorian population from the rest of the country (Coastal and Amazon regions) laying in the lowlands. In their commute between the low and highlands, many Ecuadorians have to overcome slopes of up to 4,000 m.a.s.l. that expose them to HAIs. Among the multiple HAI forms, HAPE is the most dangerous and fatal if not treated on time with specific medication, oxygen supplementation, and/or immediate descending (Bärtsch, 1997, Basnyat & Murdoch, 2003; Davis, & Hackett, 2017; Hackett & Roach, 2001; Imray, et al, 2010; Maggiorini, 2010; Rodway, Hoffman, & Sanders, 2003; Swenson, 2004; Wright, Brearey, & Imray, 2008). Looking for treatment is not always feasible in the Andes and prevention is the only option in a region with the highest HAPE incidence in the world (Lobenhoffer et al., 1982).

In this study, we retrospectively compared two cohorts of patients, one having HAPE, and a second one showing evident symptoms of AMS after a stay at very HA (>4,000 m.a.s.l.), where O_2 availability drops by a 40% of that found at sea-level. Because HAPE is deemed to be the end clinical form of most severe AMS, and given that HAPE accounts for the most deaths from HAIs, our purpose was to identify the risk factors for HAPE as compared against those leading to AMS (Bärtsch, Swenson, Paul, Jülg, & Hohenhaus, 2002; Whayne, 2014).

OBJECTIVES

General

To determine the risk factors for the development of HAPE comparing with AMS in both native dwellers and visitors of Zumbahua (Cotopaxi) during the 2007-2018 period.

Specifics

- To establish the difference between HAPE and AMS diagnosis comparing categories from health, and blood variables.
- To determine the relationships between demographic, environmental, health, and blood test variables and the prevalence of HAPE and AMS.
- To compare the relative influence of the demographic, environmental, health, and blood test risk factors in the progression of HAPE and AMS.
- To analyze demographic-environmental variables interactions and the prevalence of both HA pathologies.
- To construct a model with the most influent variables for HAPE development in order to fit variables contribution to HAPE syndrome.

METHODOLOGY

Study zone

For this study, it was browsed the clinical archives of the Claudio Benati Hospital, which was ideally chosen given its privileged location in Zumbahua (Cotopaxi), a remote town sited at 3,600 m.a.s.l. in the midway between the cities of Quevedo (only 74 meters over the sea-level) and Latacunga (2,750 m.a.s.l.).). The road to Zumbahua overcomes 4,000 m.a.s.l. of altitude (very HA) in the Andes. Chances were high that among the many visitors (100,000 every year) and the Zumbahua county inhabitants (~20,000) sojourning at 3,600-4,400 m.a.s.l., those afflicted by health problems, including HAIs, had to rush to the emergency room looking for medical attention since the next hospital offering specialized medical services is sited 64 Km away.

Diagnosis

AMS and HAPE evaluation was performed by qualified medical staff with the right expertise in HA medicine. AMS diagnosis relied on the Lake Louise Questionnaire System (LLQS) that scores the overall symptoms of HAI (Roach, Bärtsch, Hackett, & Oelz, 1993). A patient had AMS when the presence of headache following ascent over 2,500 m.a.s.l. plus the presence of one or more of the following symptoms: gastrointestinal sings (anorexia, nausea, or vomiting), insomnia, dizziness, and lassitude or fatigue. HAPE diagnosis depended on a physical examination of clinical symptoms and signs including dyspnea at rest, tachypnea, crackles or wheezing; dry cough with blood-tinged, frothy sputum and cyanosis (severe cases), decreased exercise tolerance and weakness, chest discomfort and tightness, and tachycardia (Maloney & Broeckel, 2005). The presence of edematous lung smears in the examination of chest X-ray films discarded the cardiogenic diagnosis of the pulmonary edema (Bärtsch, 1997).

Data collection and categorization

The database was extracted from patient files dated from the years 2007 to 2018 and kept in logbooks, conforming a non-probabilistic sample by convenience. Of a total of 926 clinical records scrutinized, 299 patients were admitted in the emergency room with evident signs of *mountain sickness* after sojourning at 3,600-4,400 m.a.s.l. The whole HAI-related sample included 141 women and 158 men of ages ranging from 4 months to 97 years old. A total of 240 patients (age average: 32.65 ± 0.08) were diagnosed with AMS and 59 patients (age average: 32.3 ± 3.4) had HAPE. As to the residence region, 238 patients were residents of the

lowlands (Coast <100 m.a.s.l.) and 61 patients were highlanders (*Sierra* >2,700 m.a.s.l.) including 50 patients from the Zumbahua county (3,600-4,400 m.a.s.l.). There was a total of 49 indigenes and 250 *mestizos*. To avoid transcription errors, consistency between physical and digital records was meticulously checked.

We defined the study terms as follows:

Demographic variables

Ethnics categorized as Ecuadorian (*Panzaleo*) indigenes or *mestizo* (mixed-race); sex categorized as male or female; age categorized as children (1-14 years), young (15-25 years), adult (26-64 years), or elder (≥65 years); and body mass index (BMI) categorized as underweight (<18.5), normal weight (18.5-24.9), and overweight (24.9-29.9). Age and BMI groups were based on Statistics Canada and American Cancer Society (American Cancer Society, n.d.; Government of Canada, 1998).

Environmental variables

Residence categorized as living in the *Sierra* (highlands defined as 2,700-4,400 m.a.s.l.) or lowlanders largely from the Coast (low-lands defined as <100 m.a.s.l.). A short stay at sea-level categorized as Coast trip or no Coast trip antecedent within the last 7 days.

Health variables

These constituted by systolic, diastolic, medium, and pulse (defined as the difference between systolic and diastolic), blood pressure, heart rhythm, breathing rate, blood O_2 saturation, and axillary temperature. Because HAIs susceptibility shows interindividual health differences, correct data cohorts were allotted to low, normal, and high categories based on the reference values published by the Real First Aid (Real First Aid, n.d.a, n.d.b, n.d.c).

Blood variables

Including red blood cell (RBC), white blood cells (WBC), platelets, hemoglobin (HGB), and hematocrit. Blood variables were grouped as low, normal, and high according to referential values reported by the Marshfield Labs and Alberta Health Service (Alberta Health Service, 2018; Marshfield Labs, 2013).

Statistics

A Student *t*-test was used for *a priori* comparisons of the health status and blood variables between HAPE and AMS. After categorization of the risk variables, ordinal and nominal variables were compared by contingency tables and associations computed by the Cramér's value analysis (Cramér, 1946). Using SLR and MLR analysis, the ORs were calculated (Inoue et al., 2001). Multiple Logistic Regression (MLR) analyses reckoned the HAPE-likelihood including multiple variables (McDonald, n.d.). An Overall Success Rate was automatically implemented by the statistic software to calibrate the model fit. Statistics were carried out using SPSS software (Version 22) for Windows by the software. Alpha value was set at 0.05.

RESULTS AND DISCUSSION

Level of completion of the clinical records

Demographic and health variables were annotated for at least an 80.3% of the patients, except for BMI (60.9%) Despite their low level of completion (8-10.7%), blood variables were included in the SLR analysis. Exclusions: Only variables completed in at least 80% of the patients were included in the MLR analysis.

Diagnostic accuracy of the HAPE and AMS cohorts

To control for the quality of the clinical records, we first checked whether the clinical features of each cohort matched unequivocally with either AMS or HAPE diagnoses, in addition to contrasting against each other. Table 1 shows the clinical items that could be discriminated (10 out of 12) across cohorts using *a priori* t-test analyses. It highlighted the profound hypoxemia in the HAPE cohort (60% of blood O_2 saturation) compared to that in the AMS cohort (84.47%), when the normal level is set over the 90%. Of note, breathing rate and heart rhythm in the HAPE cohort were higher compared to AMS (breathing rate: t (256) = 7.78, p <0.001; heart rhythm: (t (295) = 3.12, p <0.01). Hematocrit and HGB values in the HAPE cohort were higher compared to AMS (t (28) = 3.49, p <0.01) and t (30) = 4.08, p <0.001) respectively). Given that the hematocrit and HGB values of AMS patients were similar to those found at the sea-level, the higher values underlying HAPE were presumed to be the result of maladaptation to HA. WBC counts in the HAPE cohort were higher than in AMS (t (30) = 4.37, p <0.001) and denoted the characteristic leukocytosis (>11x10^9/L) of pulmonary edema. The diagnosis for HAPE clearly differed from that for an AMS syndrome.

Table 1.

The contrast of the health status and hemogram of the HAPE cohort against the AMS cohort.

Variable	HAPE			AMS			*p*-value (2-tailed)
	n	Mean	SD	*n*	Mean	SD	
Systolic pressure	48	113.94	29.55	193	126.22	26.39	<0.01
Diastolic pressure	48	70.85	17.1	192	79.8	14.24	<0.001
Medium pressure	48	85.22	19.97	192	95.29	16.87	<0.001
Pulse pressure	48	43.08	20.58	192	46.45	19.43	0.29
Heart rhythm	57	109.3	29.64	240	98.14	22.85	<0.01
Breathing rate	51	34.9	11.98	207	23.67	8.44	<0.001
O_2 saturation	54	60.45	18.23	230	84.47	10.14	<0.001
RBC	8	5.39	0.85	16	4.74	0.56	<0.05
WBC	12	11.38	3.53	20	7.47	1.49	<0.001
Platelets	8	289.63	77.75	16	240.88	41.4	0.055
HGB	12	17.17	6.62	20	13.4	1.59	<0.001
Hematocrit	10	49.46	8.49	20	40.62	5.37	<0.01

Clinical features were differential across cohorts (Student's *t*-test). Units: blood pressures in mm Hg; heart rhythm and breathing rate in cycles per min; hematocrit and O_2 saturation in %; RBC in 10^{12}/L; WBC and Platelets in 10^9/L; and HGB in g/dL.

