UNIVERSITAT DE BARCELONA

Análisis de los efectos globales que ocasiona la hipoxia hipobárica crónica sobre el estado físico-emocional de los pobladores que residen en altitudes mayores a los 2,500 msnm

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Esteban Ortiz-Prado

TESIS DOCTORAL

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Sección de Fisiología

Memoria presentada por **Esteban Ortiz Prado**, Médico investigador, para optar al grado de Doctor por la Universidad de Barcelona. La presente tesis doctoral, "Análisis de los efectos globales que ocasiona la hipoxia hipobárica crónica sobre el estado físico-emocional de los pobladores que residen en altitudes mayores a los 2,500 msnm" se encuentra adscrita a la línea de investigación de Fisiología del programa de Doctorado en Biomedicina de la Universidad de Barcelona y ha sido realizada bajo la dirección del Dr. Ginés Viscor Carrasco, catedrático de la Sección de Fisiología del Departamento de Biología Celular, Fisiología e Inmunología, de la Facultad de Biología de la Universidad de Barcelona y del Dr. Manuel Calvopiña del Grupo de Investigación One Health de la Universidad de las Américas, en Quito, Ecuador y ha sido tutorizada por el Dr. Ginés Viscor Carrasco.

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Dedicatoria

Esta tesis está dedicada a mi esposa Ana Lucía Iturralde y a mis hijos, Antonio y Luana. Quienes con mucha paciencia han permitido que yo cumpla mis objetivos profesionales sabiendo que el tiempo dedicado a este trabajo de titulación ha sido significativo.

También dedico esta tesis a mi madre Ivonne a mi abuela materna Rebeca por su constante lucha en pro de mi bienestar desde que era un niño.

Finalmente dedico esta tesis, a mi tío Ciro, quien en vida fue siempre un dedicado montañista y apasionado de las grandes alturas quien me incitó a conocer el mundo de las montañas, los nevados y los paisajes andinos.

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Abstract

Background

On a planetary level, at least 200 million people of the world's population resides at high altitude. Living or visiting mountainous regions can lead to significant physiological changes among those visiting these places for short periods of time or lead to more chronic adaptive modifications among those who reside there for generations.

Human beings depend on the presence of oxygen for proper functioning and to maintain their physiological homeostasis. Under hypoxic conditions, adaptive long-term or compensatory short-term mechanism generate genetic, anatomical, physiological and in some cases pathological alterations among humans.

Objectives

In this sense, we have set ourselves the objective of studying the epidemiological impact of living above 2,500 m above sea level as well as studying the most evident physiological differences between two genotype-controlled indigenous populations residing at low and high altitude.

Results

Anthropometric differences

Our study shows that low altitude women tend to be shorter and heavier, but these differences are not statistically significant ($p = 0.333$), on the other hand, high altitude men are shorter than their counterparts who live at low altitude ($p = 0.019$). In relation to body composition,

women at high altitudes have less body muscle % (-24.8%) while men at high altitudes have significantly more muscle body mass % (+ 13.5%) than their lowland counterpart. Body fat % is lower among low altitude women (-15.5%) and no differences were found among men.

Hematological, lipid profile and cardiovascular risk differences

In the low altitude group, 66% were women (n = 78) and 34% (n = 40) were men, whereas in the high altitude group, 59% (n = 56) were women and 41% (n = 41%) were men. We found the proportion of overweight and obese individuals to be higher among low altitude dwellers ($p < 0.05$). Red blood cells (RBCs), hemoglobin concentration were higher among high altitude dwellers and the erythrocyte size was found to be smaller and SpO_2% lower at high altitude. The group located at low altitude also showed lower levels of plasma cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL).

Optimism and health self-perception

High-altitude dwellers presented lower scores in all the studied dimensions of SF-36. Significant differences were found for the Role limitation sphere due to Vitality (p = 0.005), Mental Health (p = 0.002) and social functioning (p = 0.005). In all the cases, participants living at low altitudes scored higher than those living at high altitude. Lowland women were more optimistic than their high-altitude counterparts

Lung function and spirometry parameters

People from Oyacachi (3.800 m) showed a higher predicted value than those from Limoncocha (230 m). The FVC and the FEV1 were significantly greater among highlanders than lowlanders (p value < 0.001). The FEV1/FVC was significantly higher among lowlanders than highlanders for men and women. A restrictive pattern was found in 12.9% of the participants.

Conclusions

Living at an altitude elicits well-known adaptive physiological changes such as erythrocyte count, hemoglobin concentration, hematocrit level, and serum glucose level. We also report clinical differences in the plasma lipid profile, with higher levels of cholesterol, HDL, and LDL in inhabitants of the Andes Mountain vs. their Amazonian basin peers.

The anthropometric differences vary according to sex, demonstrating that high altitude population are in general lighter and shorter than their low altitude controls. Men at high altitude have more muscled bodies than their lowland counterpart but their biological age was older than their corresponding chronological age. High altitude dwellers had greater lung capacity than their low-altitude peers, a finding physiologically plausible according to published literature. When analyzing the spirometry patterns obtained in these populations, it was evident that greater lung capacities are probably linked to bigger lungs, improving systemic oxygenation despite low oxygen availability.

Resumen

Antecedentes

A nivel planetario, al menos 200 millones de personas a nivel mundial residen en poblaciones ubicadas a grandes alturas. Vivir o visitar regiones montañosas puede provocar cambios fisiológicos significativos entre quienes visitan estos lugares durante cortos periodos de tiempo o provocar modificaciones adaptativas más crónicas entre quienes residen allí durante varias generaciones.

Los seres humanos dependen de la presencia, disponibilidad y utilización de oxígeno para funcionar correctamente y mantener la homeostasis fisiológica alrededor de la respiración. En condiciones de hipoxia, los mecanismos adaptativos a largo plazo o compensatorios a corto plazo generan alteraciones genéticas, anatómicas, fisiológicas y, en algunos casos, patológicas entre los seres humanos.

Objetivos

El objetivo de nuestro estudio ha sido doble: desde un punto de vista más general, el de estudiar el impacto epidemiológico que representa el vivir por encima de los 2.500 m sobre el nivel del mar, y, más detalladamente, estudiar las diferencias fisiológicas más evidentes entre dos poblaciones indígenas, genotípicamente idénticas que residen a baja y gran altura.

Resultados

Diferencias antropométricas

Nuestra tesis ha demostrado que las mujeres que residen a bajas alturas tienden a presentar tallas más cortas y mayor peso que sus pares de las grandes alturas, aunque estas diferencias no fueron estadísticamente significativas ($p = 0,333$). A su vez, los hombres que residen a grandes alturas son más bajos de talla que sus homólogos que viven a bajas alturas, siendo estos resultados estadísticamente significativos ($p = 0,019$). En relación con la composición corporal, las mujeres de las alturas tienen un porcentaje menor de músculo corporal (-24,8%), mientras que los hombres de la misma región tienen un porcentaje de masa corporal muscular significativamente mayor (+ 13,5%) que sus homólogos de bajas alturas. El porcentaje de grasa corporal fue menor entre las mujeres de las bajas alturas (-15,5%), mientras que entre los hombres no logramos encontrar diferencias estadísticamente significativas.

Diferencias hematológicas, de perfil lipídico y de riesgo cardiovascular

Al comparar estos parámetros, nuestros resultados nos demuestran que la proporción de individuos con sobrepeso y obesidad fue mayor entre los habitantes de las bajas alturas ($p < 0,05$). A la vez, el número de glóbulos rojos (RBC), la concentración de hemoglobina y la fueron significativamente más altos entre los habitantes de las grandes alturas, mientras que la saturación de oxigeno arterial (SpO_2%) y el tamaño de los glóbulos rojos resultaron ser menores entre pobladores de las grandes alturas.

Por otro lado, el grupo viviendo cerca del nivel del mar, mostró niveles más bajos de colesterol plasmático, lipoproteínas de baja densidad (LDL) y lipoproteínas de alta densidad (HDL).

Optimismo y autopercepción

Los habitantes de las zonas altas presentaron puntuaciones más bajas en todas las dimensiones estudiadas dentro de la encuesta de salud SF-36. Las diferencias estadísticamente significativas se encontraron dentro de la esfera de vitalidad ($p = 0{,}005$), Salud Mental ($p = 0{,}002$) y funcionamiento social ($p = 0{,}005$). En todos los casos, los participantes que vivían a bajas alturas puntuaban más que los que vivían a grandes alturas. Por otro lado, las mujeres de la amazonia, que residen a baja altura, resultaron ser más optimistas que sus homólogas de las grandes alturas.

Función pulmonar y parámetros ventilatorios

Los habitantes de Oyacachi (3,800 m) mostraron tener valores predictivos mayores que los habitantes de Limoncocha (230 m). Por ejemplo, la capacidad vital forzada (CVF) y el volumen espiratorio forzado en un segundo (VEF_1) fueron significativamente mayores entre los habitantes de las tierras altas que la de sus pares amazónicos (valor $p < 0{,}001$). El índice de Tiffeneau (VEF_1/CVF) fue significativamente mayor entre los habitantes de las bajas alturas que entre los que residen a mayor elevación, siendo esto evidente tanto en hombres como en mujeres.

Conclusiones

Vivir a grandes alturas se asocia a cambios fisiológicos adaptativos bien conocidos y descritos como son el recuento de eritrocitos, la concentración de hemoglobina o el nivel de hematocrito. Nuestros resultados también demuestran que existen diferencias clínicas en el perfil lipídico plasmático, teniendo niveles más altos de colesterol, HDL y LDL entre los habitantes de las grandes alturas.

Las diferencias antropométricas varían según el sexo y la edad. Nuestros hallazgos sugieren que la población que reside por sobre los 3,800 m es en general más ligera de peso y más baja en talla que la de sus pares de bajas alturas. Los hombres que residen a grandes alturas tienen cuerpos con mayores porcentajes de masa muscular que sus homólogos de las tierras bajas, pero en términos de edad corporal, los pobladores de las alturas resultaron ser mayores que los de las bajas alturas.

Los habitantes de las grandes alturas tuvieron mayor capacidad pulmonar que la de sus pares de las bajas alturas. Al analizar los patrones espirométricos obtenidos en estas poblaciones, resultó evidente que las mayores capacidades pulmonares están probablemente relacionadas con pulmones más grandes, lo que mejora la oxigenación sistémica a pesar de la baja disponibilidad de oxígeno.

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Abreviaciones

5-HTP: 5-hidroxitriptófano

ACV: Accidente cerebrovascular

AIT: Ataque isquémico transitorio

AtmPO2: Presión parcial de oxígeno atmosférica

BP: Dolor corporal

BP: Presión barométrica

CBF: Flujo sanguíneo cerebral

CMR: Tasa metabólica cerebral

ECV: Enfermedades cardiovasculares

EP: Embolia pulmonar

EPOC: Enfermedad pulmonar obstructiva crónica

ESE: Estatus socioeconómico

FEV_1: Volumen espiratorio forzado en el primer segundo

FiO2: Fracción de oxígeno inspirado

FVC: Capacidad vital forzada

GH: Salud general

HAP: Poblaciones de grandes alturas

HC: Cambio de salud

HDL: Lipoproteínas de alta densidad

HRQOL: Escalas de calidad de vida relacionadas con la salud general.

HS: Ictus hemorrágico o hemorragia cerebral

HVR: Respuestas ventilatorias hipóxica

IM: Infarto del miocardio

IMC: Índice de masa corporal

INEC: Instituto Ecuatoriano de Estadísticas y Censos

IS: Accidente cerebrovascular isquém[1]ico

LDL: Lipoproteínas de baja densidad

MAM: Mal agudo de Montaña

MH: Salud mental (bienestar emocional)

mmHg: milímetros de mercurio

MRI: Imágenes de resonancia magnética

MSP: Ministerio de Salud

PF: Funcionamiento físico

APO_2: Presión parcial de oxigeno atmosférico

PAO_2: Presión parcial de oxigeno alveolar

PO_2: Presión parcial de oxigeno

$PACO_2$: Presión alveolar de dióxido de carbono

PtO_2: Presión parcial de oxígeno en los tejidos

PVO_2: Presión parcial de oxígeno capilar venoso

RBC: Glóbulos rojos

RE: Funcionamiento del rol/emocional

RF: Funcionamiento del rol/emocional

SF: Funcionamiento social

TC: Tomografía axial computarizada

TCV: Trombosis cerebral venosa

Test LOT-R: Test de Orientación Vital-Revisado.

TVP: Trombosis venosa profunda

VS: Vitalidad (energía/fatiga)

1. Introducción:

A nivel planetario, al menos el 5.7 % de la población vive por encima de los 1,500 m de altura (Imray et al., 2011; Tremblay and Ainslie, 2021). En esa lógica, el estar expuesto a grandes alturas nos expone no solamente a condiciones climatológicas extremas sino también a una baja de la presión barométrica a nivel atmosférico que afecta la disponibilidad de oxígeno a través de la disminución de la presión parcial de este gas (Ortiz-Prado et al., 2019a).

La exposición aguda y crónica a la altura tiene múltiples efectos sobre la morfo-fisiología del ser humano, tanto a corto como a largo plazo (Moore, 2017a). El exponerse a diferentes alturas se asocia a una disminución de la presión parcial de oxígeno atmosférico (APO_2), una disminución consecutiva de la presión parcial de oxigeno arterial (PaO_2) y por ende una baja de la disponibilidad de oxígeno a nivel tisular y celular (PtO_2) (Ortiz-Prado et al., 2019a).

Cuando un ser humano se expone a situaciones en las cuales la presión barométrica disminuye, de acuerdo a la ley de Dalton, la presión parcial de oxígeno en la atmósfera disminuye y con esto el gradiente de presión que termina finalmente por entregar el oxígeno desde la atmósfera hasta las células. Cuando una persona se expone de manera aguda a estas condiciones necesita cierto tiempo para aclimatarse, sin embargo en personas expuestas crónicamente y que dispusieron de más tiempo para sobrellevar las adversidades fisiológicas, y que además descienden de pobladores de las grandes alturas, tras muchas generaciones, estamos hablando de una etapa de adaptación a la altura (Moore, 2017a).

