

Prevalence, Clinical Profile, Iron Status, and Subject-Specific Traits for Excessive Erythrocytosis in Andean Adults Living Permanently at 3,825 Meters Above Sea Level

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BACKGROUND: Excessive erythrocytosis (EE) is a prevalent condition in populations living at high altitudes (> 2,500 m above sea level). Few large population-based studies have explored the association between EE and multiple subject-specific traits including oxygen saturation, iron status indicators, and pulmonary function.

METHODS: We enrolled a sex-stratified and age-stratified sample of 1,065 high-altitude residents aged ≥ 35 years from Puno, Peru (3,825 m above sea level) and conducted a standardized questionnaire and physical examination that included spirometry, pulse oximetry, and a blood sample for multiple clinical markers. Our primary objectives were to estimate the prevalence of EE, characterize the clinical profile and iron status indicators of subjects with EE, and describe subject-specific traits associated with EE.

RESULTS: Overall prevalence of EE was 4.5% (95% CI, 3.3%-6.0%). Oxygen saturation was significantly lower among EE than non-EE group subjects (85.3% vs 90.1%, $P < .001$) but no difference was found in iron status indicators between both groups ($P > .09$ for all values). In multivariable logistic regression, we found that age ≥ 65 years (OR = 2.45, 95% CI, 1.16-5.09), male sex (3.86, 1.78-9.08), having metabolic syndrome (2.66, 1.27-5.75) or being overweight (5.20, 1.95-16.77), pulse oximetry $< 85\%$ (14.90, 6.43-34.90), and % predicted FVC $< 80\%$ (13.62, 4.40-41.80) were strongly associated with EE. Attributable fractions for EE were greatest for being overweight (26.7%), followed by male sex (21.5%), pulse oximetry $< 85\%$ (16.4%), having metabolic syndrome (14.4%), and % predicted FVC $< 80\%$ (9.3%).

CONCLUSIONS: We found a lower prevalence of EE than in previous reports in the Peruvian Andes. Although the presence of hypoxemia and decreased vital capacity were strongly associated with excessive erythrocytosis, being overweight or having metabolic syndrome were associated with an important fraction of cases in our study population.

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ABBREVIATIONS: CMS = chronic mountain sickness; EE = excessive erythrocytosis; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MMRC = modified Medical Research Council; pro-BNP = pro-brain natriuretic peptide; TIBC = total iron-binding capacity

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Chronic mountain sickness (CMS) is defined as a clinical syndrome characterized by excessive erythrocytosis (EE), severe hypoxemia, neurologic symptoms, sleep disorders, and, in some cases, pulmonary hypertension leading to cor pulmonale. This clinical picture resolves after descending to lower altitudes and reappears upon return to high altitude. In 2005, the Committee on Chronic and Subacute High Altitude Diseases established the current defining parameters for EE as a hemoglobin concentration ≥ 21 g/dL in men and ≥ 19 g/dL in women.¹ Such high levels of hemoglobin are associated with increased blood viscosity and, thus, with a higher risk of developing heart failure and thromboembolic disease. The committee also identified major risk factors for CMS including: being male or a postmenopausal woman, previous history of CMS, sleep apnea, hypopnea, being overweight, and an inability to respond to hypoxia.¹

Approximately 140 million people worldwide live at altitudes $> 2,500$ m above sea level and are, therefore, at

risk to develop CMS.² In South America alone, 35 million people live above this altitude, primarily in Bolivia, Peru, Colombia, and Ecuador.¹ In contrast to the low prevalence of CMS and EE reported among Tibetans living at high altitudes, a higher prevalence has been historically described in South America, ranging from 5% to 18% depending on the population under study.³⁻⁵ The highest prevalence (34%) was found in Cerro de Pasco, Peru, at 4,300 m above sea level, in a group of miners aged ≥ 60 years.⁶

Although many studies have explored the relationship between high altitude, hemoglobin, and oxygen saturation, few have been undertaken in large, population-based studies. Moreover, the association between hemoglobin and iron status in normal subjects and EE participants is less well known.^{7,8} We sought to characterize the prevalence, clinical profile, iron status, and subject-specific traits for EE in a population living at 3,825 m above sea level.

Materials and Methods

Study Setting and Design

The study population was composed of adults aged ≥ 35 years living in Puno city (population 120,000) and surrounding nonmining rural communities at 3,825 m above sea level (Fig 1), located in the Puno Department in southwestern Peru. A large proportion of participants were of Aymaran ethnicity, the third largest ethnic group in Peru after mestizos (ie, mixed Amerindian and European ancestry) and Quechuas. Aymaran populations are mainly found in southern Peru and Bolivia. All participants provided verbal informed consent after our research team read the entire informed consent document to them and any questions were answered. Informed consents were verbal because sites included in this study are semiurban and rural with significant rates of illiteracy. All questionnaires were read aloud by trained field workers to study participants. Although most study participants were bilingual in Spanish and Aymara or Quechua, most of our team members were also

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bilingual and were able to perform the interview in Aymara or Quechua if necessary. The study was approved by the ethics committees of the Bloomberg School of Public Health (IRB2176), Johns Hopkins University (Baltimore, Maryland) and Universidad Peruana Cayetano Heredia (IRB55569) and Asociación Benéfica PRISMA (Lima, Peru).



Figure 1 – Location of Puno city, Peru.

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