Analysis of the HAPE risk factors

Special attention was paid to the analysis of the HAPE prevalence for being a fatal condition. Data of the Tables 2, 3, 4 and 5 represent the associations between the occurrence of HAPE and the potential descriptive (risk) variables. The Cramér's value test revealed significant demographic (ethnics: (ϕ_c = 0.58, p <0.001); sex: (ϕ_c = 0.25, p <0.001); age: (ϕ_c = 0.18, p <0.05); and BMI: (ϕ_c = 0.2, p <0.05)) and environmental (region of residence: (ϕ_c = 0.75, p <0.001), and sea-level stay: (ϕ_c = 0.45, p <0.001)) risks factors. HAPE was also associated with health variables (diastolic pressure: (ϕ_c = 0.23, p <0.01); systolic pressure: (ϕ_c = 0.19, p <0.05); medium arterial pressure (ϕ_c = 0.2, p <0.05); pulse pressure (ϕ_c = 0.19, p <0.05); heart rhythm: (ϕ_c = 0.3, P <0.001); breathing frequency (ϕ_c = 0.28, p <0.001); and blood O_2 saturation (ϕ_c = 0.12, p <0.05)). Regarding blood variables, only WBC (ϕ_c = 0.49, p <0.01) and HGB (ϕ_c = 0.68, p <0.01) had significant correlations with HAPE. The hematocrit value, however, was not a determinant factor.

Tables 2, 3, 4 and 5 also present the adjusted odds ratio (OR) values for HAPE prevalence after SLR, some of ORs are more defined and relevant than others. Being indigene was statistically associated with the suffering from HAPE (Table 2 and Figure 2). A significant lower prevalence of HAPE was associated with the female sex (Table 2 and Figure 3), while male sex increases prevalence (Figure 4). In the SLR analysis, HAPE susceptibility significantly varied with age, yet not proportionally. Figure 5 shows that overweight patients showed a trend for having AMS (OR= 3.4, between 0.98 and 17.78 more chances than underweight people), with a statistical significance of p = 0.053. HAPE prevalence in individuals living at the sea-level (Coast) was significantly lower (0.013 times) than those living in the *Sierra* (Table 3 and Figure 2). Only 11 out of the 59 HAPE patients were indeed lowlanders. When the indigenous living in the *Sierra* remained in the highlands, the absence of a Coast trip decreased the odds (OR= 0.049) of having HAPE. The *mestizo* patients (95 % lived at the sea-level) had 76.2 more odds of having AMS after sojourning at very HA (p < 0.001; Figure 6).

Despite their statistical differences, health variables were not likely to strengthen HAPE occurrence in for two reasons. One was that their values were within the normal ranges as it was the case of the arterial pressures. Second, variations in the vital signs were likely to be the sequelae rather than the cause of HAPE. Breathing difficulty (dyspnea) in the HAPE cohort were more prevalent (86.3%) than in the AMS cohort (51.7%). As to blood variables, high HGB enhanced the odds for having HAPE (Figure 1), and leukocytosis (defined as WBC

counts > $11*10^9$/L) that was present in the 33% of HAPE patients, but in none of those having AMS.

Table 2.

Cross-tabulation, ORs and p-values of demographic determinants of HAPE and NO HAPE.

Variable	Categories	HAPE		NO HAPE		OR (95% CI)	Cramér's V
		n	%	*n*	%	(*p*-value)	(*p*-value)
Total patients		59	19.7	240	80.3		
Ethnic group	Indigene	32	66.7	17	7.9	23.41 (10.75-50.97)	0.58
	Mestizo	16	33.3	199	92.1	(<0.001)	(<0.001)
Sex	Female	13	22	128	53.3	0.25 (0.13-0.48)	0.25
	Male	46	78	112	46.7	(<0.001)	(<0.001)
Age	1-14 years	20	33.9	59	24.6	1 (baseline)	0.18
						(0.028)	(0.023)
	15-24 years	14	23.7	53	22.1	0.78 (0.36-1.7)	
						(0.529)	
	25-65 years	15	25.4	108	45	0.41 (0.2-0.86)	
						(0.018)	
	> 65 years	10	16.9	20	8.3	1.48 (0.59-3.68)	
						(0.404)	

SLR (ORs) and Cramér's value test (p-value). In the case of categorical variables with more than two levels, the first level was set as reference.

Table 3.

Cross-tabulation, ORs and p-values of environmental determinants of HAPE and NO HAPE.

Variable	Categories	HAPE		NO HAPE		OR (95% CI)	Cramér's V
		n	%	*n*	%	(*p*-value)	(*p*-value)
Residence region	Coast	11	18.6	227	94.6	0.013 (0.006-0.31)	0.75
	Sierra	48	81.4	13	5.4	(<0.001)	(<0.001)
Sea-level stay	No Coast trip	17	31.6	12	5	0.049 (0.01-0.41) 0.005	0.45 (<0.001)
	Coast trip	29	68.4	1	95		

SLR (ORs) and Cramér's value test (p-value).

Table 4.

Cross-tabulation, ORs and p-values of physiological determinants of HAPE and NO HAPE.

Variable	Categories	HAPE		NO HAPE		OR (95% CI)	Cramér's V
		n	%	*n*	%	(*p*-value)	(*p*-value)
Systolic pressure	Low	5	10.4	4	2.1	1 (baseline)	0.19
						(0.025)	(0.012)
	Normal	36	75	142	73.6	0.2 (0.05-0.79)	
						(0.022)	
	High	7	14.6	47	24.4	0.11 (0.03-0.55)	
						(0.007)	
Diastolic pressure	Low	8	16.7	7	3.6	1 (baseline)	0.23
						(0.005)	(0.002)
	Normal	35	72.9	145	75.5	0.21 (0.07-0.62)	
						(0.005)	
	High	5	10.4	40	20.8	0.11 (0.03-0.43)	
						(0.005)	
Medium pressure	Low	6	12.5	5	2.6	1 (baseline)	0.2
						(0.015)	(0.007)
	Normal	37	77.1	150	78.1	0.21 (0.06-0.71)	
						(0.012)	
	High	5	10.4	37	19.3	0.11 (0.03-0.51)	
						(0.005)	
Pulse pressure	Low	2	4.2	15	7.8	1 (baseline)	0.19
						(0.017)	(0.015)
	Normal	32	66.7	83	43.2	2.89 (0.63-13.36)	
						(0.17)	
	High	14	29.2	94	49	1.12 (0.23-5.42)	
						(0.89)	

Table 4. (Cont.)

Variable	Categories	HAPE		NO HAPE		OR (95% CI)	Cramér's V
		n	%	*n*	%	(*p*-value)	(*p*-value)
Heart rhythm	Low	3	5.3	10	4.2	1 (baseline)	0.3
						(<0.001)	(<0.001)
	Normal	16	28.1	155	64.6	0.34 (0.09-1.38)	
						(0.132)	
	High	38	66.7	75	31.3	1.69 (0.44-6.5)	
						(0.446)	
Breathing rate	Normal	7	13.7	100	48.3	0.17 (0.07-0.4)	0.28
	High	44	86.3	107	51.7	(<0.001)	(<0.001)
O_2 saturation	Low	52	96.3	199	86.5	4.05 (0.94-17.48)	0.12
	Normal	2	3.7	31	13.5	(0.061)	(0.044)
Temperature	Low	12	23.5	49	22.2	1 (baseline)	0.1
						(0.246)	(0.233)
	Normal	32	62.7	157	157	0.83 (0.4-1.74)	
						(0.625)	
	High	7	13.7	15	15	1.91 (0.64-5.71)	
						(0.249)	

SLR (ORs) and Cramér's value test (p-value). In the case of categorical variables with more than two levels, the first level was set as reference. Units: blood pressures in mm Hg; heart rhythm and breathing rate in cycles per min; O2 saturation in %; and temperature in °C.

Table 5.

Cross-tabulation, ORs and p-values of blood determinants of HAPE and NO HAPE.

Variable	Categories	HAPE		NO HAPE		OR (95% CI)	Cramér's V
		n	%	*n*	%	(*p*-value)	(*p*-value)
RBC	Low	1	12.5	2	12.5	1.4 (0.1-19.01)	0.43
	Normal	5	62.5	14	87.5	(0.8)	(0.110)
	High	2	25	0	0		
WBC	Normal	8	66.7	20	100		0.49
	High	4	33.3	0	0		(0.006)
Platelets	Low	1	12.5	0	0	infinite	0.3
	Normal	7	87.5	16	100		(0.149)
HGB	Low	1	8.3	4	20	1 (baseline)	0.68
						(1)	(0.001)
	Normal	4	33.3	16	80	1 (0.86-11.59)	
						(1)	
	High	7	58.3	0	0	infinite	
Hematocrit	Low	1	12.5	5	25	1 (baseline)	0.44
						(0.1)	(0.066)
	Normal	3	37.5	13	65	1.15 (0.1-13.88)	
						(0.91)	
	High	4	50	2	10	10 (0.65-154.4)	
						(0.1)	

SLR (ORs) and Cramér's value test (p-value). In the case of categorical variables with more than two levels, the first level was set as reference. Units: RBC in 1012/L; WBC and Platelets in 109/L; HGB in g/dL; hematocrit in %.