Las diferencias en términos de adaptación en aquellas poblaciones que viven o visitan lugares ubicados a mayor altitud, ha sido de curiosidad e intriga de varios cientos de pensadores, investigadores y científicos desde hace más de 5 siglos. En la siguiente sección, haremos una reseña histórica de lo que es la fisiología de la altura y la medicina de alta montaña, para de esta forma poder entender; todos los aspectos relacionados a la importancia del estudio de estas poblaciones

1.1 Historia de la medicina de alta montaña y de la altura

La historia de la medicina de alta montaña y la fisiología de la altura es una de las ramas de la historia de la medicina menos estudiada, no solamente por lo remoto de aquellos lugares en épocas pasadas, sino también por la baja densidad poblacional que históricamente ha afectado a estas zonas montañosas (Cohen and Small, 1998). A pesar de las pocas referencias anecdóticas en relación con las destinas investigaciones biomédicas llevadas a cabo en las alturas antes del año 1500, Jhon B. West, Robert B. Schoene y James S. Milledge han logrado resumir de manera sucinta los principales hitos históricos alrededor de la medicina de las grandes alturas (West et al., 2007).

En su libro dedicado específicamente al estudio de la vida bajo condiciones de hipoxia, ellos hacen una reflexión alrededor de los principales logros de un grupo de pensadores, que lograron aportar con datos, a lo que sería en un futuro las bases de la medicina de altura. Por ejemplo, José de Acosta describe, lo que parecería ser el primer análisis del mal agudo de montaña entre personas que estaban cruzando los Andes suramericanos alrededor del año 1590.

Décadas después, Evangelista Torricelli fue el primer científico que creó una suerte de instrumento que recreaba un vacío sostenido y de esta forma; descubrió el principio de un barómetro de mercurio hacia 1644.

Con la llega del barómetro, un sin número de hallazgos e inventos verían la luz. En 1660, Robert Boyle y Robert Hooke empezaban a estudiar los efectos fisiológicos del aire, investigaciones que dieron lugar a lo que luego sería una ley física que llevaría su nombre.

Antoine-Laurent Lavoisier, un observador ensayador del siglo XVIII, revolucionó la química para siempre. El estableció la ley de conservación de la masa, determinó cuales son los factores alrededor de la combustión y la respiración, cuyas reacciones químicas darían lugar a lo que el posteriormente llamó "oxígeno". Con estas bases establecidas, varias intrigas fueron generando una serie de eventos que verían como lugar, por ejemplo, la investigación de los efectos deletéreos que podían tener los globos aerostáticos en aquella época. A su vez, y a medida que la escalada de montaña se empezaba a hacer popular en el siglo XIX, los reportes de los efectos negativos de la altura sobre el cuerpo empezaban a hacerse más frecuentes. A partir de este siglo se ha llevado a cabo en Francia e Italia numerosas investigaciones sobre la fisiopatología de la altitud y muchos médicos que se han dedicado a la medicina de montaña y la fisiología de la altura. A parte del Observatorio Vallot en Francia, otros dos lugares fueron usados como laboratorios naturales para el estudio de la altura, siendo estos el "Angelo Mosso" en el Monte Rosa (Capanna Regina Margherita y Laboratorio Angelo Mosso), y la "Pirámide" en Nepal (Cogo et al., 2000).

A principios del siglo XX, varias expediciones especiales desarrolladas a grandes alturas comenzaron a estudiar distintas variables médicas y fisiológicas. Muchos científicos y fisiólogos, fueron parte de la importante expedición "Pikes Peak" de 1911 (West, 1998; Bärtsch, 2002). Años después, Sir Edmund Hillary y Tenzing Norgay se convertían en los primeros seres humanos en haber escalado el monte Everest a mediados del año 1953. Este hito dio inicio a una serie de expediciones a distintas locaciones ubicadas a grandes alturas para comprender mejor los efectos de la hipoxia hipobárica sobre la fisiología humana; a la vez, importantes hallazgos se realizaban en ambientes controlados que simulaban condiciones de hipoxia (Houston, 1997).

Finalmente, en tiempos más contemporáneos, la fisiología de la altura y la medicina de alta montaña alcanzado niveles extraordinarios. Según el portal de búsqueda del instituto nacional de salud de los estados Unidos (NIH), al menos 20,000 trabajos científicos ha sido publicados en torno al término "*high altitude"*. Estas investigaciones han incluido estudios experimentales *in vivo* o *in vitro,* así como también miles de estudios epidemiológicos, para finalmente encontrarnos en el uso de la inteligencia artificial y la genómica avanzada para completar la gama de estudios con aquellos desarrollados *in sillico*, siendo estos los encargados de analizar los aspectos menos conocidos de la biología molecular de la hipoxia (Eichstaedt et al., 2015, 2020; Jha et al., 2021).

1.2 Efectos de la hipoxia hipobárica sobre el cuerpo humano

En esta sección, nosotros hablaremos sobre los efectos generales y específicos que tiene la hipoxia sobre el cuerpo humano. Empezaremos describiendo las características principales alrededor del intercambio gaseoso entre el oxígeno atmosférico y el CO_2 sistémico, y terminaremos hablando sobre los efectos deletéreos de la hipoxia y la capacidad del cuerpo para aclimatarse o adaptarse.

1.3 Gradiente de presión de oxígeno en el cuerpo humano

Cuando un ser humano se expone a situaciones en las cuales la presión barométrica disminuye, la presión parcial de oxígeno en la atmósfera disminuye y con esto el gradiente de presión que termina finalmente por entregar el oxígeno desde la atmósfera hasta las células.

El cuerpo humano, aerobio por naturaleza, al exponerse a diferentes concentraciones de oxígeno inspirado, a través de la administración de cualquier mezcla de gases, responderá a la cantidad de oxígeno disponible dentro de los alveolos. Es decir, una baja presión parcial de oxígeno a nivel alveolar (PAO_2) generará una respuesta compensatoria a nivel pulmonar y cardiaco en búsqueda de la mantener el equilibrio en la entrega de oxígeno a los tejidos. Esta presión de oxigeno (y de cada uno de los gases inspirados) dependerá de la concentración que cada gas tiene y por ende, la sumatoria de todos ellos generara una presión determinada en función de la concentración de cada uno de los gases (Gill and Bell, 2004). En términos generales, los cambios en la presión barométrica (BP) y la fracción de oxígeno (FiO_2) suministrada arbitrariamente dentro de la vía aérea son los métodos más utilizados para cambiar artificialmente la presión parcial de oxigeno arterial (PaO_2) que determina el estado de oxigenación del organismo (West, 1993, 2006; Ortiz-Prado et al., 2010).

1.3.1 Presión parcial de oxigeno atmosférico (APO_2)

El ser humano depende del oxígeno para sobrevivir y este gas se adquiere de la atmósfera donde la presión parcial de oxígeno varía según la presión barométrica, afectando así a la presión atmosférica de oxígeno ($AtmPO_2$) según la siguiente fórmula (sin considerar la presión de vapor de agua):

$$_{Atm}PO_2=0.21\ (760) = 159\ mmHg$$

Los seres humanos, al desplazarse constantemente por su hábitat geográfico, están expuestos a diferentes niveles de presión barométrica, lo que afecta a la presión del oxígeno al menos dentro de la troposfera (Figura 1).

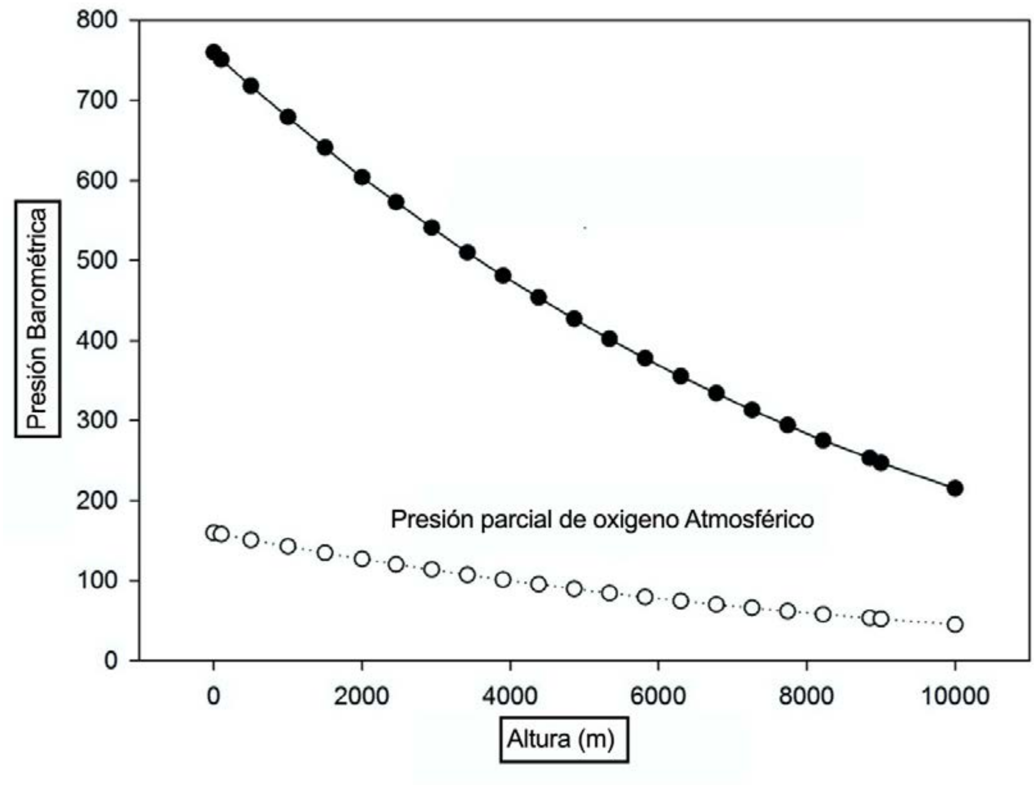

Figura 1 Presión parcial de oxigeno atmosférico versus presión barométrica. Adaptado de Ortiz-Prado et, al 2019

1.3.2 Presión parcial de oxigeno alveolar (PAO_2)

Una vez que el aire inspirado se calienta y se humedece en la nariz y la tráquea, la PO_2 disminuye. Esta reducción es causada por la adición de vapor de agua a toda la mezcla de gases (47 mmHg), reduciendo así, la presión de los otros gases (Hall, 2016).

Debido a este gradiente de presión, a nivel del mar la reducción representa aproximadamente el 6 % de la $AtmPO_2$ total. Es probable que esta reducción de la presión parcial alveolar de oxígeno (PAO_2) de 159 a 149 mmHg no sea fisiológicamente relevante a nivel del mar (Ortiz-Prado et al., 2019a). Sin embargo, cuando la BP ya es baja, como en la cima del Monte Everest (8.848 m de altitud), una reducción de 47 mmHg (presión de vapor de agua) representa casi el 20% de la $AtmPO_2$ disponible, lo que hace se traduce a una marcada diferencia entre la sobrevivencia y la muerte en la famosa zona de la muerte (West and Wagner, 1980; West et al., 1983).

Una vez que el aire inspirado se ha humedecido en la vía aérea, una reducción adicional de la PO_2 es evidenciada debido al espacio muerto anatómico y al espacio muerto fisiológico pulmonar por la mezcla de gas inspirado con el expirado (Hall, 2016). Esta caída de la presión de oxígeno desde las vías superiores hasta el alvéolo se explica casi en su totalidad por la presión alveolar de dióxido de carbono ($PACO_2$) (Möller et al., 2015). Dado que la PCO_2 inspirada es cero bajo condiciones normales, el oxígeno se transporta desde el alveolo a la sangre capilar pulmonar gracias al gradiente de presión, al mismo tiempo que el CO_2 entra en los alvéolos para ser expulsado a una atmosfera con baja PCO_2 (Hall, 2016).

La presión parcial de oxígeno alveolar (PAO_2) en la barrera alveolo-capilar a nivel del mar se calcula mediante la siguiente ecuación:

$$PAO_2 = FiO_2 (PB-47) - 1.2 (PACO_2)$$

1.3.3 Presión parcial de oxigeno arterial (PaO_2)

Los pulmones extraen el oxígeno de la atmósfera y la barrera alveolo-capilar transporta el oxígeno de los pulmones a la circulación capilar con menor PO_2 y mayor PCO_2. El gradiente de difusión inicial de las presiones en la circulación surge cuando la sangre capilar arterial (PaO_2) con una mayor presión de oxígeno se mezcla con la sangre capilar venosa (PVO_2) con menores presiones de oxígeno (Mayer et al., 2016). La velocidad de difusión del oxígeno a través de la membrana alvéolo-capilar, además de una eliminación más rápida y fácil del CO_2, asegura que la PaO_2 capilar sea casi igual a la PO_2 alveolar (Ortiz-Prado et al., 2019a). En condiciones normales, a nivel del mar, la presión parcial arterial de oxígeno (PaO_2) oscila entre 75 y 100 mmHg, sin embargo, cuando una persona se expone de forma aguda a distintas alturas, el gradiente de presión disminuye (Figura 2) (Hall, 2016).

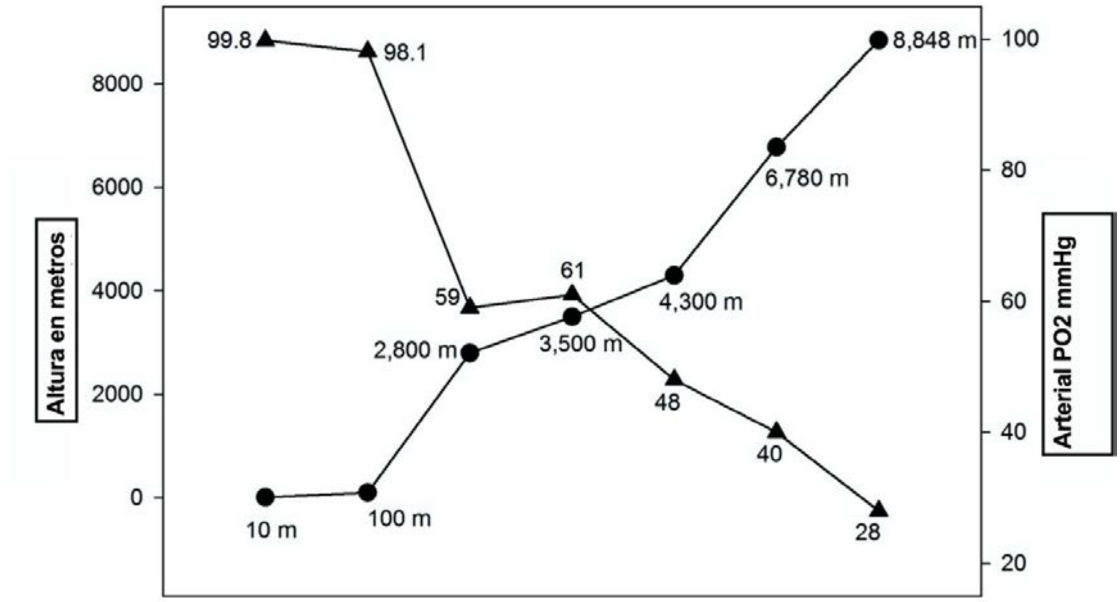

Figura 2 Altitud ganada en metros versus presión parcial de oxigeno arterial en seres humanos. Adaptado de Ortiz-Prado 2019

1.3.4 Presión parcial de oxigeno tisular (PtO_2) e intracelular

Una vez que el oxígeno ha llegado a los capilares arteriales, la diferencia de presiones (gradiente de presión) entre el capilar y los tejidos ávidos de oxígeno, permite que este gas difunda a través de la matriz extracelular, generando un último gradiente entre el tejido y el interior de la célula. En condiciones normales, los tejidos tienen rangos de PtO_2 que varían de los 8 mmHg en la epidermis, hasta más de 50 mmHg en la medula ósea (Ortiz-Prado et al., 2019a).

En condiciones normales, la única situación en la que la presión parcial de oxígeno en los tejidos de la célula disminuye, es cuando existe una demanda elevada debido a un incremento en la utilización de energía oxidativa, como cuando ocurre durante el ejercicio intenso. Sin embargo, en situaciones de las cuales existe una disminución de la oferta de oxígeno desde la atmosfera hacia la mitocondria (grandes alturas), el cuerpo tiene que adaptarse o aclimatarse a estos cambios y de esa forma, sobrellevar de mejor manera, la baja disponibilidad de oxígeno a nivel ambiental (Dunn et al., 2000; Gaur et al., 2021).

1.4 Hipoxia, anoxia e isquemia.

Una vez que los tejidos no logran equilibrar la oferta versus la demanda de oxígeno, los tejidos, las células y la mitocondria pueden entrar en un estado de baja disponibilidad, oferta, consumo o utilización de oxígeno, situación que podría resumirse como hipoxia. En esta lógica, es muy dificultoso describir lo que en términos generales significa la hipoxia, ya que existen varias definiciones, tipos y clasificaciones (Span and Bussink, 2015).

En los siguientes párrafos, haremos un esfuerzo para resumir de manera práctica, una definición ampliamente usada del balance oferta/demanda de oxígeno e incluiremos una clasificación resumida de la anoxia y la hipoxia.

1.4.1 Definición de la hipoxia

Etimológicamente hablando, el termino hipoxia se refiere a la conjunción de la palabra formadora hipo que significa "debajo, debajo; menos, menos que" y que viene del griego hypo (preposición. y adverbio) "debajo, debajo; arriba de debajo; hacia y debajo (es decir, dentro)" junto a la palabra oxigeno (RAE, 2001). En términos prácticos, describimos la hipoxia como la reducción de la concentración, la cantidad o la disponibilidad de oxígeno que afecta una célula, un grupo de células, un tejido específico, un órgano o todo el organismo en su conjunto (Ortiz-Prado, 2010).

Debido a la complejidad en describir el termino hipoxia sin entrar en simplicidades, describiremos a continuación la clasificación más usada para entender el concepto de hipoxia desde una visión etiológica.

1.4.1.1 Hipoxia hipoxémica

La hipoxia hipoxémica se define como los niveles subnormales de oxígeno en sangre debido a una reducción de la presión parcial de oxígeno (PaO_2) en la circulación arterial. Este tipo de hipoxia suele atribuirse a una reducción en la entrada de oxigeno por vía pulmonar, posiblemente debida a una inadecuada ventilación pulmonar o a una disponibilidad deficiente del oxígeno inspirado (FiO_2).

1.4.1.2 Hipoxia anémica

Este tipo de hipoxia está causado por una reducción de la capacidad de transporte de oxígeno de la sangre. Al ser los glóbulos rojos quienes transportan mayoritariamente el oxígeno en la sangre, una reducción marcada en el hematocrito y por ende la hemoglobina ocasionara una baja en la PO_2 arterial pero no por falta de oferta, sino por demanda insatisfecha debido al inadecuado transporte. Este subtipo de hipoxia puede incluir varias causas, entre ellas hemorragias masivas, deficiencias de hierro o falta de algunas de las vitaminas del complejo B, la intoxicación por monóxido o dióxido de carbono, la anemia de células falciformes y en casos más raros, alguna reducción de la capacidad intrínseca de la hemoglobina para ligarse al oxigeno como sucede en la metahemoglobinemia (Pastor, 2000; Samuel and Franklin, 2008; Feiner et al., 2010).

1.4.1.3 Hipoxia histotóxica

La hipoxia histotóxica es una causa muy rara, pero potencialmente mortal de un evento patológico que se caracteriza por una incapacidad para la utilización del oxígeno disponible a nivel celular y mitocondrial (Lloyd JR, 1965; Gibson et al., 1991; Aboul-Enein and Lassmann, 2005). Este tipo de hipoxia está causada por el efecto directo de algunos agentes tóxicos como el cianuro o el cobalto que afectan la respiración celular, caracterizándose por una incapacidad de usar el oxígeno disponible que en condiciones generales no se ha visto afectado (McAllister et al., 2020).

1.4.1.4 Hipoxia estagnante o hipoxia isquémica

La hipoxia isquémica o estagnante tiene mecanismos de acción potencialmente reversibles pero consecuencias potencialmente graves debido a su etiología (Lin et al., 1998; Nair and Kumar, 2018). La fisiopatología y el desarrollo de la hipoxia isquémica se inician por la restricción en el suministro de sangre a un grupo de células, un tejido, un órgano o una parte del cuerpo, provocando una interrupción parcial o completa del suministro de sangre y oxígeno hacia dicho territorio (Greco et al., 2020). Las causas principales o más conocidas de hipoxia isquémica suelen ser mecánicas, sin embargo, varias condiciones que afectan al gasto cardíaco o a la regulación del flujo sanguíneo local pueden causar una alteración del equilibrio entre el suministro y el consumo de consumo de oxígeno (Ortiz-Prado, 2010).

Algunas de las causas principales asociadas a estas alteraciones del suministro de oxígeno incluyen al paro cardio-respiratorio, la hipotensión severa, algún tipo de malformaciones vasculares, la aterosclerosis, la trombosis, la embolia o algunas otras alteraciones vasculares sistémica (Li et al., 2017; Greco et al., 2020).

1.4.2 Definición de la anoxia

En términos generales el prefijo "A" viene del latín "sin", En ese sentido textualmente describiendo anoxia, podemos decir que es la ausencia de flujo sanguíneo que ocasiona una presión parcial de oxígeno de cero (0 mmHg). En ese sentido, la anoxia rápidamente se convierte en isquemia si el flujo sanguíneo no es restituido, o en términos experimentales, la presión parcial de oxigeno fuera de los tejidos no se restituye.

1.4.3 Daño celular causado por hipoxia o anoxia

Los mecanismos bioquímicos del daño celular durante la hipoxia, posterior anoxia y la potencialmente remediable isquemia, generan eventualmente muerte celular. Los órganos más afectados son en general aquellos susceptibles a la hipoxia, tal cual sucede con el corazón, el cerebro, el intestino o el riñón, que son los órganos más estudiados en términos de anoxia, brindando información valiosa alrededor de este tema (Grace, 1994; Carden and Granger, 2000; Cox and Gillis, 2020).

1.5 La hipoxia debida a la exposición a las grandes alturas.

El vivir o visitar lugares montañosos o aquellos ubicados a grandes alturas, está asociado con una baja progresiva de la presión barométrica (BP). Esta disminución, que es inversamente proporcional a la ganancia de elevación, ocasiona una baja constante de la presión de oxígeno en la atmosfera y en el resto del gradiente de presión (Ortiz-Prado, 2010).

En esa lógica, el cuerpo humano se expone de forma aguda o crónica ante un ambiente con una menor presión parcial de oxígeno atmosférico; que ocasionará, una baja en la disponibilidad de oxígeno a nivel fisiológico. Esta baja fisiológica se debe a la baja disponibilidad y utilización de oxígeno, ya que la concentración de este gas en la atmosfera es la misma a cualquier elevación siempre y cuando este dentro de la troposfera (20.946%) (USA, 1976).

El impacto que puede tener la exposición a las grandes alturas (hipoxia hipobárica) pueden ser también simulados en lugares no necesariamente ubicados en zonas montañosas, sino en laboratorios con la capacidad de reducir la presión barométrica (hipoxia hipobárica) o de reducir la FiO_2 ocasionando un ambiente con una reducida concentración de oxigeno (hipoxia normobárica) aunque actualmente se debate acerca de si ambos sistemas son estímulos fisiológicos equivalentes (Millet et al., 2012).

Independientemente del origen de la hipoxia, es vital considerar que la exposición rápida, aguda y que dura menos de 28 días, especialmente en personas no adaptadas, puede aumentar el riesgo de desarrollar no solo enfermedad aguda de montaña, sino también otras patologías asociadas a la hipoxia (Khan and Katramados, 2010; Khattar et al., 2019). Si la exposición es crónica (> 28 días) las probabilidades de aclimatarse aumentan considerablemente, generando una mejor respuesta a estas condiciones adversas (Lundby et al., 2018; Gaur et al., 2021).

A la vez, se calcula que un grupo poblacional que rodea los 150 a 200 millones de personas viven y residen permanentemente por sobre los 2,500 m de altura, habiendo descendido de ancestros adaptados a la altura. Es decir, esta población ha adquirido una serie de ventajas evolutivas que les permiten funcionar mejor en situaciones de hipoxia hipobárica (Moore, 2017a; Tremblay and Ainslie, 2021). Sin embargo, no todos se hallan igualmente adaptados a la altura, ya que la datación, un largo tiempo de colonización de ese ambiente, es necesario para establecer características genéticas específicas que permiten una fisiología optimizada en dichas condiciones.

Con esta lógica, las diferencias fisiológicas que caracterizan a las personas adaptadas a la altura pueden imponer ciertas diferencias respecto de los abajeños. Así, varias patologías o enfermedades se han asociado con una mayor incidencia y prevalencia en pobladores que viven a grandes alturas, sin embargo, otras patologías o entidades nosológicas han sido reportadas como menos frecuentes en aquellos pobladores que residen, usualmente por encima de los 2,500 m de altura (Al-Huthi et al., 2006; Brenner et al., 2011; Ezzati et al., 2012; Ortiz-Prado et al., 2021a).

1.6 Respuesta fisiológica y adaptativa a la altura

La exposición a un ambiente donde la presión parcial de oxígeno ha disminuido considerablemente ocasiona una disminución en la disponibilidad relativa del oxígeno alveolar, arterial, tisular y finalmente celular (Dunn et al., 2000; Ortiz-Prado et al., 2019a; Gaur et al., 2021).

Bajo estas condiciones, los humanos respondemos con ajustes fisiológicos de emergencia lo suficientemente eficaces para permitirnos la capacidad de aclimatarnos a cambios bruscos y para darle tiempo al sistema cardiorrespiratorio de regular la entrega de oxígeno a los tejidos mientras se inician una serie de señales bioquímicas y hormonales que tienen como fin el tratar de contraponerse a los efectos de la hipoxia a la cual el cuerpo humano se ve sometido (Hall, 2016).

1.2.1 aclimatación a la altura

La aclimatación se la puede definir como aquel estado fisiológico que le permite al organismo regular sus procesos internos y homeostáticos con el fin de mantener un determinado nivel de capacidad funcional y que no se trasmite de generación en generación (Ortiz-Prado, 2010). Así pues, la aclimatación es transitoria, es decir, los cambios inducidos duran el tiempo al cual el organismo se expone al estímulo.

La aclimatación a la altura, mejora el suministro de oxígeno dentro de los tejidos, especialmente aquellos tejidos más susceptibles a la hipoxia, como son el cerebro o el corazón (Ainslie and Burgess, 2008). Durante la exposición aguda a presiones barométricas bajas, la reducción de la PO_2 constituye el mayor desafío para nuestro organismo.

Entre seres humanos y otros mamíferos no aclimatados, el primer mecanismo compensatorio es un marcado aumento de la frecuencia respiratoria (Busch et al., 1985; Reeves et al., 1993; Powell et al., 2000; Ivy and Scott, 2017). La respuesta ventilatoria hipóxica aguda (HVR) es un mecanismo que desencadena la hiperventilación durante un cuadro de hipoxia, de manera similar, pero a través de diferentes mecanismos, que la respuesta de hiperventilación causada por la hipercapnia (Moore et al., 1986; Buchholz et al., 2020).

Una reducción marcada en la presión parcial de oxígeno atmosférico (APO_2) se traducirá en una baja de la presión parcial de oxígeno arterial (PaO_2). La presencia disminuida de oxígeno a nivel arterial es detectada por los quimiorreceptores ubicados en los cuerpos aórticos y carotídeos (Siebenmann et al., 2019; Niewinski et al., 2021). Estos sensores químicos, despiertan una cadena de eventos nerviosos que terminan con la conducción de señales eléctricas hacia el centro respiratorio, que posteriormente retroalimentan a los músculos de la respiración, para aumentar de esta forma la fuerza, profundidad y frecuencia ventilatoria (Hall, 2016; Lindsey et al., 2018). Éstos quimio receptores periféricos, detectan no solamente los niveles de oxígeno en la sangre arterial, sino también los del dióxido de carbono y la cantidad de hidrogeniones (H^+) circulantes por la misma sangre.

En condiciones normales, un individuo no aclimatado podrá desencadenar una serie de mecanismos compensatorios temporales de la mano de un aumento de la frecuencia cardiaca y ventilatoria principalmente (Ainslie and Burgess, 2008). Sin embargo, días después de la primera exposición, estas respuestas poco sostenibles desde el punto de vista del coste energético y del gasto cardíaco, por lo que empiezan a disminuir mientras otros mecanismos más efectivos a largo plazo empiezan aparecer (León-Velarde et al., 2000).

Por ejemplo, después de 4 a 5 días en promedio tenemos la disminución de la frecuencia cardiaca y respiratoria en personas que visitan de forma aguda en las grandes alturas, mientras la producción de eritropoyetina empieza aumentar gradualmente, hasta lograr que, en 14 días en promedio, la cantidad de glóbulos rojos aumente significativamente (Winslow, 1984).

Cuando un ser humano se expone de forma rápida, sin dar tiempo al proceso de aclimatación, se puede presentar una serie de alteraciones patológicas que podrían indicar que la relación entre demanda y oferta ha sido excedida. El mal agudo de montaña, es una condición que afecta a hombres y mujeres generalmente sanos que ascienden de forma rápida a altitudes que no acostumbran a experimentar. Los síntomas, que aparecen pocas horas tras el acenso incluyen la cefalea, la náusea, la anorexia o falta de apetito, el cansancio, el malestar general y las alteraciones en el sueño (Roach et al., 2018).