The MLR analysis gave information about the attributable fraction (or *weight*) of each variable predicting the occurrence of a specific HAI form. It was conducted on those variables that turned out significant in the Cramér's value test and had an annotated value in at least 80% of the patients. Demographic and environmental variables were computed separately given the complex collinearity structure that in some cases disguised the statistical significance. Table 6 shows that the environmental variables were statistically significant for the fit model. Likelihood of having HAPE was reckoned by the following equation: Predicted logit of HAPE = 2.64 - (5.665) * Region - (2.15) * Sea-level stay. The residence on the coast region and no Coast-trip antecedent were inversely related to the likelihood of having HAPE. Their relative influence on lowering HAPE prevalence was as follows: Coast residence > no Coast-trip antecedent (a short stay at the sea-level). Table 7 shows the MLR analysis for demographic variables. Likelihood of having HAPE was reckoned by the following equation: Predicted logit of HAPE = -0.942- (1.099) * Sex + 3.94 * Ethnics - (1.303) * $Age_{(1-14)}$ - (1.321) * $Age_{(15-24)}$ - (1.535) * $Age_{(25-65)}$. Table 7 reflects a better dependence relationship of HAPE prevalence with ethnics in indigene individuals. Female sex and aging were negatively related to HAPE likelihood whilst indigenous ethnic was positively related. Their relative influence on HAPE prevalence was as follows: Indigenous ethnic > Female sex > $Age_{(1-14)}$ ≃ $Age_{(15-24)}$ > $Age_{(25-65)}$. Regarding AMS, it is only worth at mentioning that region of residence rather than age was determinant for its prevalence: Predicted logit of AMS = -2.574 + 4.598*Region + 1.929*$Age_{(15-24)}$.

Table 6.

MLR analysis of the environmental variables determining HAPE prevalence

Variable	B	S.E.	Wald	df	p.	Exp(B)	95% C.I. for Exp (B)
Sea-level stay (1)	-2.150	0.825	6.791	1	0.009	.116	0.023 - 0.587
Region (1)	-5.665	0.794	50.923	1	0.000	.003	0.001 - 0.016
Constant	2.642	0.732	13.035	1	0.000	14.042	

Each variable is represented by one category number as follows: Region (1) = Coast, and Sea-level stay (1) = no Coast trip. To make feasible the MLR analysis, the residents of the Coast were counted like they made a "Coast trip". The Overall Success Rate reflects that the model fit was correct the 91.9% of the time. S.E.: standard error.

Table 7.

MLR analysis of the demographic variables determining HAPE prevalence.

Variable	B	S.E.	Wald	df	p.	Exp(B)	95% C.I. for Exp (B)
Ethnic (1)	3.094	0.432	51.375	1	0.000	22.068	9.469 - 51.428
Sex (1)	-1.099	0.453	5.889	1	0.015	0.333	0.137 - 0.809
Age			7.354	3	0.061		
Age (1)	-1.303	0.601	4.706	1	0.030	0.272	0.084 - 0.882
Age (2)	-1.321	0.646	4.189	1	0.041	0.267	0.075 - 0.946
Age (3)	-1.535	0.607	6.388	1	0.011	0.215	0.065 - 0.708
Constant	-0.942	0.485	3.774	1	0.052	0.390	

Each variable is represented by one category number as follows: Ethnics (1) = indigene, Sex (1) = female, Age= > 65 years, Age (1) = 1-14 years, Age (2) = 15-24 years, and Age (3) = 25-65 years. The Overall Success Rate reflects that the model fit was correct the 81.8% of the time. S.E.: Standard error.

Given de impossibility of computing the whole variables in a single MLR model, demographic-environmental interactions were graphically shown in clustered bar charts, which did not show differences with the result tendencies from SLR, ORs, and MLR. Clustered bar charts exhibited AMS and HAPE prevalence across ethnics contrasted against the environmental variables. Figure 6 graphically suggests that ascending to very HA from the sea-level increased the prevalence of HAPE in the indigenous living in the *Sierra*, whilst the *mestizo* dwellers from the Coast were at risk for AMS. Because almost two out of three HAPE-prone patients had a short sea-level stay prior to suffering from HAPE, the HAPE cohort was split by their Coast-trip antecedent and the health status of the two subgroups compared using *t*-tests. Interestingly, the heart rhythm of those who reported a Coast-trip antecedent was higher than those who did not do it (t (53) = 2.885, $p< 0.01$). There were not found any other significant health status differences.

Several findings were worth highlighting. Among the individual risk factors, some were not well known to be associated with HAPE like the ethnic group, residence region, and HGB in the Ecuadorian population. Indigenous dwellers of the highlands were HAPE-prone at very HA. Interestingly, the HAPE seizure was precipitated after returning from a short stay at the sea-level. In contrast, *mestizo* patients residing at the sea-level only had mild AMS. Female were more HAPE resilient than men. Lower HGB was presumed to be determinant in the resilience to HAPE. However, AMS stroke people regardless of sex, and HGB levels. Differential risk patterns suggest that HAPE might not be the extreme clinical expression of AMS as it is generally believed.

Based on the medical records browsed, clinical features of the HAPE cohort were unambiguously distinguished from those of the AMS cohort. We could check that AMS was accurately diagnosed as a mild self-limiting illness that occurred after sojourning at very HA and with no potential independent ailments (Barry and Pollard, 2003; Imray et al, 2010). HAPE detection did not seem to present the difficulties associated with the AMS diagnosis such as nonspecific symptoms (Hackett, Rennie, Grover, & Reeves, 1981; Imray et al., 2011; Maloney & Broeckel, 2005; Rabold, 1989; Roach et al., 1993). The HAPE hallmarks including dyspnea, tachycardia, erythrocytosis, and profound hypoxemia coincided with the clinical features of the selected HAPE cohort (Barry and Pollard, 2003; Hyers, Scoggin, Will, Grover, & Reeves, 1979; Rabold, 1989). The leukocytosis present in a third of the HAPE patients could be accounted for the close relationship between inflammation as well as the tightness of the pulmonary lymphatic vessel network (Ahmad et al., 2011; Bärscht, 1997; Carter, Mayo,

MacInnis, McKenzie, & Koehle, 2014). Thus, putative misleading nuances were definitely ruled out from our analysis.

AMS is a polygenic disorder involving multiple physiological processes including a lack of acclimatization to HA-induced hypoxia, low rate of arterial O_2 saturation, and a reduced ventilatory drive in response to hypoxia (Burtscher, Flatz, & Faulhaber, 2004; Hornbein & Schoene, 2001; Imray et al., 2010; Imray et al, 2011). Variants in up to eight genes from a variety of pathways show positive associations with AMS (MacInnis, Wang, Koehle, & Rupert, 2011). HAPE etiology also has a genetic background since antecedents of HA-related pulmonary illnesses including HAPE contribute to HAPE recurrence (Hotta et al., 2004; Mortimer, Patel, & Peacock, 2004; Soree et al., 2016). Yet preceded by HAPH, the precise origin of HAPE is not completely understood (Bärtsch et al., 1991; Bärtsch P., Mairbäurl H., Maggiorini M., & Swenson E. R., 2005; Dehner et al., 2007; Duplain et al., 2000; Grimminger et al, 2017; Hyers et al., 1979; Hohenhaus, Paul, McCullough, Kücherer, & Bärtsch, 1995; Hopkins & Levin, 2006; Humphries, 2017; Sartori et al, 2000; Scherrer, Rexhaj, Jayet, Allemann, & Sartori, 2010). AMS and HAPE are multifactorial syndromes whose susceptibility present strong interindividual differences that cannot easily be predicted by genetic variability.

Deciphering the predisposing factors for HAIs constitutes a significant requirement of health. This analysis suggested that the predisposing patterns for HAPE were different from that of AMS. Interestingly, when sojourned at very HA, Andean indigenous highlanders had more chances of developing HAPE (even more prone to HAPE after returning from a short stay at the sea-level). In contrast, the *mestizo* lowlanders just had benign AMS. It was also confirmed some previous evidence that women are less susceptible to HAPE, and have a better adaptation to HA than men (Hultgren, Honigman, Theis, & Nicholas, 1996; Sophocles, 1986; Wu et al., 2005). Although the role of sex as a risk factor for developing HAPE has been controversial, women actually manage hypoxic ventilation better and have less erythropoietin and HGB than men (Maloney & Broeckel, 2005; Soliz, Thomsen, Soulage, Lundby, & Gassmann, 2009; Murphy, 2014). On the other hand, the fact that age is a risk factor for HAPE also was corroborated, yet in this study included other factors like ethnic and sex (see Table 7; Hultgren & Marticorena, 1978; Lobenhoffer et al., 1982; Roach et al. 1995; Penaloza, Sime, & Ruiz, 2008). HAPE vulnerability was reported higher in the early years of life than other stages. The tolerance to HA increases with age because of HGB decreasing levels, which are age- and time of residence- dependent (Pesce et al., 2005; Salive et al., 1992). The association of age with AMS was much weaker than with HAPE, which agrees with the notion that a link between

both variables does not exist (Moraga, Pedreros, & Rodríguez, 2008; Wu, Zhang, Chen, & Luo, 2018). As reported by others, we observed that AMS susceptibility somewhat relied on the overweight patients (see Figure 5; Akunov, Sydykov, Toktash, Doolotova, & Sarybaev, 2018; Ri-Li et al., 2003).

The progress of AMS and HAPE have been regarded as environmentally mediated by factors like the ascent rate, altitude attained, and prior HA stay (Barker et al., 2016; Basnyat & Murdoch, 2003; MacInnis et al., 2015; MacInnis & Koehle, 2016; Maloney & Broeckel, 2005; Mortimer et al., 2004; Imray et al., 2010; Staab et al., 2013; Luks et al., 2017). The combination of HA residence and the Coast-trip antecedent (a short sea-level stay) increased the odds for having HAPE, a phenomenon named the *re-entry HAPE* (Bhagi, Srivastava, & Singh, 2014; Lobenhoffer et al, 1982; Luks et al., 2017). There is evidence that a rapid HA ascent (4,000 m.a.s.l. in this case) alters the distribution of body fluids and consequently blood viscosity (Frayser, Rennie, Gray, & Houston, 1975; Singh, Rawal, & Tyagi, 1990). Hyperviscous blood may account for the elevated heart rhythm in HAPE patients and perhaps HAPH after a Coast trip (Hainsworth & Drinkhill, 2007). It is then hypothesized that changes in the rheologic properties of blood could produce HAPE (Basnyat & Murdoch, 2003; Imray et al, 2010; Rabold,1989; Palareti et al., 1984; Schneider, Bernasch, Weymann, Holle, & Bartsch, 2002). The environmental factors were likely to play complex interactions with demographic (and likely genetic) factors because their combination in a single MLR analysis distinguished the statistical significance obtained when were computed separately and the results from the clustered bar chart analyses (Maloney & Broeckel, 2005).

Altered blood component levels may account for HAPE occurrence. Native Andean populations get adapted to HA hypoxia by rising HGB levels (Basu et al., 2007; Frisancho, 2013; Bigham, 2016). Yet the HGB in the HAPE cohort (approx. 18 mg/dL) could be considered optimal for acclimatization to HA, but it may provide no further benefit in O_2 transport (Reeves & Leon-Velarde, 2004; Villafuerte, Cárdenas, & Monge-C, 2004). Besides O_2, HGB also carries nitric oxide (NO), a potent vasodilator of pulmonary capillaries (McMahon et al., 2002; Settergren et al, 1998; Veeramachaneni, Harken, & Cairns, 1999;). By hijacking NO, an excess of HGB may provoke vasoconstriction of the pulmonary capillaries and sub-acute HAPE (Bärtsch et al., 2005; Busch et al., 2001; Cremona et al., 2002; Duplain et al, 2000). Another influents blood element about HAPE is leukocytes. It could be argued that judging by the leukocytosis, the cause of HAPE was an infection (Humphries, 2017). However, inflammation-related leukocytosis could be the consequence rather than the cause of HAPE (Duplain et al., 2000; Swenson et al., 2002; Basnyat & Starling, 2016; Koeppen, Eckle, &

Eltzschig, 2011; Luks et al., 2017). Furthermore, HAPE also can be explained by abrupt altitude shifts producing significant HGB increments (Beall, 2006; Windsor & Rodway, 2007). Thus explaining the high HAPE prevalence in our sample (6.3%), similar to that reported elsewhere (Hultgren & Marticorena, 1978; Luks et al., 2017). Taking into account the importance of high HGB levels only for HAPE progression and not for AMS, HAPE could not be considered an extreme AMS state that occurs eventually as other authors recorded (Bärtsch et al., 2002; Ge et al., 1997; Paralikar, 2012; Whayne, 2014). Our viewpoint along with others is that risk factors and etiology vary from AMS to HAPE (Hackett et al., 1981; Hackett & Roach, 2001; Hohenhaus et al., 1995; Imray et al., 2011; West, 2004).

CONCLUSIONS AND RECOMMENDATIONS

Summarizing, the complex demographic-environmental-hemoglobin confluence denotes a differential etiology between AMS and HAPE. HAPE shows categories from a different nature that made some people prone to develop the pathology. Indigenous highlanders were more exposed to HAPE development, whilst *mestizo* newcomers to very HA mostly were struck by AMS. HAPE risk in indigenous dwellers increased after returning from a short stay at sea-level. HAPE risk also was incremented in male individuals rather than females. Additionally, HAPE syndrome predominated in younger patients. Ethnicity-dependent HGB levels also seemed to influence HAPE progressing, HGB high levels increased the disease development. Even though our results suggest HGB and HAPE association, the role of HGB in the etiopathogenesis of HAPE deserves further research.

Ecuador requires more research in HA medicine and public health. The present epidemiological analysis of the prevalence of HAIs conducted in Ecuador gives a better understanding of HAPE and AMS development, and further, it could allow establishing preventive measures more efficiently. Our profile of an individual at risk for HAPE is as follows: an indigenous male living the *Sierra* (Highlanders) with elevated HGB and who commutes frequently from the sea-level to very HA. Individuals presumed to be HAPE-prone should be under surveillance for high HGB levels (HA maladaptation), leukocytosis, and chest X-ray looking for suspicious lung smears. They should be advised to make a slow, progressive ascent during their commuting to the very HA lands, preferably by spanning the trip between two or three days. As prophylaxis, a treatment with acetazolamide (250 mg twice a day) from one day before ascent along with keeping hydrated are also highly recommended.

Finally, we propose the following research avenues:

1. Given the distinctive genetic background of the Ecuadorian indigenes with respect to other countries, and the complex interaction with the environment, it should be researched the epigenetics of HAPE-related genes as those involved in the HIF-alpha pathway, HGB synthesis, EPO, endothelial function, and NO production to cite some.
2. It is necessary to conduct a comprehensive clinical biochemistry analysis to detect HAPE biomarkers as well as other forms of HAIs. A complete hemogram searching for sub-chronic Mountain Sickness and leukocytosis are highly recommended.
3. This study warrantee further investigation on subclinical forms of HAPE using larger samples of indigenes from other native communities of the Ecuadorian Andes.

ABBREVIATIONS

AMS	Acute Mountain Sickness
BMI	Body Mass Index
CMS	Chronic Mountain Sickness
EPO	Erythropoietin
HA	High Altitude
HAI	High Altitude Illness
HAPE	High Altitude Pulmonary Edema
HAPH	High Altitude Pulmonary Hypertension
HGB	Hemoglobin
HIF-alpha	Hypoxia-Inducible Factor-alpha
m.a.s.l.	Meters above sea level
MLR	Multiple Logistic Regression
NO	Nitric Oxide
O2	Oxygen
OR	Odds Ratio
SLR	Simple Logistic Regression
RBC	Red Blood Cell
WBC	White Blood Cells

REFERENCES

Ahmad Y., Shukla D., Garg I., Sharma N., Saxena S, Malhotra V., & Bhargava K. (2011). Identification of haptoglobin and apolipoprotein A-I as biomarkers for high altitude pulmonary edema. *Funct Integr Genomics*, (11), 407-417. doi:10.1007/s10142-011-0234-3.

Alberta Health Service. (2018). *Hematology Reference Intervals*. Retrieved from https://www.albertahealthservices.ca/assets/wf/lab/wf-lab-edm-hematology-reference-ranges.pdf

American Cancer Society. (n.d.). *Normal weight ranges: Body mass index (BMI).* Retrieved from https://www.cancer.org/cancer/cancer-causes/diet-physical-activity/body-weight-and-cancer-risk/adult-bmi.html

Akunov A., Sydykov A., Toktash T., Doolotova A., & Sarybaev A. (2018). Hemoglobin changes after long-term intermittent work at high altitude. *Front Physiol,* (9), 1552. doi: 10.3389/fphys.2018.01552.

Barker K., Conroy A., Hawkes M., Murphy H., Pandey P., & Kain K. (2016). Biomarkers of hypoxia, endothelial and circulatory dysfunction among climbers in Nepal with AMS and HAPE: a prospective case-control study. *J Travel Med*., (23). doi: 10.1093/jtm/taw005.

Bärtsch P. (1997). High altitude pulmonary edema. *Respir Int Rev Thorac Dis*, 64:435-443.

Bärtsch P., Mairbäurl H., Maggiorini M., & Swenson E. R. (2005). Physiological aspects of high-altitude pulmonary edema. *J Appl Physiol*, (98), 1101-1110.

Bärtsch P., Maggiorini M., Ritter M., Noti C., Vock P., & Oelz O. (1991). Prevention of high-altitude pulmonary edema by nifedipine. *N Engl J Med*, (325), 1284-1289.

Bärtsch P., Swenson E. R., Paul A., Jülg B., & Hohenhaus E. (2002). Hypoxic ventilatory response, ventilation, gas exchange, and fluid balance in acute mountain sickness. *High Alt Med Biol*, (3), 361-376.

Barry P.W., & Pollard A. J. (2003). Altitude illness. *BMJ*, (326), 915-919.

Basnyat B., & Murdoch D. R. (2003). High-altitude illness. *Lancet*, (361), 1967-1974.

Basnyat B., & Starling J.M. (2016). Infectious Diseases at High Altitude. *Microbiol Spectr*, (3). doi: 10.1128/microbiolspec.IOL5-0006-2015.

Basu M., Malhotra A.S., Pal K., Prasad R., Kumar R., Prasad B.A., & Sawhney R.C. (2007). Erythropoietin levels in lowlanders and high-altitude natives at 3450 m. *Aviat Space Environ Med*, (78), 963-967.

Beall C.M. (2006). Andean, Tibetan, and Ethiopian patterns of adaptation to high-altitude hypoxia. *Integr Comp Biol*, (46), 18-24. doi: 10.1093/icb/icj004.

Bhagi S., Srivastava S., & Singh S.B. (2014). High-altitude pulmonary edema: review. *J Occup Health,* (56), 235-243.

Bigham A.W. (2016) Genetics of human origin and evolution: high-altitude adaptations. *Curr Opin Genet Dev*, (41), 8-13. doi: 10.1016/j.gde.2016.06.018.

Bloch K.E., Buenzli J.C., Latshang T.D., & Ulrich S. (2015). Sleep at high altitude: guesses and facts. *J Appl Physiol*. (119), 1466-1480. doi: 10.1152/japplphysiol.00448.2015.

Burtscher M., Flatz M., & Faulhaber M. (2004). Prediction of susceptibility to acute mountain sickness by SaO_2 values during short-term exposure to hypoxia. *High Alt Med Biol*, (5), 335-340.

Busch T., Bärtsch P., Pappert D., Grünig E., Hildebrandt W., Elser H., …Swenson E.R. (2001). Hypoxia decreases exhaled nitric oxide in mountaineers susceptible to high-altitude pulmonary edema. *Am J Respir Crit Care Med*, (163), 368-373.