Estos síntomas suelen aparecer entre 8 y 24 horas después de ascenso agudo a un nuevo lugar de gran altitud, pero suelen ser peores en el segundo y tercer día (Berger et al., 2020). En condiciones generales, si la persona desciende nuevamente altitudes menores a las que desencadenaron el mal agudo de montaña (MAM), los síntomas de signos empiezan a desaparecer espontáneamente, sin embargo, en un grupo pequeño de personas que permanecen a grandes alturas los síntomas pueden evolucionar hacia otras formas más severas de enfermedad.

El edema pulmonar de altura (HAPE) y el edema cerebral de altura (HACE) son potencialmente letales y se caracterizan por ser la forma más grave de enfermedades de altitud, y no siempre están precedidas por el MAM. Aunque la fisiopatología de estos procesos no se conoce con exactitud, distintas respuestas biomoleculares y hormonales desencadenan una serie de respuestas medidas por el VEG-F, el óxido nítrico, algunas citoquinas reactivas o por la presencia de radicales libres; dando como resultado alteraciones hemodinámicas que causan vasodilatación cerebral y pulmonar, aumento de la perfusión vascular y daño micro vascular que puede terminar en edema (Jensen and Vincent, 2021).

Aunque la incidencia del MAM depende de la velocidad de ascenso y de la altura alcanzada, es muy poco frecuente por debajo de los 2.000 m, sin embargo, no solo la altura es uno de los factores determinantes de su aparición, sino factores intrínsecos de las distintas poblaciones. Factores genéticos relacionados con los diferentes mecanismos adaptativos podrían estar ligados a la aparición o no de estas condiciones. Por ejemplo, existe una heterogeneidad en la aparición de síntomas relacionados al MAM o el mal crónico de montaña (MCM) entre los pobladores andinos y aquellos que residen en los Himalaya (Pei et al., 1989; Beall, 2006; Espinoza et al., 2014; Tang et al., 2014). Extensa cantidad de literatura ha sido publicada sobre este tema y radica principalmente en componentes genéticos, anatómicos y fisiológicos que determina que una población sea más susceptible que otra a este tipo de cuadros.

1.2.2 Adaptación a la altura

La adaptación es el proceso por el que un determinado organismo se ajusta mejor a su entorno en términos fisiológicos, genéticos o inclusive anatómicos (Ortiz-Prado, 2010). Este proceso tiene lugar como resultado de la selección natural a lo largo de la exposición continua, de generación en generación, que le confiere al organismo adaptado, algún tipo de beneficio evolutivo o una mayor "aptitud" para sobrevivir (Moore et al., 2002; Moore, 2017a). Es decir, es un proceso que deriva de la presión ejercida en una especie o población por la selección natural. Tal cual como sucede para otras características, la adaptación a las alturas (o a la hipoxia hipobárica) se expresa genéticamente y se transmite de una generación a otra (Beall, 2007).

Estas adaptaciones o cambios adaptativos incluyen alteraciones a todos los niveles, pudiendo inclusive ser evidentes desde el punto de vista anatómico, genético y fisiológicos, difiriendo de una población a otra, dependiendo del tiempo transcurrido desde la colonización de las alturas en diferentes áreas de nuestro planeta, como las tierras altas de África Oriental, las altas mesetas del Asia Central y el altiplano andino, y por consiguiente, del tiempo disponible para la adaptación en la historia natural de la especie humana (Moore, 2001; Ortiz-Prado, 2010; Moore, 2017a).

Las diferencias entre poblaciones residentes a bajas versus grandes alturas han sido ampliamente descritas en lo referente a la función ventilatoria, cardiovascular, muscular, neurológica, hematológica y con menos frecuencia, a la psicológica disposicional (Hartley, 1971; Beall et al., 1997; Moore et al., 2002; Naeije, 2010; Crawford et al., 2017; Álvarez-Herms et al., 2020).

En lo referente a la variabilidad anatómica y morfológica, son pocos los estudios que de manera bien controlada, han demostrado diferencias significativas en relación a las variables antropométricas (Leatherman et al., 1984; Fulco et al., 1985; Yanamandra et al., 2019). Los cambios que más se ha descrito son tallas cortas entre pobladores de los Andes, menos índices de sobrepeso y obesidad y cajas torácicas más anchas y profundas (Monge, 1937; Hurtado, 1978; Fiori et al., 2000a; Toselli et al., 2001). A la vez, cuando analizamos los efectos que tiene la altura y la hipoxia crónica en las distintas poblaciones sobre el comportamiento humano en relación con la autopercepción o el optimismo disposicional, desde las esferas psicológicas, físicas y emocionales, así como de su visión personal sobre el futuro, vemos que no hay estudios que hayan logrado identificar diferencias significativas en términos de autopercepción u optimismo entre pobladores de las grandes alturas. Sin embargo, la altura geográfica y las condiciones meteorológicas pueden afectar sin duda a los hábitos culturales y, concretamente, la forma de socializar de las personas (Ahmad and Hussain, 2017). Las personas que viven a gran altitud viven en comunidades de carácter rural y típicamente más pequeñas y pasan más tiempo dentro de sus casas debido a la dureza del clima, lo que sin duda afecta a la socialización. Todas estos contrastes morfológicos y funcionales, en algunos casos se traducen también en diferencias bioquímicas u hormonales que podrían aumentar o disminuir el riesgo de adquirir una u otra enfermedad (Mohanna et al., 2006). Por ejemplo, se ha descrito en múltiples ocasiones que las variables hematológicas principales (conteo de glóbulos rojos, bancos y plaquetas) y sus características morfológicas tienen en algunos casos, relación con la altura y que aquellas personas que se han expuesto crónicamente a la hipoxia hipobárica pueden desarrollar policitemia, estasis sanguíneo pero también pueden desarrollar más vasos sanguíneos colaterales y mejor perfusión de oxigeno tisular (Bhalla et al., 1988; Zhong et al., 2002; Ortiz-Prado et al., 2010; Aryal et al., 2017). Esto se podría traducir en un mayor riesgo de desarrollar isquemia cerebral o infarto de miocardio en personas que se exponen de forma aguda. Pero en cambio, la altura podría convertirse en un efecto protector en aquellas personas que han nacido o que viven a grandes alturas (Alper et al., 2009; Faeh D et al., 2009; Faeh et al., 2016; Damodar et al., 2018). En ese sentido, es fundamental seguir estudiando y explorando esta compleja relación entre la hipoxia aguda y la hipoxia crónica con el desarrollo de alteraciones patológicas, funcionales o inclusive el desarrollo de enfermedades o a su vez el entender mejor los efectos protectores que la altura podría tener entre aquellos habitantes adaptados que han logrado doblegar las adversidades climatológicas y ambientales a través de la aparición de nuevas ventajas adaptativas.

1.7 Clasificación de la altura

Aunque es clara la relación entre altura e hipoxia, una de las principales dificultades que encuentra la fisiología de la altura es determinar el umbral en el cual, la hipoxia hipobárica se hace más o menos significativa en términos fisiológicos, clínicos o patológicos. En ese sentido, Imray et al., 2011 propuso una clasificación asociada a la exposición a grandes alturas (Imray et al., 2011). Según esta categorización, la baja altitud se define como todo lo que se encuentra por debajo de los 1.500 m, la altitud moderada o intermedia entre los 1.500 m y los 2.500 m, las grandes alturas de los 2.500 m a los 3.500 m, las muy grandes alturas de los 3.500 m a los 5.800 m, la altura extrema todo por encima de los 5.800 m y finalmente la zona de la muerte pasando los 8,000 m (Pollard and Murdoch, 2003). Aunque esta clasificación parece bastante aceptada, en 2007 la Comisión Médica del Deporte de la FIFA y el Centro de Evaluación e Investigación Médica de la FIFA (F-MARC) invitaron a 12 científicos y clínicos internacionales a revisar la literatura científica disponible y a llegar a un consenso sobre la clasificación de las alturas. Como resultado de este debate, se propuso que todo por debajo de los 500 m sería considerado "nivel del mar", de los 500 a los 2,000 m seria baja altura, de los 2,000 a los 3,000 m seria altura moderada, de los 3,000 a los 5,500 m seria gran altura, y altura extrema seria todo por encima de los 5.500 m (Bärtsch et al., 2008).

Con esta clasificación, muchos fisiólogos han quedado satisfechos, sin embargo, varios científicos de todo el mundo han clasificado la exposición a la altitud en dos categorías simplificadas: por debajo de 2.500 m se considera baja altura y todo por encima de 2.500 m se considera gran altura (Bailey et al., 2019). En ese sentido, cabe pensar que los residentes permanentes de las grandes alturas tienen adquiridas genéticamente ciertas adaptaciones fisiológicas y morfológicas que les permiten afrontar con ventaja dichas condiciones atmosféricas, mientras que los residentes de bajas alturas deben aclimatarse una vez que ascienden a tales elevaciones (West, 2006).

1.8 Efectos de la altura sobre la salud poblacional

Aunque parezca paradójico, el estudio de la fisiología de la altura con relación a la aclimatación a la hipoxia ha surgido principalmente en respuesta a los procesos relacionados con el ascenso a grandes nevados, el rescate de montañistas y la visita a zonas remotas por parte de poblaciones primordialmente provenientes de occidente. No fue hasta 1920, cuando por primera vez la importancia de estudiar poblaciones que residen crónicamente a grandes alturas se hizo notoria. Carlos Monge Medrano (1884-1970), un médico peruano que dedicó gran parte de su carrera a estudiar los efectos a largo plazo de vivir en zonas montañosas de los Andes, abrió el camino a futuras investigaciones (Monge, 1937).

Él es considerado uno de los padres de la fisiología de la altura y definitivamente es el primero o uno de los primeros investigadores que se dedicó a estudiar aquellas poblaciones que viven y residen a grandes alturas en los Andes latinoamericanos. Este pionero de la medicina de alta montaña generó una escuela de investigadores que continuaron de la mano de Albert Hurtado Padilla, de Carlos Monge Casinelli (su propio hijo) y otros investigadores a mediados y finales del siglo XX, quienes ostentan el laudo de ser un grupo privilegiado por haber estudiado poblaciones nuca antes visitadas (Monge and Mauricio San Martín, 1956; Reyna, 2006).

En este sentido, la mayoría de la información se enfocado en estudiar los defectos a corto y mediano plazo de la altura, descuidando los efectos deletéreos que puede tener el residir en dichas áreas. Desde la visión de la salud pública, tenemos más dudas que certezas sobre el impacto real que puede tener el vivir a grandes alturas sobre el funcionamiento del cuerpo humano y sobre la predisposición de desarrollar algún tipo de proceso nosológico con mayor frecuencia que aquellas personas que viven a moderada o baja altura.

En los últimos 30 años, hemos tenido muy pocos reportes sobre los efectos de la altura y el riesgo de desarrollar enfermedades. Por ejemplo, a nivel poblacional se habla de algún tipo de interacción entre el ambiente y el desarrollo del accidente cerebro vascular, algunos tipos de cánceres, el suicidio entre otros (Faeh D et al., 2009; Ezzati et al., 2012; Reno et al., 2018; Burtscher et al., 2021; Ortiz-Prado et al., 2021a). Sin embargo, mucha información no ha sido recolectada históricamente ya que muy pocos países y regiones comparten poblaciones que residen a distintas alturas y con un rango amplio de elevación.

Algunas de las dudas que nos competen, vienen de la mano de desconocer exactamente a qué nivel estamos hablando ya de una exposición a grandes alturas o a qué nivel estamos nosotros experimentando baja o moderada altitud. En ese sentido, existen varios trabajos previos con el fin de identificar la mejor clasificación de altitud geográfica que nos permite conocer cuando, en términos de impacto fisiológico, una población realmente reside a baja, moderada, alta o muy alta altura (Pollard and Murdoch, 2003; Bärtsch et al., 2008; Imray et al., 2011).

En este sentido, nosotros hemos propuesto el estudio de dos poblaciones genéticamente idénticas que viven a dos alturas considerablemente diferentes (230 m versus 3,800 m) como una gran oportunidad para poder entender un poco más de esta compleja relación entre altura y salud y a la vez sentar precedentes para futuras investigaciones que nos permitan ahondar en el tema de la fisiología de la altura, pudiendo de esta forma aportar con nuevo conocimiento a la aun no tan conocida área de la medicina asistencial de alta montaña.

1.9 Poblaciones expuestas a las grandes alturas

A nivel global y acorde a la clasificación de la altura revisada en secciones anteriores podemos decir que la gran mayoría de los cambios clínicos, fisiológicos, anatómicos y bioquímicos que se producen a consecuencia de la altura se los empieza a evidenciar por sobre los 2,500 m en la gran mayoría de los casos. En relación con la heterogeneidad genética e histórico-cultural de las distintas poblaciones que residen a grandes alturas, muchas personas no adaptadas podrían desarrollar efectos clínicos evidenciables a niveles tan bajos como los 2,000 m.

En general, la exposición aguda (< 28 días) a elevaciones entre los 4,600 – 4,900 m podría representar el nivel máximo aceptable para vivir permanentemente en dicha ubicación, sin embargo, para poblaciones adaptadas, residir a los 5,800 – 6,000 m representan retos máximos de supervivencia y funcionamiento a largo plazo (West, 2002).

La estimación de cuantas personas realmente residente a grandes alturas es un tema complejo. Varias estimaciones se han realizado y se han usado como referencia. La más común es la de Imray et,. al en el 2011 que estimaba que alrededor de 180 millones de personas residen por sobre los 2,500 m de altura a nivel mundial (Imray et al., 2011). Sin embargo, una reciente publicación de Joshua C. Tremblay and Philip N. Ainslie en 2021 usó un enfoque basado en el sistema de información geográfica (SIG) para cuantificar la población humana en intervalos de 500 m de altitud para cada uno de los países del mundo (Tremblay and Ainslie, 2021). Según ellos, al menos 500,3 millones de seres humanos viven por sobre los 1,500 m de altura, al menos 81,6 millones desde los 2,500 m a los 3,500 m y 14,4 millones por sobre los 3,500 m (Tremblay and Ainslie, 2021).

La importancia de conocer los efectos que la altitud presenta sobre las distintas poblaciones radica en que la hipoxia hipobárica provoca un sinnúmero de respuestas fisiológicas y de adaptación que directamente pueden afectar la carga epidemiológica o la gravedad de distintas enfermedades (Faeh D et al., 2009; Burtscher et al., 2021; Ortiz-Prado et al., 2021a). Otra necesidad adicional de estudiar estas poblaciones radica en que la mayoría de las investigaciones sobre fisiología de la altura se basan en residentes occidentales que viven a bajas alturas, en países con altas tasas de educación, industrializados y con buenos niveles socioeconómicos (Tremblay and Ainslie, 2021).