Carter E. A., Mayo J. R., MacInnis M. J., McKenzie D. C., & Koehle M. S. (2014). Individual susceptibility to high altitude and immersion pulmonary edema and pulmonary lymphatics. *Aviat Space Environ Med.*, (85), 9-14.

Chawla S., & Saxena S. (2014). Physiology of high-altitude acclimatization. *Resonance*, (19), 538-548.

Cramér, H. (1946). *Mathematical Methods of Statistics*. New York, United States of America: Princeton University Press.

Crawford J. E., Amaru R., Song J., Julian C. G., Racimo F., Cheng J. Y., …Nielsen R. (2017). Natural Selection on Genes Related to Cardiovascular Health in High-Altitude Adapted Andeans. *Am J Hum Genet*, (101), 752-767. doi: 10.1016/j.ajhg.2017.09.023.

Cremona G., Asnaghi R., Baderna P., Brunetto A., Brutsaert T., Cavallaro C., … Wagner P. D. (2002). Pulmonary extravascular fluid accumulation in recreational climbers: a prospective study. *Lancet*, (359), 303-309.

Davis C., & Hackett P. (2017). Advances in the prevention and treatment of high altitude illness. *Emerg Med Clin North Am.,* (35), 241-260. doi: 10.1016/j.emc.2017.01.002.

Dehnert C., Berger M. M., Mairbäurl H., & Bärtsch P. (2007). High altitude pulmonary edema: a pressure-induced leak. *Respir Physiol Neurobiol.*, (158), 266-273.

Duplain H., Sartori C., Lepori M., Egli M., Allemann Y., Nicod P., & Scherrer U. (2000). Exhaled nitric oxide in high-altitude pulmonary edema: role in the regulation of pulmonary vascular tone and evidence for a role against inflammation. *Am J Respir Crit Care Med.*, (162), 221-224.

Frayser R., Rennie I. D., Gray G.W., & Houston C. S. (1975) Hormonal and electrolyte response to exposure to 17,500 ft. *J Appl Physiol*., (38), 636-642.

Frisancho A. R. (2013). Developmental functional adaptation to high altitude: review. *Am J Hum Biol*., (25),51-168. doi: 10.1002/ajhb.22367.

Ge R. L., Matsuzawa Y., Takeoka M., Kubo K., Sekiguchi M., & Kobayashi T. (1997). Low pulmonary diffusing capacity in subjects with acute mountain sickness. *Chest*, (111), 58-64.

Government of Canada SC. (1998). Age Categories, Life Cycle Groupings. Retrieved from https://www.statcan.gc.ca/eng/concepts/definitions/age2

Grimminger J., Richter M., Tello K., Sommer N., Gall H., & Ghofrani H. A. (2017). Thin air resulting in high pressure: Mountain Sickness and Hypoxia-Induced Pulmonary Hypertension. *Can Respir J.*, (2017), 8381653. doi: 10.1155/2017/8381653.

Hackett P. H., Rennie D., Grover R. F., & Reeves J. T. (1981). Acute mountain sickness and the edemas of high altitude: a common pathogenesis? *Respir Physiol*., (46), 383-390.

Hainsworth R., & Drinkhill M. J. (2007). Cardiovascular adjustments for life at high altitude. *Respir Physiol Neurobiol*., (158), 204-211.

Hackett P. H., & Roach R. C. High-altitude illness. (2001) *N Engl J Med*., (345), 107-114.

Hohenhaus E., Paul A., McCullough R. E., Kücherer H., & Bärtsch P. (1995). Ventilatory and pulmonary vascular response to hypoxia and susceptibility to high altitude pulmonary oedema. *Eur Respir J*., (1998), 1825-1833.

Hopkins S. R., & Levin D. L. (2006). Heterogeneous pulmonary blood flow in response to hypoxia: a risk factor for high altitude pulmonary edema? *Respir Physiol Neurobiol*., (151), 217-228.

Hornbein T. F. (1992). Long term effects of high altitude on brain function. *Int J Sports Med*., 13 (1), 43-45.

Hornbein T. F., & Schoene R. B. (2001). High altitude—an exploration of human adaptation. *Lung biology in health and disease*, (161).

Hotta J., Hanaoka M., Droma Y., Katsuyama Y., Ota M., & Kobayashi T. (2004). Polymorphisms of renin-angiotensin system genes with high-altitude pulmonary edema in Japanese subjects. *Chest*, (126), 825-830.

Hultgren H. N., Honigman B., Theis K., & Nicholas D. (1996). High-altitude pulmonary edema at a ski resort. *West J Med*., (164), 222-227.

Hultgren H. N., & Marticorena E. A. (1978). High altitude pulmonary edema. Epidemiologic observations in Peru. *Chest*, (74), 372-376.

Humphries C. P. (2017). Lower Respiratory Tract Infection: An Unrecognised Risk Factor for High Altitude Pulmonary Oedema? *Eur J Case Rep Intern Med*., 4 (000539). doi: 10.12890/2017_000539.

Hyers T. M., Scoggin C. H., Will D. H., Grover R. F., & Reeves J.T. (1979). Accentuated hypoxemia at high altitude in subjects susceptible to high-altitude pulmonary edema. *J Appl Physiol Respir Environ Exerc Physiol*., (46), 41-46.

Imray C., Booth A., Wright A., & Bradwell A. (2011). Acute altitude illnesses. *BMJ*, 343 (d4943).

Imray C., Wright A., Subudhi A., & Roach R. (2010). Acute mountain sickness: pathophysiology, prevention, and treatment. *Prog Cardiovasc Dis*., (52), 467-484.

Instituto Nacional de Estadística y Censos. (n.d.). *Población por área, según provincia, cantón y parroquia de empadronamiento y grupos étnicos*. Retrieved from http://www.ecuadorencifras.gob.ec/?s=grupos+etnicos

Inoue A., Kunitoh H., Sekine I., Sumi M., Tokuuye K., & Saijo N. (2001). Radiation pneumonitis in lung cancer patients: a retrospective study of risk factors and the long-term prognosis. *Int J Radiat Oncol Biol Phys*., (49), 649-655.

Jacovas V. C., Couto-Silva C.M., Nunes K., Lemes R. B., de Oliveira M. Z., Salzano F. M., …Hünemeier T. (2018). Selection scan reveals three new loci related to high altitude adaptation in Native Andeans. *Sci Rep*., 8 (12733). doi: 10.1038/s41598-018-31100-6.

Koeppen M., Eckle T., & Eltzschig H. K. (2011) The Hypoxia-Inflammation Link and Potential Drug Targets. *Curr Opin Anaesthesiol*., (24), 363-369.

Lobenhoffer H. P., Zink R. A., & Brendel W. (1982). High Altitude Pulmonary Edema: Analysis of 166 Cases. *High Altitude Physiology and Medicine*, 219-31.

Luks A. M., Swenson E. R., & Bärtsch P. (2017). Acute high-altitude sickness. *Eur Respir Rev*. (26), 160096. doi: 10.1183/16000617.0096-2016.

MacInnis M. J., & Koehle M. (2016). Evidence for and Against Genetic Predispositions to Acute and Chronic Altitude Illnesses. *High Alt Med Biol*. (17), 281-293

MacInnis M. J., Wang P., Koehle M. S., & Rupert J. L. (2011). The genetics of altitude tolerance: the evidence for inherited susceptibility to acute mountain sickness. *J Occup Environ Med*., (53), 159-168. doi: 10.1097/JOM.0b013e318206b112.

MacInnis M. J., Widmer N., Timulsina U., Subedi A., Siwakoti A., Pandit B. P., …Koehle M. S. (2015). A Preliminary Genome-Wide Association Study of Acute Mountain Sickness Susceptibility in a Group of Nepalese Pilgrims Ascending to 4380 m. *High Alt Med Biol*., (16), 290-297. doi: 10.1089/ham.2015.0065.

Maloney J. P., & Broeckel U. (2005). Epidemiology, risk factors, and genetics of high-altitude-related pulmonary disease. *Clin Chest Med*., (26), 395-404.

Marmura M. J., & Hernandez P. B. (2015). High-altitude headache. *Curr Pain Headache Rep*., (19), 483. doi: 10.1007/s11916-015-0483-2.

Maggiorini M. (2010). Prevention and treatment of high-altitude pulmonary edema. *Prog Cardiovasc Dis*. (52), 500-506.

Maggiorini M., Mélot C., Pierre S., Pfeiffer F., Greve I., Sartori C., …Naeije R. (2001). High-altitude pulmonary edema is initially caused by an increase in capillary pressure. *Circulation*, (103), 2078-2083.

Marshfield Labs. (2013). *Hemogram/Platelet Complete Blood Count Reference Ranges*. Retrieved from https://www.marshfieldlabs.org/

McDonald J. H. (n.d.). *Multiple logistic regression - Handbook of Biological Statistics*. Retrieven from http://www.biostathandbook.com/multiplelogistic.html

McMahon T. J., Moon R. E., Luschinger B. P., Carraway M. S., Stone A. E., Stolp B.W., …Stamler J. S. (2002) Nitric oxide in the human respiratory cycle. *Nat Med*., (28), 711-777.

Moore L. G. (2017). Human Genetic Adaptation to High Altitudes: Current Status and Future Prospects. *Quat Int*., (461), 4-13. doi: 10.1016/j.quaint.2016.09.045.

Moore L. G. (2001). Human genetic adaptation to high altitude. *High Alt Med Biol*. (2),257-279.

Moraga F. A., Pedreros C. P., & Rodríguez C. E. (2008). Acute mountain sickness in children and their parents after rapid ascent to 3500 m (Putre, Chile). *Wilderness Environ Med*., (19), 287-292. doi: 10.1580/06-WEME-BR-084.1.

Mortimer H., Patel S., & Peacock A. J. (2004). The genetic basis of high-altitude pulmonary oedema. *Pharmacol Ther*., (101), 183-192.

Murphy W. G. (2014). The sex difference in haemoglobin levels in adults - mechanisms, causes, and consequences. *Blood Rev*., (28), 41-47.

Naeije, R., Mélot, C., & Lejeune, P. (1986). Hypoxic pulmonary vasoconstriction and high altitude pulmonary edema. *The American Review of Respiratory Disease,* 134(2), 332–333.

Painschab M. S., Malpartida G. E., Dávila-Roman V. G., Gilman R. H., Kolb T. M., León-Velarde F., …Checkley W. (2015). Association between serum concentrations of hypoxia inducible factor responsive proteins and excessive erythrocytosis in high altitude Peru. *High Alt Med Biol*., (16), 26-33. doi: 10.1089/ham.2014.1086.

Palareti G., Coccheri S., Poggi M., Tricarico M. G., Magelli M., & Cavazzuti F. (1984). Changes in the rheologic properties of blood after a high altitude expedition. *Angiology*, (35), 451-458.

Paralikar S. J. (2012). High altitude pulmonary edema-clinical features, pathophysiology, prevention and treatment. *Indian J Occup Environ Med*., (16), 59-62. doi: 10.4103/0019-5278.107066

Pasha M. A., & Newman J. H. (2010). High-altitude disorders: pulmonary hypertension: pulmonary vascular disease: the global perspective. *Chest*, (137), 13S-19S. doi: 10.1378/chest.09-2445.

Paul S., Gangwar A., Bhargava K., Khurana P., & Ahmad Y. (2018). Diagnosis and prophylaxis for high-altitude acclimatization: Adherence to molecular rationale to evade high-altitude illnesses. *Life Sci*., (203), 171-176.

Penaloza D., Sime F., & Ruiz L. (2008). Pulmonary hemodynamics in children living at high altitudes. *High Alt Med Biol*., (9), 199-207. doi: 10.1089/ham.2008.1004.

Peng Y., Yang Z., Zhang H., Cui C., Qi X., Luo X., …Wu T., Ouzhuluobu, Basang, Ciwangsangbu, Danzengduojie, Chen H., Shi H., Su B. (2011). Genetic variations in Tibetan populations and high-altitude adaptation at the Himalayas. *Mol Biol Evol*., (28), 1075-1081. doi: 10.1093/molbev/msq290.

Pesce C., Leal C., Pinto H., González G., Maggiorini M., Schneider M., & Bärtsch P. (2005). Determinants of acute mountain sickness and success on Mount Aconcagua (6962 m). *High Alt Med Biol*, (6), 158-166.

Rabold M. (1989). High-altitude pulmonary edema: a collective review. *Am J Emerg Med*., (7), 426-433.

Real First Aid. (n.d.). *Pulse & SpO2*. Retrieved from https://www.realfirstaid.co.uk/pulse

Real First Aid. (n.d.). *Hypothermia Guidelines*. Retrieved from https://www.realfirstaid.co.uk/hypothermia

Real First Aid. (n.d.). *Blood Pressure*. Retrieved from https://www.realfirstaid.co.uk/bloodpressure

Reeves J. T., & Leon-Velarde F. (2004). Chronic mountain sickness: recent studies of the relationship between hemoglobin concentration and oxygen transport. High Alt Med Biol., (5), 147-155.

Ri-Li G., Chase P. J., Witkowski S., Wyrick B. L., Stone J. A., Levine B. D., & Babb T. G. (2003) Obesity: associations with acute mountain sickness. *Ann Intern Med*., (139), 253-257.

Roach R. C., Bärtsch P., Hackett P. H., & Oelz O. (1993). The Lake Louise acute mountain sickness scoring system. *Hypoxia and molecular medicine*, 272-274.

Roach R. C., Houston C. S., Honigman B., Nicholas R. A., Yaron M., Grissom C. K., … Hultren H. N. (1995) How well do older persons tolerate moderate altitude? *West J Med*., (162), 32-36.

Rodway G. W., Hoffman L. A., & Sanders M. H. (2003) High-altitude-related disorders--Part I: Pathophysiology, differential diagnosis, and treatment. *Heart Lung J Crit Care*, (32), 353-359.

Salive M. E., Cornoni-Huntley J., Guralnik J. M., Phillips C. L., Wallace R. B., Ostfeld A. M., & Cohen H. J. (1992). Anemia and hemoglobin levels in older persons: relationship with age, gender, and health status. *J Am Geriatr Soc*., (40), 489-496.

Sartori C., Allemann Y., Trueb L., Lepori M., Maggiorini M., Nicod P., & Scherrer U. (2000). Exaggerated pulmonary hypertension is not sufficient to trigger high-altitude pulmonary oedema in humans. *Schweiz Med Wochenschr*, (130), 385-389.

Scherrer U., Rexhaj E., Jayet P. Y., Allemann Y., & Sartori C. (2010). New insights in the pathogenesis of high-altitude pulmonary edema. *Prog Cardiovasc Dis*., (52), 485-492. doi: 10.1016/j.pcad.2010.02.004.

Schneider M., Bernasch D., Weymann J., Holle R., & Bartsch P. (2002). Acute mountain sickness: influence of susceptibility, preexposure, and ascent rate. *Med Sci Sports Exerc*., (34), 1886-1891.

Serrano Dueñas, M. (1998). High altitude pulmonary edema. Study of 21 cases. *Medicina Clinica,* 110(12), 446–449.

Settergren G., Angdin M., Astudillo R., Gelinder S., Liska J., Lundberg J. O., & Weitzberg E. (1998). Decreased pulmonary vascular resistance during nasal breathing: modulation by endogenous nitric oxide from the paranasal sinuses. *Acta Physiol Scand*., (163), 235-239.

Siebenmann C., Robach P., & Lundby C. (1985). Regulation of blood volume in lowlanders exposed to high altitude. *J Appl Physiol*., (123), 957-966.

Simonson T. S., McClain D. A., Jorde L. B., & Prchal J. T. (2012). Genetic determinants of Tibetan high-altitude adaptation. *Hum Genet*., (131), 527-5233. doi: 10.1007/s00439-011-1109-3.

Simonson T. S., Wei G., Wagner H. E., Wuren T., Qin G., Yan M., …Ge R. L. (2015). Low haemoglobin concentration in Tibetan males is associated with greater high-altitude exercise capacity. *J Physiol*., (593), 3207-3218. doi: 10.1113/JP270518.

Singh M., Rawal B., & Tyagi A. (1990). Body fluid status on induction, reinduction and prolonged stay at high altitude of human volunteers. *Int J Biometeorol*., (34), 93-97.

Soliz J., Thomsen J. J., Soulage C., Lundby C., & Gassmann M. (2009). Sex-dependent regulation of hypoxic ventilation in mice and humans is mediated by erythropoietin. *Am J Physiol Regul Integr Comp Physiol*., (296), R1837-1846.

Sophocles A. M. (1986). High-altitude pulmonary edema in Vail. *West J Med*., (144), 569-573.

Soree P., Gupta R. K., Singh K., Desiraju K., Agrawal A., Vats P., …Singh S. B. (2016). Raised HIF1α during normoxia in high altitude pulmonary edema susceptible non-mountaineers. *Sci Rep*., (6), 26468. doi: 10.1038/srep26468.

Staab J. E., Beidleman B. A., Muza S. R., Fulco C. S., Rock P. B., & Cymerman A. (2014). Efficacy of residence at moderate versus low altitude on reducing acute mountain sickness in men following rapid ascent to 4300 m. *High Alt Med Biol*., (14), 13-18. doi: 10.1089/ham.2012.1065.

Swenson E. R. (2004). ACE inhibitors and high altitude. *High Alt Med Biol*., (5), 92-94.

Swenson E. R., Maggiorini M., Mongovin S., Gibbs J. S., Greve I., Mairbäurl H., & Bärtsch P. (2002). Pathogenesis of high-altitude pulmonary edema: inflammation is not an etiologic factor. *JAMA*, (287), 2228-2235.

Veeramachaneni N. K., Harken A. H., & Cairns C. B. (1999). Clinical implications of hemoglobin as a nitric oxide carrier. *Arch Surg*., (134), 434-437.

West J. B. (2004). The physiologic basis of high-altitude diseases. *Ann Intern Med*., (141), 789-800.

Whayne T. F. (2014). Cardiovascular medicine at high altitude. *Angiology*, (65), 459-472. doi: 10.1177/0003319713497086.

Villafuerte F. C., Cárdenas R., & Monge-C C. (2004). Optimal hemoglobin concentration and high altitude: a theoretical approach for Andean men at rest. *J Appl Physiol*., (96), 1581-1588.

Wilson M. H., Newman S., & Imray C. H. (2009). The cerebral effects of ascent to high altitudes. *Lancet Neurol*., (8),175-191. doi: 10.1016/S1474-4422(09)70014-6.

Windsor J. S., & Rodway G.W. (2007). Heights and haematology: the story of haemoglobin at altitude. *Postgrad Med J*., (83), 148-151.

Wright A., Brearey S., Imray C. (2008). High hopes at high altitudes: pharmacotherapy for acute mountain sickness and high-altitude cerebral and pulmonary oedema. *Expert Opin Pharmacother*, (9), 119-127.

Wu T., Wang X., Wei C., Cheng H., Wang X., Li Y., …Wang Z. (2005). Hemoglobin levels in Qinghai-Tibet: different effects of gender for Tibetans vs. Han. *J Appl Physiol*., (98), 598-604.

Wu Y., Zhang C., Chen Y., & Luo Y. J. (2018). Association between acute mountain sickness (AMS) and age: a meta-analysis. *Mil Med Res*., (5), 14. doi: 10.1186/s40779-018-0161-x.