A nivel territorial y geográfico, la mayoría de las poblaciones ubicadas por sobre los 2,500 m sobre el nivel del mar están ubicadas en las principales cadenas montañosas, incluyendo:

*La cordillera del Himalaya y sus valles

*La meseta tibetana

*Las cordilleras del este de Turquía, Irán, Afganistán y Pakistán

*Las Montañas Rocosas y Sierra Nevada de los Estados Unidos y Canadá

*La Sierra Madre de México

*Los Andes de América del Sur

*Los Alpes europeos

*Los Pirineos entre España y Francia

*La cordillera del Atlas en el norte de África

*Las tierras altas de Etiopía

*Las montañas de África oriental y meridional

*La meseta y las montañas de la Antártida

*Unas pocas partes de Nueva Guinea

*Algunas áreas de islas de gran relieve como Hawái, Tenerife y Nueva Zelanda (West et al., 2007).

1.10 Población Ecuatoriana expuestas a las grandes alturas

1.10.1 Geografía del Ecuador

El Ecuador está situado en la costa noroeste de Sudamérica, entre Perú al sur y al este y Colombia al norte. Las Islas Galápagos pertenecen a Ecuador y se encuentran a unos 1.000 kilómetros de la costa continental. Este pequeño país, el tercero más pequeño después de Guayanas y Uruguay tiene una superficie de alrededor de 283.000 Km^2. El país está dividido en 4 regiones geográficas, la costa, la sierra, la región amazónica y las islas Galápagos. La división política comprende 24 provincias, 10 de la sierra, 7 de la costa, 6 de la región amazónica y 1 de la región insular de las Galápagos. Estas provincias contienen 223 subdivisiones llamadas cantones, distribuidos en 92 de la sierra, 86 de la costa, 42 de la región amazónica y 3 de las islas Galápagos (Figura 3).

Los Andes se extienden por el centro de Ecuador, cubriendo aproximadamente una cuarta parte de la superficie total del país. En ella se incluyen dos cordilleras, con más de 22 cumbres de más de 4.200 m de altura. En la actualidad hay al menos 8 volcanes activos en Ecuador, de entre ellos cabe destacar el Sangay (5,286 m) uno de los más activos del mundo, el Reventador (3,562 m) que actualmente está en actividad, el Cotopaxi (5,897 m) el volcán activo más alto del mundo y el Chimborazo (6,263 m) cuya cumbre es el punto más alto desde el centro de la Tierra.

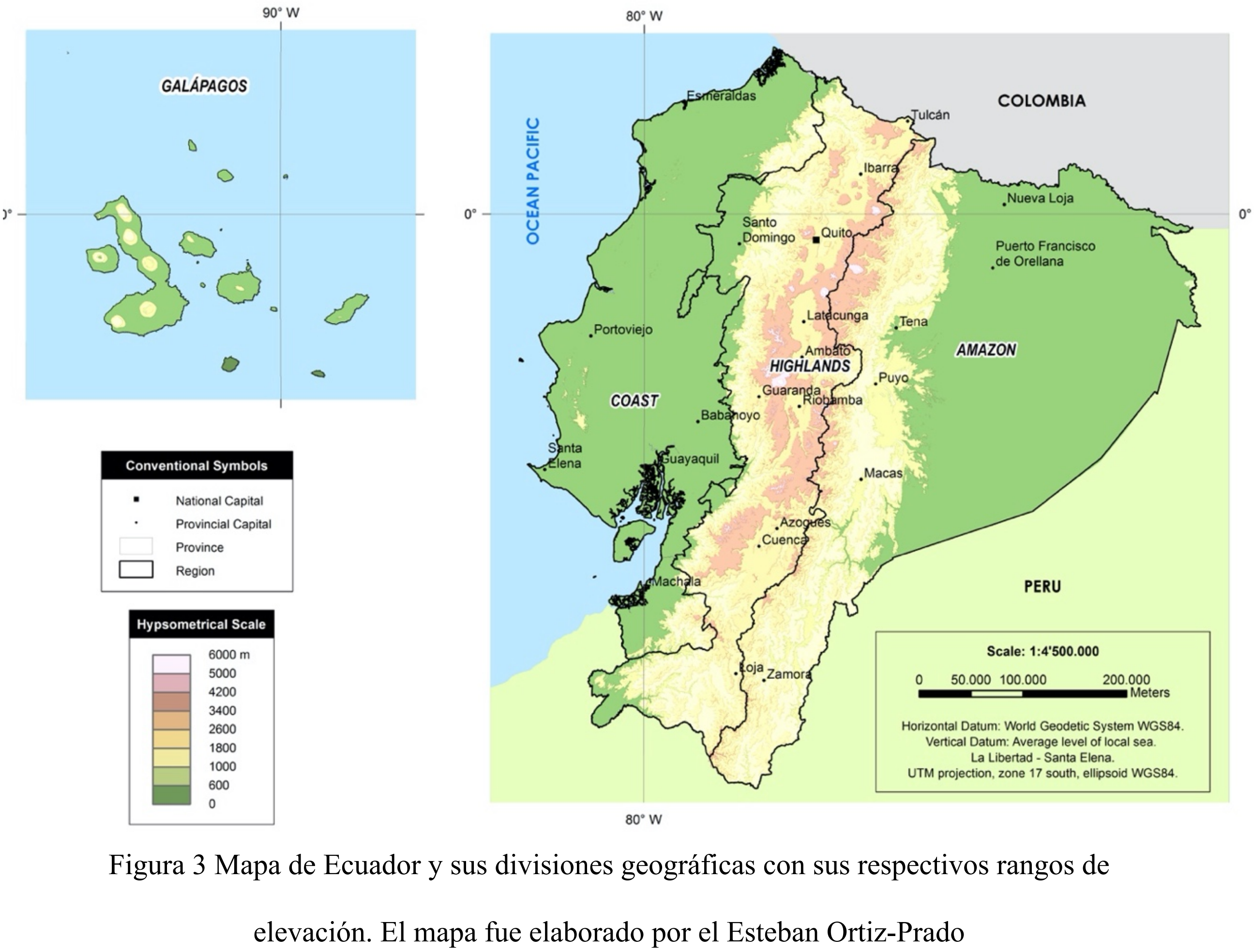

Figura 3 Mapa de Ecuador y sus divisiones geográficas con sus respectivos rangos de elevación. El mapa fue elaborado por el Esteban Ortiz-Prado

1.10.2 Población del Ecuador

La población ecuatoriana al 2016 ha sido estimada en base al último censo realizado por el INEC en el año 2010 (INEC, 2010). Para ese año, las proyecciones poblacionales han fijado la actual situación del país en 16.528.730, teniendo una relación mujer-hombre de 51/49 (INEC, 2018). En términos de etnicidad, Ecuador es muy diverso. La mayoría de las personas que viven en el país son mestizos, representando el 79,3% de la población, seguidos por los afroecuatorianos con el 7,2%, los indígenas con el 7,1%, los descendientes de blancos o caucásicos con el 6,1% y otros grupos con el 0,4%.

1.10.3 Población del Ecuador por altura

Ecuador es uno de los pocos países del mundo que cuenta con toda una gama de ciudades situadas a diferentes alturas, que van desde el nivel del mar hasta los 4.300 m, sin considerar parroquias pequeñas que pueden llegar a los 4,500 m. Estas ciudades y cantones se distribuyen por todo el país, la mayoría de ellas a nivel del mar y de la selva amazónica, mientras que una parte más pequeña se encuentra en las regiones montañosas (figura 4).

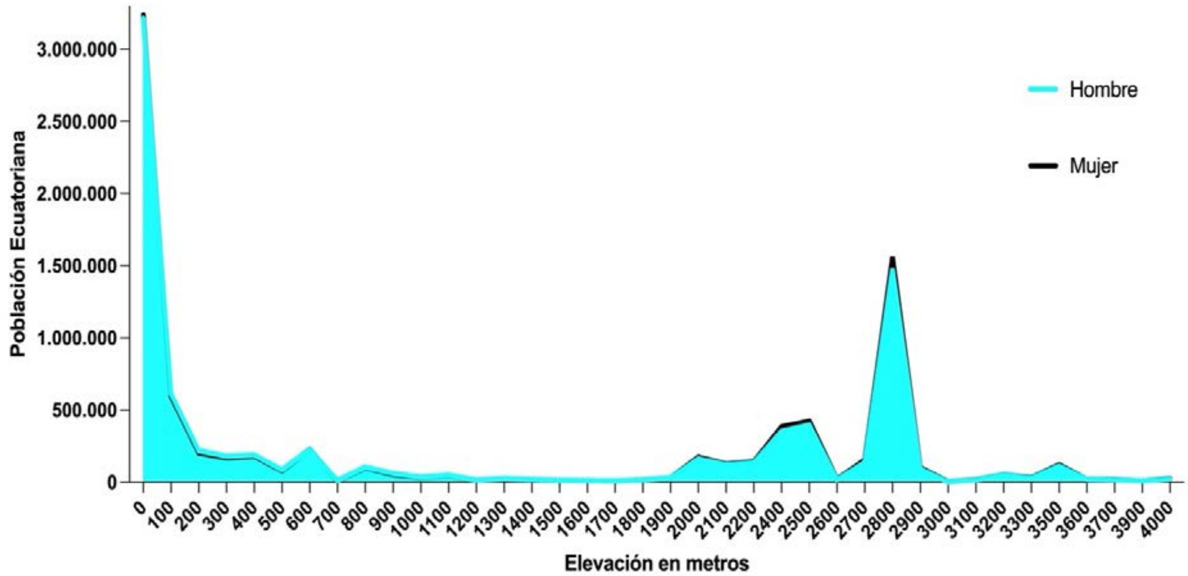

Figura 4 Población por elevación en Ecuador por sexo

Para calcular con exactitud la población que vive en el Ecuador en relación con la altura de cada uno de los 221 cantones, usamos las proyecciones poblacionales y las dividimos de acuerdo con cada 500 m de elevación. Usamos un método de estandarización por sexo y edad. Este ejercicio nos permitió identificar que más del 50% de la población vive por debajo de los 500 m de altura, un 28% de la población reside por encima de los 2,500 m y solo un 0.3% reside por encima de los 4,000 m (Tabla 1).

Tabla 1 Distribución de la población en Ecuador por rangos de altura en metros.

	Hombre		Mujer	
	Población 2016	**%**	**Population**	**%**
0-500 m	4’446,729	53.5%	4’418,935	52.2%
501-1000 m	483,488	5.8%	470,014	5.5%
1001-1500 m	139,293	1.7%	131,561	1.6%
1501-2000 m	195,654	2.4%	202,684	2.4%
***2001-2500 m**	652,688	7.9%	703,315	8.3%
2501-3000 m	2’117,206	25.5%	2’253,828	26.6%
3001-3500 m	93,184	1.1%	99,739	1.2%
3501-4000 m	155,688	1.9%	16,5577	2.0%
>4000 m	22,627	0.3%	24,767	0.3%
Total	8’306,557	100%	8’470,420	100%

1.11 Grupo poblacional de Estudio

1.11.1 Limoncocha

Limoncocha es una de las parroquias más conocidas del cantón Shushufindi de la provincia de Sucumbios. Está ubicada en la amazonia ecuatoriana y tiene una altura promedio de 230 m de altura. Limoncocha es parte de un sistema de bosques amazónicos pertenecientes a la reserva biológica Limoncocha, el corazón de la selva amazónica ecuatoriana.

En esta reserva, el clima es el de bosque húmedo tropical con una temperatura promedio de 24 °C y una precipitación anual de aproximadamente 3,000 mm. La distribución de la lluvia es muy regular a lo largo de todo el año con una humedad relativa del 98 %. Según el censo poblacional del 2010 esta parroquia tiene 6,817 habitantes de los cuales el 59.9 % son hombres y el 40.1% son mujeres (GAG Limoncocha, 2019). Esta parroquia presentaba un crecimiento anual promedio para el 2015 del 2.44 %. En esta parroquia, el 51.6 % de la población es indígena (Figura 5).

Figura 5 Mujeres amazónicas de bajas alturas de la comunidad de Limoncocha (230 m)

Foto autorizada por las pacientes y tomada por Esteban Ortiz

Su autodeterminación étnica corresponde a la de Kichwa amazónico y su idioma oficial es el Kichwa. Dentro de las actividades económicas principales de la parroquia se destaca la agricultura, la ganadería, la silvicultura y la pesca, aunque un porcentaje importante de gente se dedica a la construcción como obreros, a la explotación de minas y canteras, a la atención al turista, la cocina, el transporte y a las actividades de servicios administrativos (Figura 6).