Zubieta-Castillo G., Zubieta-Calleja G. R., & Zubieta-Calleja L. (2006). Chronic mountain sickness: the reaction of physical disorders to chronic hypoxia. *J Physiol Pharmacol*., 57 (4), 431-442.

APPENDICES

Appendix A: Simple Clustered Bar Chart of HGB

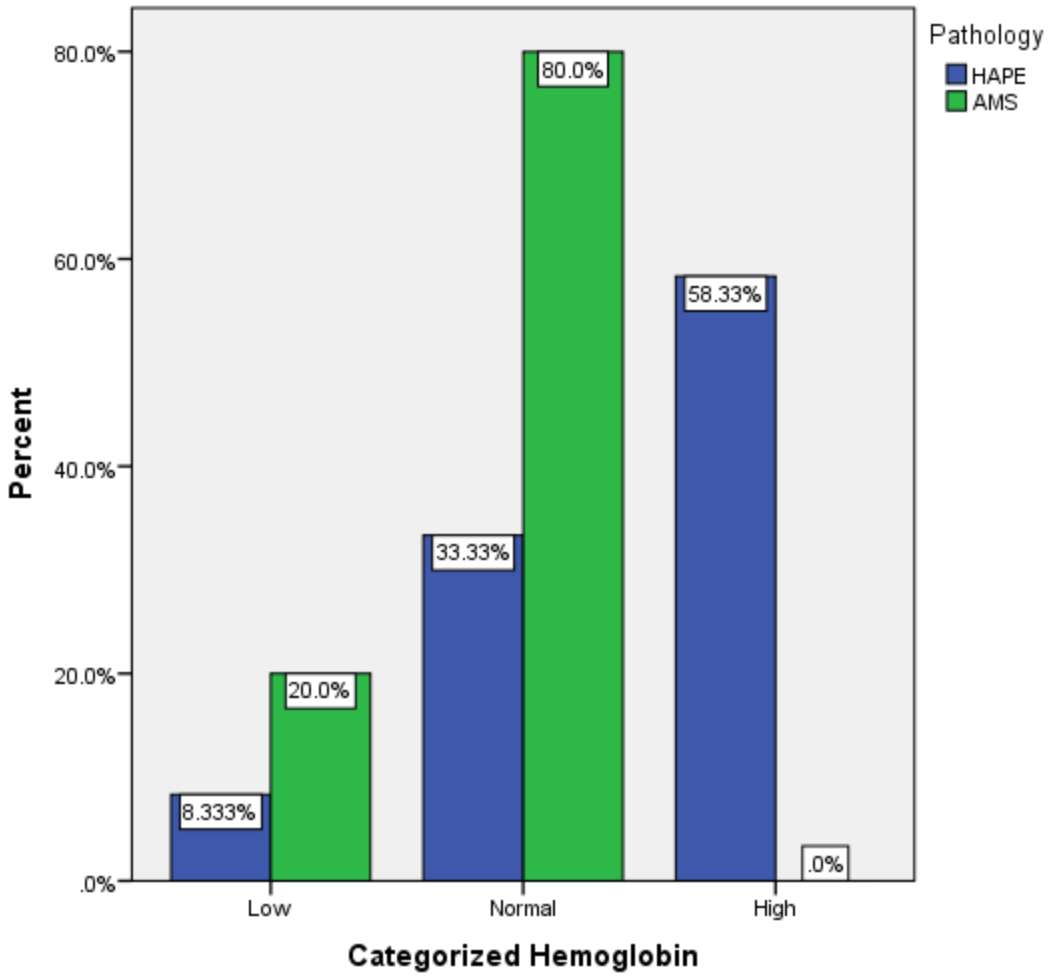

Figure 1. Association of HGB with HAIs prevalence. The bar chart shows percentages of HAPE and AMS prevalence against categorized HGB levels. Notice the positive linear association between HGB and HAPE prevalence. None of the AMS patients analyzed had the HGB elevated.

Appendix B: Two-variable Clustered Bar Chart of Demographics and Environmental Variables

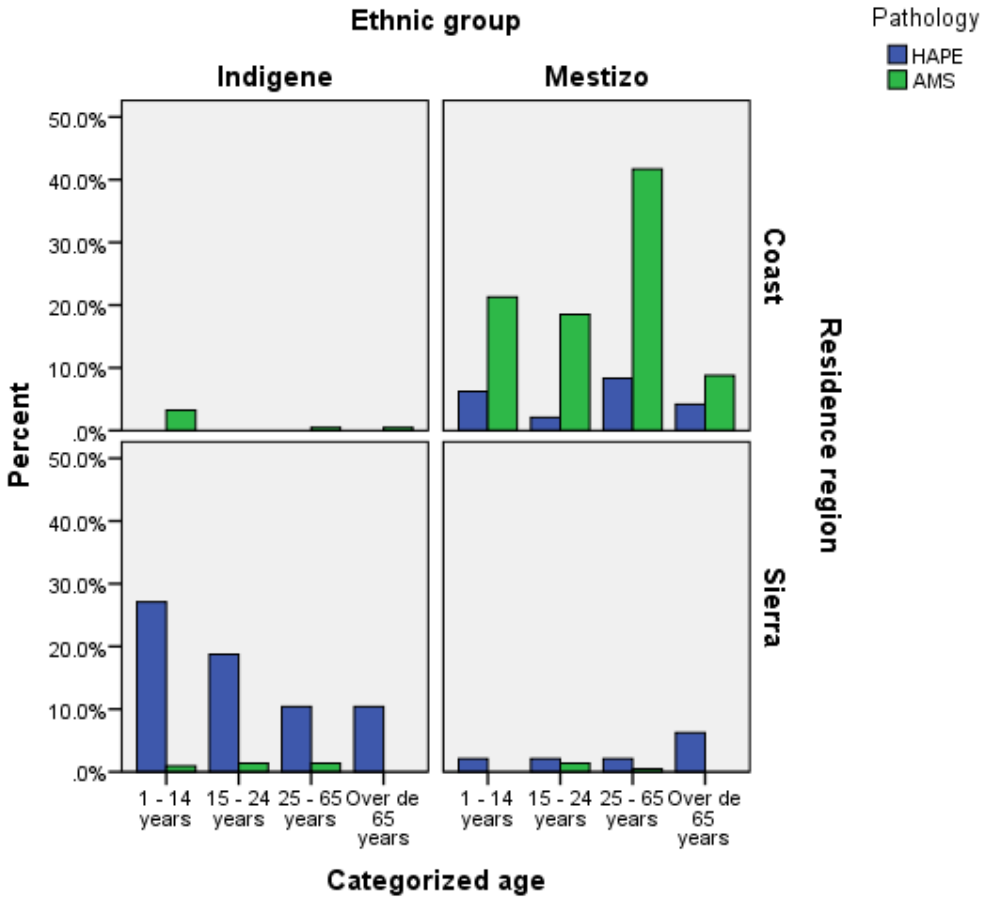

Figure 2. Two-variable (ethnic group versus residence region) clustered bar charts of the distribution of AMS and HAPE prevalence across age segments: Prevalence pattern with no sex distinction. *Mestizo* from the coast suffered from AMS. Indigenes from the *Sierra* were HAPE-prone, although it decreased with age.

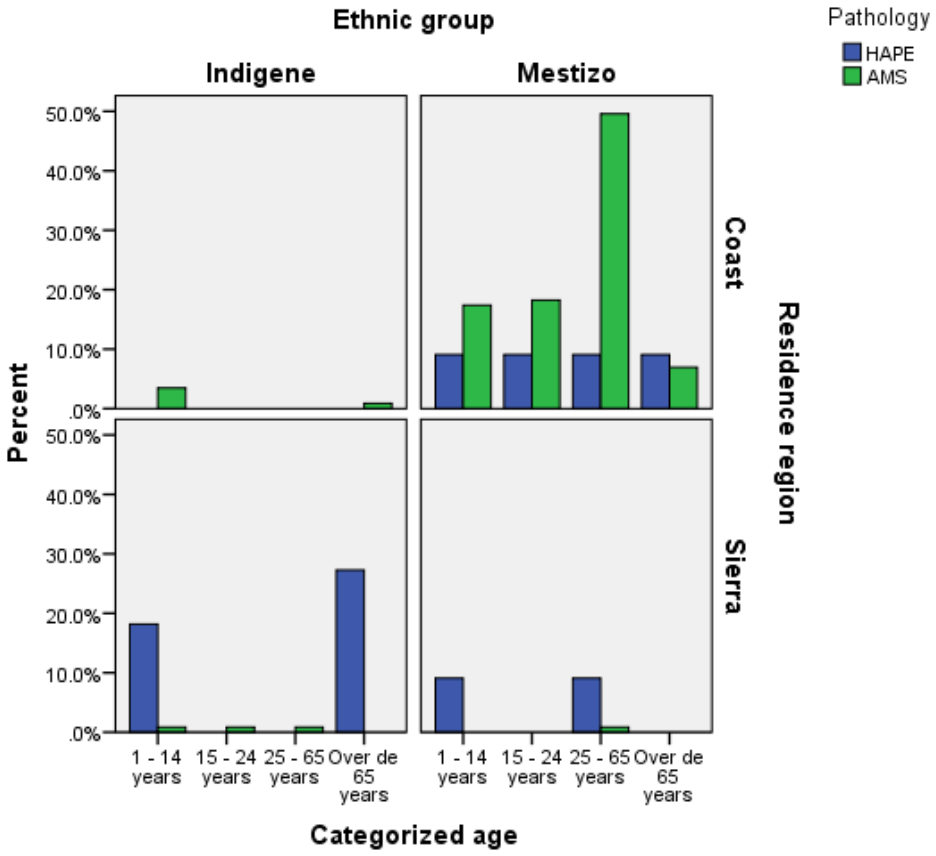

Figure 3. Two-variable (ethnic group versus residence region) clustered bar charts of the distribution of AMS and HAPE prevalence across age segments: Prevalence pattern for female sex.