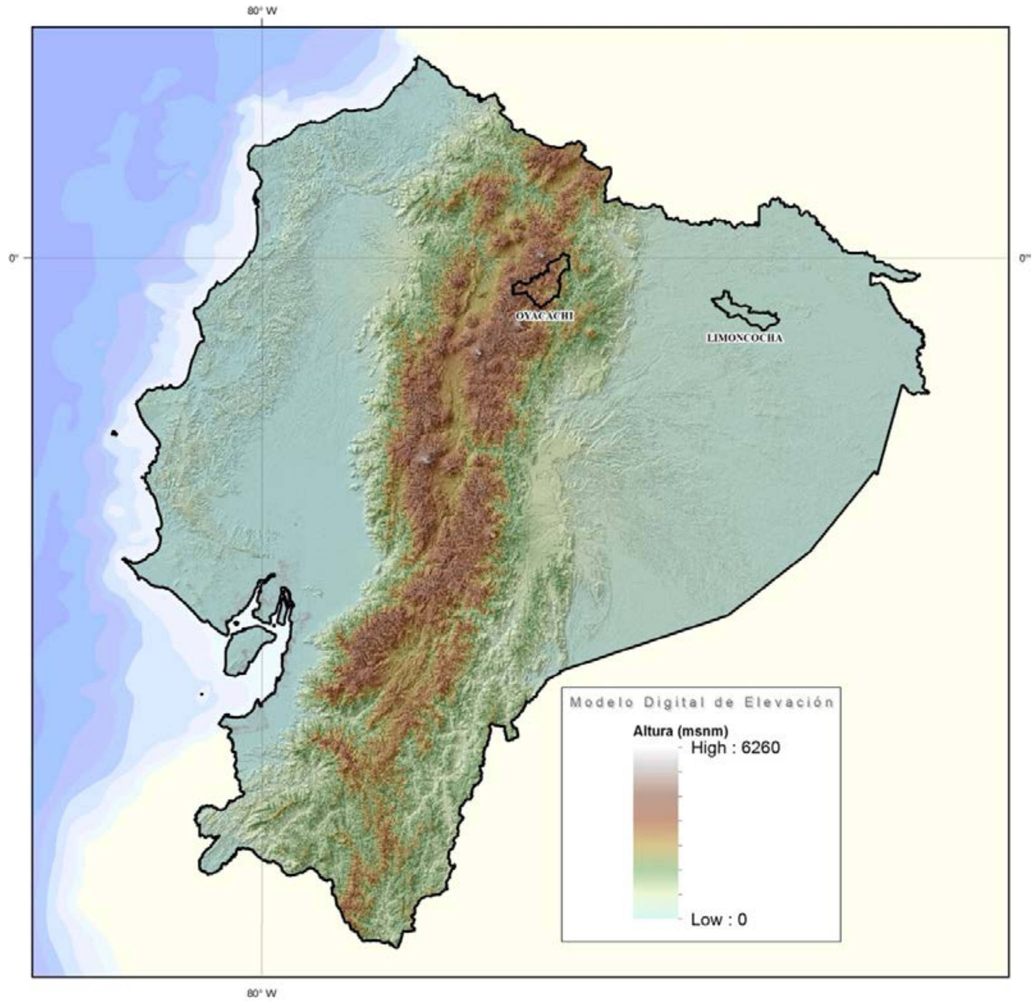

Figura 6 Mapa Ecuatoriano con representación de la parroquia de Limoncocha y de la parroquia de Oyacachi

1.11.2 Oyacachi

La parroquia de Oyacachi es una comuna de 63.000 ha que tiene una extensión de aproximadamente 513 km². Esta parroquia su ubica en la región montañosa de los andes ecuatorianos en la provincia de Napo colindando con la provincia de Imbabura y Pichincha. La conformación territorial de esta parroquia es principalmente cordillera (99%) y un 1 % ha sido catalogado como serranía y glaciar (GAD Oyacachi, 2019). En esta parroquia gran parte (93%) de su población es indígena, siendo los Kichwas los más representativos (51.7%). Según el último censo poblacional esta parroquia tenía una población de 766 habitantes en su territorio sin del 51% hombres y 49% mujeres (Figura 7).

Figura 7 Mujeres de la comunidad de Oyacachi (3,800 m) Foto autorizada por las pacientes y tomada por Esteban Ortiz

Gran parte de la población se dedica a la agricultura, la pesca y el turismo. En esta zona existen varias fuentes de agua volcánica que atraen a un gran número de turistas. Tiene acceso a electricidad y agua potable y en relación a otras zonas, su acceso es dificultoso por lo alejado del terreno, la altitud y el camino.

Variable	Oyacachi	Limoncocha
Acceso Vehicular	Camino Empedrado	Carretera Asfaltada
Población total	570	6,817 habitantes.
Altitud (metros)	3,800 to 4,300 m	228-230 m
Agricultura	Papas, granos, zanahoria , quínoa	Palma africana, cacao, café, maíz, bananos y plátanos
Clima	Bosque lluvioso de montaña	Bosque lluvioso tropical
Temperatura (°C)	-2 °C – 17°C	18 °C – 26°C
Pluviosidad (mm)	1,200 – 3,000	3,200 – 3,400
Humedad Relativa (%)	89%	> 90%
Manejo de Excretas	Tributarios naturales	Tributarios naturales
Analfabetismo (%)	13.75%	5.43%
Establecimientos escolares (n)	3	34
Centros de Salud (n)	1	3
Población Econ. Activa (%)	66%	49.74%
Explotación petrolera	No	Yes
Electricidad (%)	96.72%	86.65%
Recolección de basura (%)	88.52%	13.3%
Agua potable (%)	89.3%	26.2%

En cuanto a la asistencia educativa de la población, se puede evidenciar lo que remarca la escolaridad promedio en las zonas montañosas de los antes ecuatorianos. Gran parte de la población se concentra en terminar la primaria y luego, va disminuyendo paulatinamente la población que permanece en niveles más altos de instrucción superior. El acceso a la salud consta de un centro de salud público ubicado en el medio de la parroquia que anualmente consta de la rotación de un o una médica rural, una o un enfermero y un o una odontóloga (Tabla 2).

Tabla 2 Diferencias principales entre las parroquias de Limoncocha y Oyacachi

2. Objetivos

2.1 Objetivos Principales:

a) Determinar el nivel de autopercepción del estado de salud, de su estado de ánimo y de su nivel de optimismo disposicional en dos poblaciones de estirpe Kichwa residentes a dos altitudes diferentes.

b) Determinar las diferencias genotípicas para la determinación de ancestria en dos poblaciones de estirpe Kichwa residentes a dos altitudes diferentes en el Ecuador.

c) Determinar las diferencias hematológicas, del perfil lipídico y por ende de su riesgo cardiovascular en dos poblaciones de estirpe Kichwa residentes a dos altitudes diferentes.

d) Evaluar la función respiratoria entre dos poblaciones Kichwas ubicadas a distintas alturas a través de la realización de pruebas espirométricas funcionales que nos permitan determinar diferencias adaptativas en relación a sus respectivas capacidades ventilatorias

e) Determinar las diferencias de peso, talla, del índice de masa corporal (IMC) y de las distintas medidas antropométrica en estas dos poblaciones Kichwas ubicadas a diferentes alturas para de esta forma determinar si es que existen diferencias anatómico-adaptativas asociadas a la altura de residencia.

2.3 Objetivos Secundarios:

a) Determinar el riesgo global que tienen las poblaciones de desarrollar **enfermedades crónico-degenerativas** como el accidente cerebrovascular o el cáncer en relación con la altura de residencia usando un análisis epidemiológico descriptivo de tipo ecológico con los datos obtenidos a nivel nacional de las bases oficiales de egresos hospitalarios y defunciones en el Ecuador.

b) Determinar el riesgo global que tienen las poblaciones de desarrollar enfermedades **infectocontagiosas** en relación con la altura de residencia usando un análisis epidemiológico descriptivo de tipo ecológico con los datos obtenidos a nivel nacional de las bases oficiales de egresos hospitalarios y defunciones en el Ecuador.

c) Determinar el impacto del **suicidio** en relación con la altura de residencia usando un análisis epidemiológico descriptivo de tipo ecológico con los datos obtenidos a nivel nacional de defunciones en el Ecuador

3. Informe de los directores de la tesis doctoral sobre factor de impacto de los artículos publicados

El doctor Ginés Viscor como codirector y tutor y el Dr. Manuel Calvopiña como codirector de la Tesis Doctoral presentada por Esteban Ortiz Prado, hacen constar que el doctorando ha participado activamente en la elaboración de los artículos que conforman esta memoria, tal como queda reflejado en el orden y la composición del conjunto de autores de cada uno de ellos. El doctorando ha jugado un papel clave en el diseño experimental, en la obtención de datos, en su tratamiento estadístico y ha participado activamente en el razonamiento de los resultados de la totalidad de los estudios que constituyen el núcleo de su tesis. También ha asumido el protagonismo en los procesos de difusión y publicación de los resultados y de las conclusiones. Esteban Ortiz-Prado ha desempeñado un papel muy importante en la conducción de su tema de tesis, encabezando un grupo de colaboradores, elaborando varios artículos científicos y completando el proceso de recolección, escritura y divulgación científica de sus datos. En todos los artículos presentados en esta tesis ha sido el autor principal y corresponsal, demostrando así, su capacidad para cumplir con los retos planteados para elaboración de la tesis.

A continuación, se presentan todos los documentos ya publicados y los aceptados para publicación y aquellos que han sido enviados para revisión por pares, pero que aún no han sido aceptados. Esta información incluye información bibliométrica de cada uno de los documentos.

3.1 Artículos publicados

3.1.1 Primera Publicación

Título: Hematological parameters, lipid profile and cardiovascular risk analysis among genotype controlled indigenous Kichwa men and women living at low and high altitude.

Autores: Ortiz-Prado, Esteban, David Portilla, Johanna Mosquera, Katherine Simbaña-Rivera, Diego Duta, Israel Ochoa, German Burgos, Juan S. Izquierdo-Condoy, Eduardo Vásconez, Manuel Calvopiña y Ginés Viscor

Autor corresponsal y primer autor : Esteban Ortiz-Prado

Revista: Frontiers in Physiology

DOI: 10.3389/fphys.2021.749006

Volumen: 12 **Año:** 2021

ISSN: 1664042X **H-Index:** 102 **Rango JIF:** Q1 **SJR:** 1.32

Impact Factor (WoS): 4.566 **CiteScore:** 5.6. **Número de citas: 0**

Participación del doctorando: Elaboración del diseño y concepto de la investigación, así como también de la ejecución del protocolo de investigación. El doctorando fue el encargado de diseñar la metodología junto con el tutor, reclutar participantes y fue responsable de la obtención de las muestras y las distintas variables sociodemográficas.

El doctorando fue el responsable del análisis estadístico de los resultados y elaboración de las distintas figuras y tablas, así como también de la elaboración del primer borrador y la coordinación hasta generar la versión final del manuscrito.

3.1.2 Segunda Publicación (aceptada en prensa)

Título: Optimism and health self-perception-related differences in indigenous Kichwas of Ecuador at low and high altitude: a cross-sectional analysis.

Autores: Esteban Ortiz-Prado, Katherine Simbaña-Rivera, Diego Duta, Israel Ochoa, Juan S Izquierdo-Condoy, Eduardo Vásconez, Kathia Carrasco , Manuel Calvopiña, Ginés Viscor and Clara Paz

Autor corresponsal y primer autor : Esteban Ortiz-Prado

Revista: High Altitude Medicine & Biology

DOI: 10.1089/ham.2021.0079

Volumen: 22 **Number:** 4, 2021

Año: 2021

ISSN: 15270297, 1557868 **H-Index:** 52 **Rango JIF:** Q2 **SJR:** 0.52.

Impact Factor (WoS): 1.981 **CiteScore:** 2.8 **Número de citas:** N/A

Participación del doctorando: Elaboración del diseño y concepto de la investigación, así como también de la ejecución del protocolo de investigación. El doctorando fue el encargado de diseñar la metodología junto con el tutor, reclutar participantes y fue responsable de la obtención de las muestras y las distintas variables sociodemográficas. También fue el responsable de elaborar las distintas figuras y tablas, así como también de la elaboración del primer borrador y la versión final del manuscrito.

3.1.3 Tercera Publicación (aceptada en prensa)

Título: Analysis of excess mortality data at different altitudes during the COVID-19 outbreak in Ecuador.

Autores: Esteban Ortiz-Prado, Raúl Fernández, Eduardo Vásconez, Katherine Simbaña-Rivera, Trigomar Correa-Sancho, Alex Lister, Manuel Calvopiña y Gines Viscor

Autor corresponsal y primer autor : Esteban Ortiz-Prado

Revista: High Altitude Medicine & Biology

DOI: 10.1089/ham.2021.0070

Volumen: 22 **Number:** 4, 2021

Año: 2021

ISSN: 15270297, 1557868 **H-Index:** 52 **Rango JIF:** Q2 **SJR:** 0.52

Impact Factor (WoS): 1.981 **CiteScore:** 2.8 **Número de citas:** N/A

Participación del doctorando: Elaboración del diseño y concepto de la investigación, así como también de la ejecución del protocolo de investigación. El doctorando fue el encargado de diseñar la metodología. El doctorando fue el responsable de elaborar las distintas figuras y tablas, así como también de la elaboración del primer borrador y la versión final del manuscrito.

3.1.4 Cuarta Publicación

Título: Stroke Related Mortality at Different Altitudes: A 17-Year Nationwide Population-Based Analysis from Ecuador

Autores: Esteban Ortiz-Prado, Patricio S. Espinosa, Alfredo Borrero, Simone P. Cordovez, Jorge E. Vásconez, Alejandra Barreto-Grimales, Marco Coral-Almeida, Aquiles R. Henríquez-Trujillo, Katherine Simbaña-Rivera, Lenin Gómez-Barreno, Gines Viscor y Paul Roderick.

Autor corresponsal y primer autor : Esteban Ortiz-Prado

Revista: Frontiers Physiology

DOI: 10.3389/fphys.2021.733928

Volumen: 12 **Año:** 2021

ISSN: 1664042X **H-Index:** 102 **Rango JIF:** Q1 **SJR:** 1.32

Impact Factor (WoS): 4.566 **CiteScore:** 5.6. **Número de citas: 0**

Participación del doctorando: Elaboración del diseño y concepto de la investigación, así como también de la ejecución del protocolo de investigación. El doctorando fue el responsable del análisis estadístico de los resultados y elaboración de las distintas figuras y tablas, así como también de la elaboración del primer borrador y la versión final del manuscrito.

3.1.5 Quinta Publicación

Título: The disease burden of suicide in Ecuador, a 15 years' geodemographic cross-sectional study (2001-2015)

Autores: Esteban Ortiz-Prado, Katherine Simbaña, Lenin Gómez, Aquiles R Henríquez-Trujillo, Fernando Cornejo-León, Eduardo Vásconez, Diana Castillo, Ginés Viscor.

Autor corresponsal y primer autor : Esteban Ortiz-Prado

Revista: BMC Psychiatry

DOI: 10.1186/s12888-017-1502-0

Volumen: 17 **Año:** 2017

ISSN: 1471244X **H-Index:** 97 **Rango JIF:** Q2 **SJR:** 1.44

Impact Factor (WoS): 3.630 **CiteScore:** 3.5 **Número de citas: 12**

Participación del doctorando: Elaboración del diseño y concepto de la investigación, así como también de la ejecución del protocolo de investigación. El doctorando fue el responsable del análisis estadístico de los resultados y elaboración de las distintas figuras y tablas, así como también de la elaboración del primer borrador y la versión final del manuscrito.

3.1.6 Sexta Publicación

Título: Partial pressure of oxygen in the human body: a general review

Autores: Esteban Ortiz-Prado, Jeff F Dunn, Jorge Vásconez, Diana Castillo, Ginés Viscor.

Autor corresponsal y primer autor: Esteban Ortiz-Prado

Revista: American journal of blood research

DOI: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6420699/

Volumen: 9 **Año:** 2019

ISSN: 21601992 **H-Index:** 5 **Rango JCI:** Q3 **SJR:** 0

Impact Factor (WoS): 0.86 **CiteScore:** 0 **Número de citas:** 103

Participación del doctorando: Elaboración del diseño y concepto de la investigación, así como también de la ejecución del protocolo de investigación. El doctorando fue el responsable del análisis y la revisión de la literatura, así como de la escritura y revisión del manuscrito.

3.2 Artículos científicos sometidos a revisión por pares

3.2.1 Séptima Publicación

Título: A comparative analysis of lung function and spirometry parameters in genotype-controlled natives living at low and high altitude.

Autores: Esteban Ortiz-Prado, Sebastián Encalada, Johanna Mosquera, Katherine Simbaña-Rivera, Lenin Gómez-Barreno, Diego Duta, Israel Ochoa, Juan S. Izquierdo-Condoy, Eduardo Vásconez, German Burgos, Manuel Calvopiña y Ginés Viscor.

Autor corresponsal y primer autor: Esteban Ortiz-Prado

Revista: BMC Pulmonary Medicine

DOI: 10.21203/rs.3.rs-900188/v1 (preprint)

Volumen: **Año:** 2022 (Previsible)

ISSN: 1664042X **H-Index:** 59 **Rango:** Q1 **SJR:** 1.23

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Participación del doctorando: Elaboración del diseño y concepto de la investigación, así como también de la ejecución del protocolo de investigación. El doctorando fue el encargado de diseñar la metodología junto con el tutor, reclutar participantes y responsable de la obtención de las muestras y las distintas variables sociodemográficas.

El doctorando fue el responsable del análisis estadístico de los resultados y elaboración de las distintas figuras y tablas, así como también de la elaboración del primer borrador y la versión final del manuscrito.

3.2.2 Octava Publicación

Título: Anthropometric and body composition differences among genotype controlled indigenous adult Kichwa natives living at low (230 m) and high altitude (3,800 m) in Ecuador.

Autores: Esteban Ortiz-Prado, Gonzalo Mendieta, Katherine Simbaña-Rivera, Lenin Gómez-Barreno, Samanta Landázuri, Eduardo Vásconez, Manuel Calvopiña and Ginés Viscor.

Autor corresponsal y primer autor: Esteban Ortiz-Prado

Revista: Journal of Physiological Anthropology

DOI: N/A

Volumen: N/A **Año:** 2022 (previsible)

ISSN: 18806791, 18806805 **H-Index:** 50 **Rango:** Q1 **SJR:** 0.52

Impact Factor (WoS): 3.317 **CiteScore:** 2.82 **Número de citas:** N/A

Participación del doctorando: Elaboración del diseño y concepto de la investigación, así como también de la ejecución del protocolo de investigación. El doctorando fue el encargado de diseñar la metodología junto con el tutor, reclutar participantes y responsable de la obtención de las muestras y las distintas variables sociodemográficas.

El doctorando fue el responsable del análisis estadístico de los resultados y elaboración de las distintas figuras y tablas, así como también de la elaboración del primer borrador y la versión final del manuscrito

3.2.3 Novena Publicación

Título: High altitude exposure and the epidemiology of ischemic stroke, A Systematic literature review

Autores: Esteban Ortiz-Prado, Simone P. Cordovez, Eduardo Vascones, Gines Viscor y Paul Roderick.

Autor corresponsal y primer autor : Esteban Ortiz-Prado

Revista: BMJ Open

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Participación del doctorando: Elaboración del diseño y concepto de la investigación, así como también de la ejecución del protocolo de investigación. El doctorando fue el responsable del análisis y la revisión de la literatura, así como de la escritura y revisión del manuscrito.

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Ginés Viscor Manuel Calvopiña

4. Publicaciones científicas

4.1 Hematological parameters, lipid profile and cardiovascular risk analysis among genotype controlled indigenous Kichwa men and women living at low and high altitude

frontiers in Physiology

ORIGINAL RESEARCH
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Hematological Parameters, Lipid Profile, and Cardiovascular Risk Analysis Among Genotype-Controlled Indigenous Kiwcha Men and Women Living at Low and High Altitudes

Esteban Ortiz-Prado[1,2], David Portilla[1], Johanna Mosquera-Moscoso[1], Katherine Simbaña-Rivera[1], Diego Duta[3], Israel Ochoa[4], German Burgos[5], Juan S. Izquierdo-Condoy[1], Eduardo Vásconez[1], Manuel Calvopiña[1] and Ginés Viscor[2]*

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Introduction: Human adaptation to high altitude is due to characteristic adjustments at every physiological level. Differences in lipid profile and cardiovascular risk factors in altitude dwellers have been previously explored. Nevertheless, there are no reports available on genotype-controlled matches among different altitude-adapted indigenous populations.

Objective: To explore the possible differences in plasma lipid profile and cardiovascular risk among autochthonous Kiwcha people inhabitants of low and high-altitude locations.

Methodology: A cross-sectional analysis of plasmatic lipid profiles and cardiovascular risk factors in lowland Kiwchas from Limoncocha (230 m) and high-altitude Kiwchas from Oyacachi (3,800 m).

Results: In the low altitude group, 66% were women ($n = 78$) and 34% ($n = 40$) were men, whereas in the high altitude group, 59% ($n = 56$) were women and 41% ($n = 41\%$) were men. We found the proportion of overweight and obese individuals to be higher among low altitude dwellers ($p < 0.05$). Red blood cells (RBCs), hemoglobin concentration, and SpO_2% were higher among high altitude dwellers and the erythrocyte size was found to be smaller at high altitude. The group located at low altitude also showed lower levels of plasma cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL), but most of these differences are not influenced by gender or elevation.

Conclusions: Living at an altitude elicits well-known adaptive physiological changes such as erythrocyte count, hemoglobin concentration, hematocrit level, and serum glucose level. We also report clinical differences in the plasma lipid profile, with higher levels of cholesterol, HDL, and LDL in inhabitants of the Andes

Mountain vs. their Amazonian basin peers. Despite this, we did not find significant differences in cardiovascular risk.

Keywords: high altitude, hypoxia, hematological profile, adaptation, lipid profile, cardiovascular risk

INTRODUCTION

Humans have developed adaptive mechanisms that allow them to live under extreme conditions. These conditions include cold and harsh environments such as those found at high-altitude locations. It has been difficult to define at which elevation the effects of high-altitude become more severe and where the threshold is located in terms of mild or severe hypoxia (West et al., 2007). Imray et al. (2011) used classification of high-altitude exposure in accordance with recommendations from the International Society of Mountain Medicine, a categorization that seems to be the most pragmatic (Imray et al., 2011). The author defined low altitude as everything that is located below 1,500 m, moderate or intermediate altitude from 1,500 to 2,500 m, high-altitude from 2,500 to 3,500 m, very high-altitude from 3,500 to 5,800 m, extreme high-altitude above 5,800 m, and death zone above 8,000 m (Imray et al., 2011).

Worldwide, more than 140 million people reside above 2,500 m (Pasha and Newman, 2010). Studying high-altitude dwellers is essential to understand the environmental, physiological, and genetic factors that are linked to the incidence and prevalence of different maladies in these populations (Miranda et al., 2019).

Acute and chronic exposure to high altitude has a variety of effects on human physiology and can be the cause of the occurrence of many diseases (Milledge, 2020). Barometric pressure decreases exponentially with increasing altitude. Consequently, the partial pressure of oxygen also decreases, despite which the composition of gases in the atmosphere remains unaltered. The physiological consequences of this reduction in oxygen availability begin to be noticeable, even at rest, from an altitude of 2,500 m (Ortiz-Prado et al., 2019). For that reason, residents at high altitudes have physiological and morphological adaptations that allow them to deal with these environmental conditions, whereas habitual residents at low altitudes must acclimatize once they ascend to these elevations (West, 2006). The anatomical, ventilatory, and cardiovascular differences between populations (residents at low vs. high altitudes) have been widely described; nevertheless, it is still unclear if those physiological alterations act as protective ("strain") or risk ("stress") factors (Sherpa et al., 2011; Ortiz-Prado et al., 2017; Dhiman et al., 2018).

One of the most controversial issues is the potentially higher cardiovascular risk among high altitude dwellers. The cardiovascular health of populations permanently living at high altitude may not only depend on the degree of altitude adaptation reached by this particular population but also on lifestyle factors and genetic predisposition (Aryal et al., 2015). In particular, various risk factors can be noticed among Andean highland populations including excessive erythrocytosis (Monge's disease or chronic mountain sickness) and a hypercoagulable-prothrombotic state linked to a higher incidence of thrombosis, probably due to venous blood flow stasis and secondary polycythemia (Zangari et al., 2013). On the other hand, factors such as hypercholesterolemia and hyperlipidemia seem to have a lower prevalence among highlanders, thus indicating a reduced risk of developing atherosclerosis and stroke (Faeh et al., 2009; Aryal et al., 2017; Ortiz-Prado et al., 2019).

Long-term exposure to hypobaric hypoxia seems to be linked to healthier blood lipid profiles when compared with those of residents living at sea level (Mohanna et al., 2006; Siqués et al., 2007; Vats et al., 2013). According to the report by Gonzales et al., who studied 158 people living at 4,100 m, the fraction of non-high-density lipoprotein (HDL) cholesterol and triglycerides is directly associated with the value of hemoglobin, and their increase, in turn, is associated with higher diastolic blood pressure. More specifically, high hemoglobin levels were directly associated with higher levels of total cholesterol, low-density lipoprotein (LDL), HDL, and triglycerides, and no association was found between hemoglobin and glucose (Gonzales and Tapia, 2013). Al Riyami et al. (2015) showed that altitude was the most significant factor affecting HDL-C, followed by gender, serum triglycerides, and finally the 2-h post prandial plasma glucose. Also, Vats et al. (2013) pointed out that in the process of acclimatization to high altitude, there is an increase in the diastolic blood pressure and heart rate, in addition to an increase in HDL levels. Although these responses have been described previously, the differences between the two indigenous groups, which shared the same ancestry but adapted to life at very different altitudes, have never been reported before. This fortunate circumstance gives us a great opportunity to understand the role of exposure to the altitude as a causal determinant of these differences disregarding genetic ancestry.

The objective of the current report is to explore the plasma lipid profile and cardiovascular risk differences among autochthonous Kiwcha populations permanently living at low and high altitudes.

METHODOLOGY

Study Design

A cross-sectional analysis of the differences in plasmatic lipid profiles and cardiovascular risk was carried out in two populations of Kiwcha natives from Ecuador living at two different elevations.

Abbreviations: LDL, Low-density lipoprotein; HDL, High-density lipoprotein; AHA, American Heart Association; HGDP-CEPH, Human Genome Diversity Project – Centre d'Étude du Polymorphisme Humain; EUR, European; AFR, African; NAM, Native American; AIMs, Ancestry Informative Markers; IQR, Interquartile Range; DS, Deviation Standard.

Setting

This study was carried out in Ecuador in two geographically different areas, the Andes mountain range and the Amazon Basin.

Participants

This study was carried out in 134 women and 79 men who voluntarily accepted to participate in the study. All the participants who voluntarily agreed are members of the Kiwcha indigenous group from Ecuador. The high-altitude group came from Oyacachi, a small Kiwcha community located at 3,800 m of elevation while the low-altitude group was the Kiwcha people living at Limoncocha, located at 230 m of elevation.

Inclusion Criteria

The study was conducted among healthy volunteers of both sexes without any type of comorbidity or chronic disease, between the ages of 18 and 85, who were born and currently residing in Oyacachi (high-altitude group), and in Limoncocha (low-altitude group).

Exclusion Criteria

Volunteers who were under 18 years of age, those who were born in another community, and those who do not habitually reside in the aforementioned parishes were excluded from the study.

Variables and Outcomes

Sociodemographic variables, such as age, sex, marital status, and place of residence were recorded. Vital signs were obtained by our team that included five doctors in the field. To assess arterial blood pressure, we used an upper arm blood pressure monitor 3 Series® Model: BP7100 from OMRON based on the American Heart Association (AHA) Recommendations for Blood Pressure Measurement (Smith, 2005). To evaluate body fat percentage, body mass index (BMI), and body weight we use the Omron Body Composition Monitor & Scale HBF-514C manufactured by OMRON which measures fat using the bioimpedance method. The temperature was measured using a portable Non-Contact Professional Medical Grade Infrared Thermometer. For the entire blood laboratory work, we included the following lipid profile serum parameters: LDL (mg/dl), HDL (mg/dl), triglycerides (mg/dl), and total cholesterol (mg/dl). We have also included mean fasting blood glucose levels (mg/dl) and clinical parameters including systolic and diastolic blood pressure, heart and respiratory rate, height and body weight, and BMI. We computed the 10-year risk of heart disease or stroke for ages between 40 and 79 years using the AHA risk calculator (http://Kiwcha.cvriskcalculator.com/). A blood sample was used to extract RNA to determine ancestry roots from both populations and confirm that they share the same genetic traits.

Outcome

The main outcome is to determine the different lipid profiles and cardiovascular risk ratios among genotype-matched Kiwcha indigenous people who live at high altitude vs. their counterparts who live at low altitude.

Data Sources

Individual-level sociodemographic information, place of residence, and past medical history were obtained *in situ* in both communities. A complete physical examination including measurement of body weight and height, arterial blood pressure, body temperature, resting heart, and respiratory rate, and arterial oxygen saturation was performed.

Study Size and Sample Size Calculation

In terms of the number of patients required to achieve significance, the sample size (n) and margin of error (E) were given by the following formula:

$$x = Z({}^{c}/_{100})^{2} r(100 - r)$$

$$n = {}^{Nx}/_{[(N-1)E^2 + x]}$$

$$E = Sqrt[{}^{(N-n)x}/_{n(N-1)}]$$

where N is the population size ($n = 570$ in Oyacachi and $n = 890$ in Limoncocha), (r) is the fraction of expected responses (50%), and $Z(c/100)$ is the critical value for the confidence level (c). The total number of medical and physical evaluations required to achieve statistical significance was 82 for the high-altitude group and 96 for the low-altitude group. Through a nonprobability convenience-based sampling technique, 118 patients (40 men and 78 women) were included for Limoncocha and 95 patients were included for (39 men and 56 women) for Oyacachi.

Data Analysis

Descriptive statistics were used to analyze and visualize differences between the two populations. A chi-square test was performed to check the association or independence of categorical variables. When the expected values were <5 in any of the categories, Fisher's exact test or Spearman's test were used when the variable had evident asymmetries with histograms prior to the selection of the test. Additionally, a two-way ANOVA test was performed to determine the influence of gender and altitude of the populations on the continuous dependent variables, followed by age correction.

To compare the population ancestries for Oyachachi and Limoncocha, a t-test was performed, considering individual genotypes. Normal distribution and equal variance were assumed; the test concludes ($p = 0.05$) that there is no difference between any of the continental contributions of the three founding ethnic groups considered.