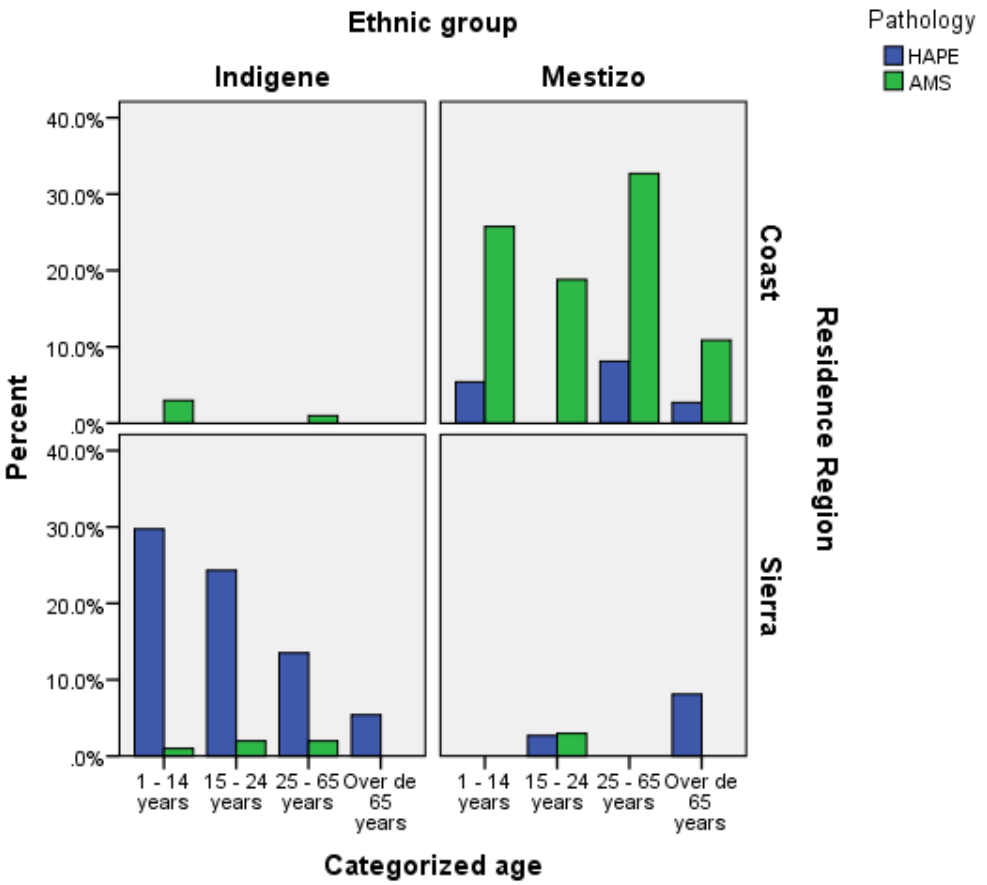

Figure 4. Two-variable (ethnic group versus residence region) clustered bar charts of the distribution of AMS and HAPE prevalence across age segments: Prevalence pattern for the male sex. This pattern applied to men rather than to women, who were more resilient to HAPE.

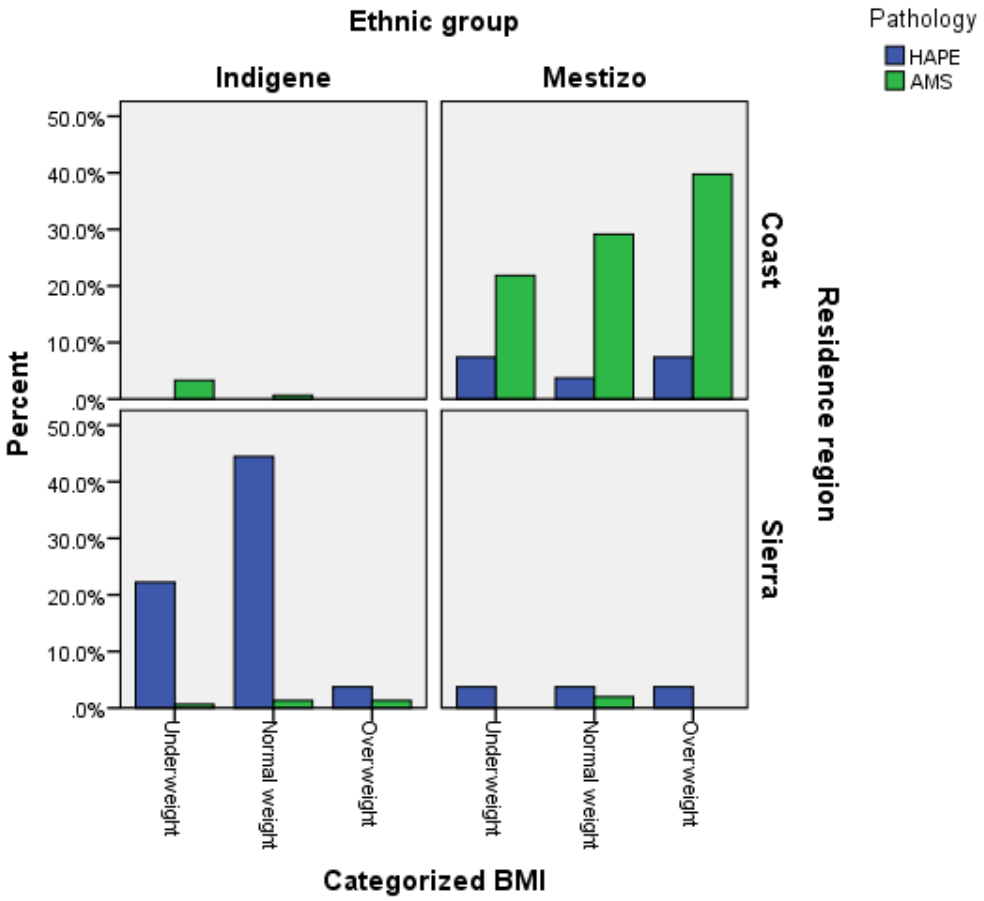

Figure 5. Two-variable (ethnic group vs. residence region) clustered bar charts of the distribution of AMS and HAPE prevalence across BMI categories. Within the Coast *mestizo* subgroup, overweight patients showed a non-significant trend (p= 0.053) for having AMS. HAPE-prone indigenous dwellers of the *Sierra* normally have a thin build which may explain their tendency toward underweight.

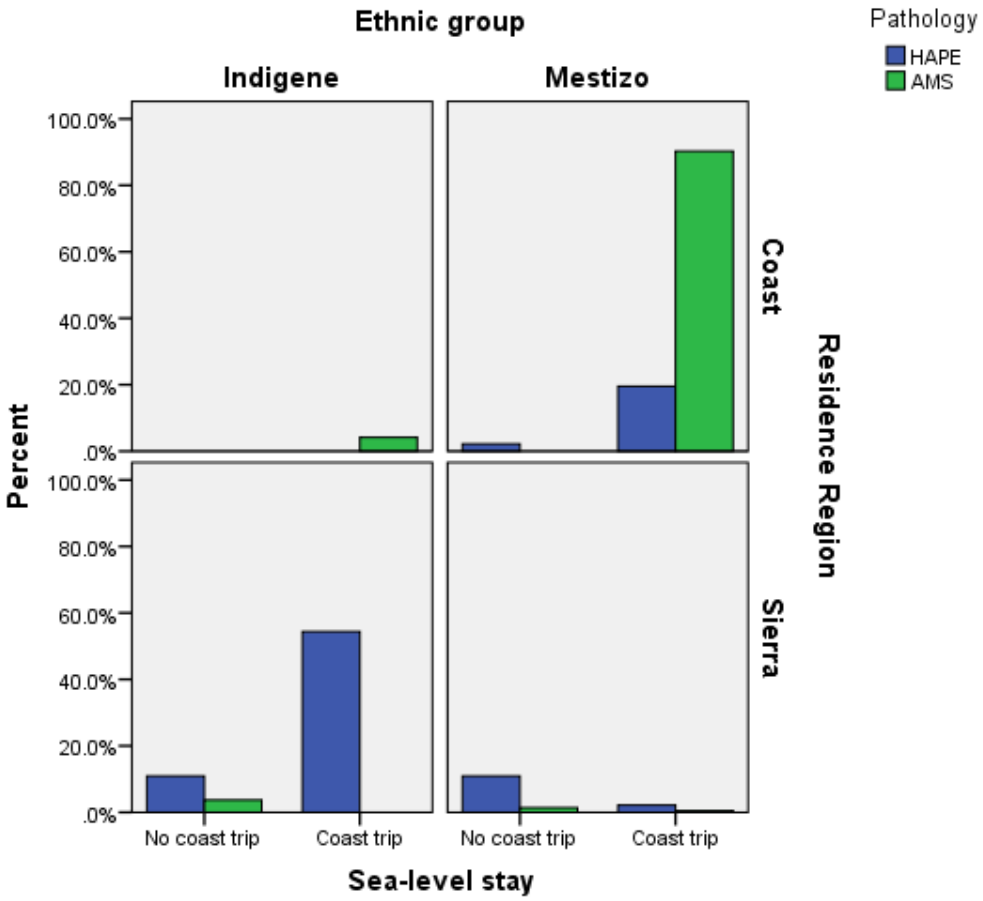

Figure 6. Two-variable (ethnic group vs. residence region) clustered bar charts of the distribution of AMS and HAPE prevalence contrasted against coast-trip antecedent. A recent stay at sea-level precipitated HAPE (the *re-entry HAPE*) just in the indigenous dwellers of the *Sierra*. By defect, Coast dwellers were considered as having a Coast trip before ascending to very HA.