All statistical analyses accepted significance when p-value < 0.05. Calculations were completed using the IBM Corp. Released 2014. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: and R Core Team software 2018 version 3.5.1. Cartography was generated using QGIS Development Team 2.8 and all the references were managed using the open-source software Zotero 5.0.85.

DNA Extraction and Analysis of Ancestry Ratios

To compare the ancestry of the two populations, a subsample of 47 unrelated individuals (30 Oyacachi vs 17 Limoncocha) was selected. We looked for a subsample among all the individuals to identify those subjects who did not have any first-order degree of consanguinity, a condition that is based on our laboratory protocol for ancestry analysis. DNA extraction was performed from FTA cards (GE Healthcare) by the Chelex method. The extracts were then diluted to a concentration of 5 ng/ul using the NanoDrop 2000 UV-Vis spectrophotometer (Thermo Scientific, Waltham, MA; Walsh et al., 1991). 46-plex autosomal ancestry informative deletion-insertion markers (46-plex AIMs-InDel) were amplified. Fluorescent amplicons were sized by capillary electrophoresis in Pop-7 polymer using a genetic analyzer ABI 3130 (Applied Biosystems, Austin, TX). Alleles were named by the software Genemapper V 3.1 (Life Technologies, Carlsbad, CA) following nomenclature described by Pereira et al. (2012). Taking into account trihybrid historic mixture in Ecuador (Santangelo et al., 2017; Toscanini et al., 2018; Zambrano et al., 2019), inference of ancestry proportions was obtained considering the admixture model with $K = 3$ (based on runs consisting of 100,000 burn-in steps, followed by 100,000 Markov Chain Monte Carlo (MCMC) using the STRUCTURE V2.3.4 software (Pritchard et al., 2000).

All runs were made without any prior information on the origin of samples and only considered the genetic background for the ancestral continental populations based on reference samples: European, EUR ($n = 158$); African, AFR ($n = 105$); and Native American, NAM ($n = 64$). Reference genotypes were extracted from the diversity panel of the Human Genome Diversity Project-Center d'Etude du Polymorphisme Humain (HGDP-CEPH). The populations selected as comparative groups for Africa were: Angola ($n = 1$), Botswana ($n = 4$), Central African Republic ($n = 23$), Congo ($n = 13$), Kenya ($n = 11$), Lesotho ($n = 1$), Namibia ($n = 6$), Nigeria ($n = 22$), Senegal ($n = 22$), and South Africa ($n = 2$); for South America: Brazil ($n = 22$), Colombia ($n = 7$), and Mexico ($n = 35$); and for Europe: France ($n = 52$), Italy ($n = 49$), Orkney Islands ($n = 15$), and Russia ($n = 42$).

Ethical Consideration

Full ethical approval was obtained (#MED.EOP.17.01) throughout the Universidad de las Americas bioethics committee (CEISH). All patients voluntarily signed informed consent. For people who could not read or write, an official community translator and a family member capable of understanding what was described in the document were used to explain the entire context of the project and ensure that there were no doubts about it. To protect the identity and autonomy of patients, all personal information was coded to ensure anonymity.

RESULTS

Demographic Results

A total of 213 subjects were recruited in both communities. 52.9% ($n = 118$) were included from the Limoncocha low altitude group and 47.1% ($n = 95$) from the Oyacachi high altitude group. In general, women represented 63% ($n = 134$) of the entire cohort and men 37% ($n = 79$).

Age and Sex Differences

In the low altitude group, 66% were women ($n = 78$) and 34% ($n = 40$) were men, whereas at high altitude, 59% ($n = 56$) were women and 41% ($n = 41\%$) were men (**Table 1**).

The median age for the low altitude group was 41 years and 36 years for men and women, respectively. The sex–age intergroup differences were not significant for all the groups (**Table 1**).

Weight and BMI Differences

In relation to weight, we found that women at low altitudes are on average 1.9 kilos lighter than women at high altitudes (60.84 kg $\pm$ 8.33 kg), but this difference was not statistically significant ($p = 0.374$). Men living at high altitudes are 20.7% lighter than their counterparts at low altitudes ($p < 0.0001$). We did not find any underweight adult subjects in any group; however, we found the proportion of overweight patients and those with obesity type I, II, and extreme obesity to be significantly higher among low altitude dwellers (**Table 1**).

Vital Signs Differences by Sex and Elevation

We found that arterial blood pressure tends to be higher in men (106/75 mmHg) than in women (102/70 mmHg). Nevertheless, this small difference is not significant. The Mean Arterial Blood Pressure (MAP) and systolic blood pressure were 6.2 and 7.5%, respectively, lower in men from the high-altitude group when compared to men from the low altitude group. These differences are statistically significant ($p = 0.01$ and 0.029) (**Table 2**).

In terms of heart rate frequency (beats per minute), high altitude dwellers have a 9.4% lower heart rate; nevertheless, gender and level of altitude did not influence heart rate calculated by a two-way ANOVA and the difference was not statistically significant ($p = 0.911$).

Despite this, we found a 5.2% lower peripheral blood oxygen saturation for the low altitude group. Gender and altitude did not influence SpO_2% calculated by a two-way ANOVA ($p = 0.076$) (**Table 2** and **Figure 1**).

Complete Blood Count (CBC), Biochemical Analysis, and Cardiovascular Risk Analysis Between Groups

Differences in white blood cell counts were not observed among the low and high-altitude groups (**Table 3**). For red blood cells (RBCs) count and microscopic features, we found that high altitude dwellers have higher cells counts and high levels of hematocrit and hemoglobin; however, they have smaller RBCs that contain less hemoglobin per erythrocyte. Nevertheless, after correcting for age, altitude, and sex, the differences did not reach the 5% established significant level (**Figure 2**).

In terms of serological biochemical parameters, we did not find significant differences in mean fasting blood glucose levels or lipid profiles. For instance, low altitude dwellers have significantly lower total cholesterol, lower HDL, and

TABLE 1 | Demographic characteristics, weight, height, and body mass index (BMI) of the two populations in relation to sex.

		Low altitude (230 m)	High altitude (3800 m)	(%) Diff.	*p*-value
Median age (IQR)	Men	42.0 (30.0–52.0)	36.0 (25.0–57.0)	15.4	0.137
	Women	41.0 (30.0–59.0)	36.0 (29.0–48.0)	13	
Young adult (18–35 Kiwcha)	Men	24 (54.5)	27 (67.5)	11.8	0.475
	Women	45 (57.0)	41 (73.2)	9.3	0.086
Adult (36–64 Kiwcha)	Men	15 (34.1)	10 (25.0)	40	0.475
	Women	19 (24.1)	11 (19.6)	53.3	0.086
Elderly (>65 Kiwcha)	Men	5 (11.4)	3 (7.5)	50	0.475
	Women	15 (19.0)	4 (7.1)	115.8	0.086
Weight (kg)	Men	74.2 ± 10.8	60.3 ± 8.71	20.7	**0.0001**
	Women	62.7 ± 14.4	60.8 ± 8.3	3.1	
Height (cm)	Men	159.9 ± 6.3	155.5 ± 9.93	2.8	**0.001**
	Women	149.2 ± 7.0	152.6 ± 8.6	2.3	
Normal weight (18.5–24.9)	Men	5 (12.5)	21 (53.8)	123.1	**0.001**
	Women	25 (32.1)	20 (35.7)	22.2	**0.036**
Overweight (25–29.9)	Men	22 (55.0)	16 (41.0)	31.6	**0.001**
	Women	31 (39.7)	29 (51.8)	6.67	**0.036**
Obesity type I and II (30–39.9)	Men	7 (17.5)	2 (5.1)	111.1	**0.001**
	Women	12 (15.4)	7 (12.5)	52.6	**0.036**
Extreme obesity (>40)	Men	6 (15.0)	0 (0.0)		**0.001**
	Women	10 (12.8)	0 (0.0)		**0.036**

Mean ± SD; IQR, interquartile range. Bold values are Statistically significant difference at 95% confidence level.

TABLE 2 | Description of the main vital signs of both populations including arterial blood pressure, heart and respiratory rate, temperature, and blood peripherical oxygen saturation.

Vital sign		Low altitude (230 m)	High altitude (3,800 m)	(%) Diff	Sig.
SBP	Women	100 (90–110)	104 (90–120)	3.9	0.029
	Men	110 (100–120)	102(99–110)	7.5	
DBP	Women	70.0 (60–80)	70 (70–80)	0	0.016
	Men	80 (70–80)	70 (60–80)	13.3	
MAP	Women	74.9 ± 8.7	77 ± 11	3	0.010
	Men	80.2 ± 8.3	75.3 ± 8.6	6.2	
HR' (m ±SD)	Women	73. ± 10	66.0 ± 11	10.1	0.911
	Men	71 ± 13	65 ± 9	8.8	
RR' (m ±SD)	Women	18 ± 18–19	18 ± 18–23	0	0.346
	Men	18 ± 18–22	18 ± 18–21	0	
SpO_2 %	Women	98 ± 97–99	93 ± 91–94	5.2	0.076
	Men	98 ± 97–98	93 ± 92–94	5.2	
T°	Women	36.7 ± 36.3–37.2	36 ± 36–36	0.8	0.565
	Men	36.5 ± 36.3–37.2	36.1 ± 35.7–36.7	1.1	

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR', Heart Rate Beats per minute; RR', Respiratory rate breaths per minute; m ±SD, Mean ± standard deviation; IQR, interquartile range; SpO_2%, peripheral Blood Oxygen saturation; T°, Body Temperature; MAP, Mean Arterial Blood Pressure (mmHg).

lower LDL values for both sexes. Nevertheless, triglycerides are on average 26% lower among high altitude dwellers. Despite these clinical differences, after correcting for age, sex and altitude, they did not reach significance at 5% level (**Figure 3**).

When computing a 10-year risk of heart disease or stroke using the atherosclerotic cardiovascular disease (ASCVD) algorithm published in the 2013 American college of cardiology (ACC)/AHA Guideline on the Assessment of Cardiovascular Risk, we did not find any statistically significant difference between groups (**Table 3**).

Gender and the level of altitude did not influence the overall blood biochemical analysis calculated by the two-way ANOVA. However, the combination of gender and altitude showed to significantly affect mean corpuscular hemoglobin concentration ($p = 0.031$),

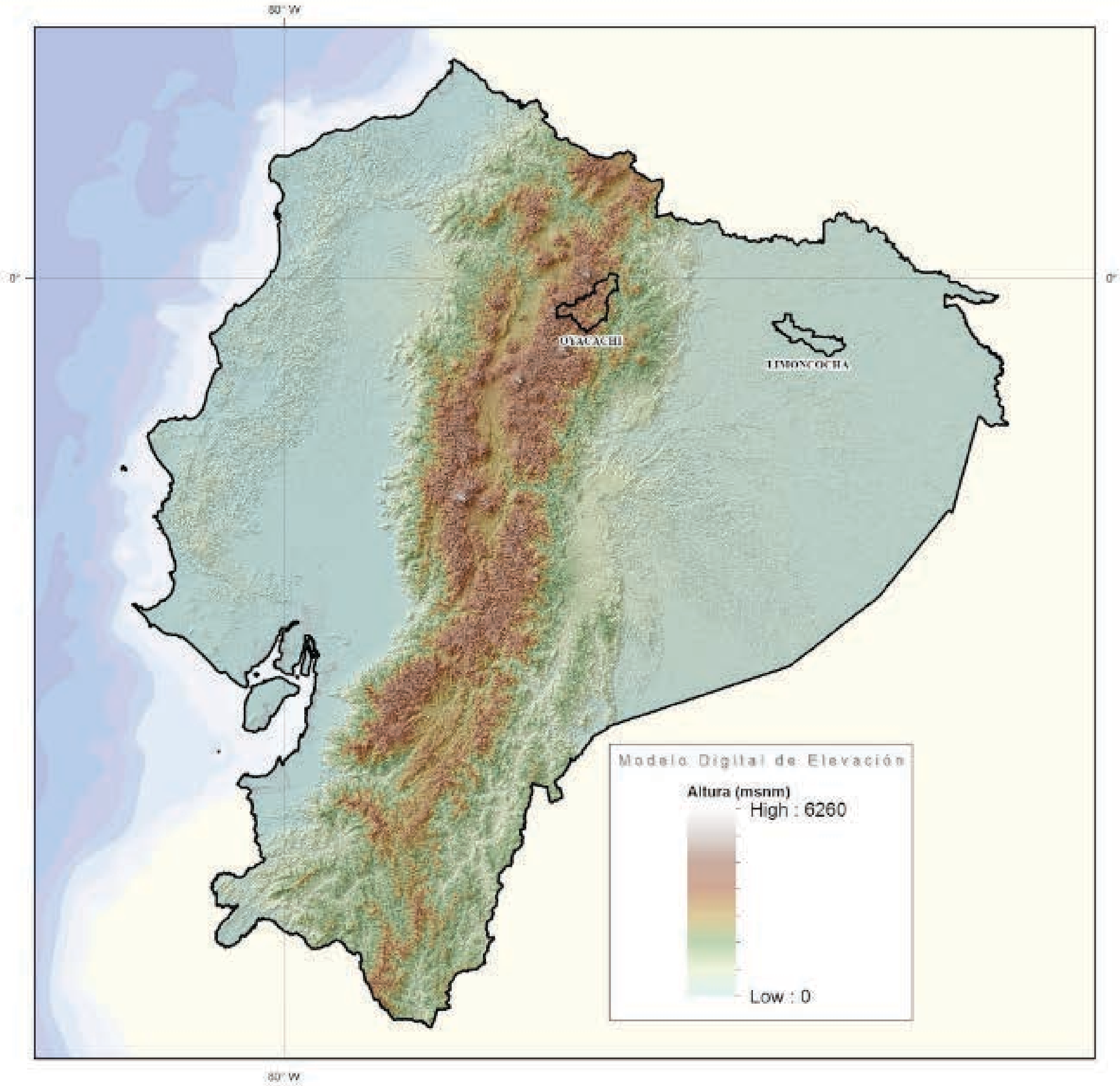

FIGURE 1 | Vital signs differences according to sex and altitude.

even when this relationship considers adjustment for age ($p = 0.033$).

Ancestry proportions between Oyacachi and Limoncocha are not statistically different. Both communities retain Native American ancestry >97% and vary slightly in the European (0.6 vs. 1.4%) and Afro (0.3 vs. 0.7%) contributions. However, they are highly conserved populations in general, Oyacachi being the most mixed, considering the data obtained from this sample and analysis (**Figure 4**).

DISCUSSION

Our study demonstrates that hematological, biochemical, and some clinical parameters differ between the two populations that share the same ancestral origin but have resided for centuries at two different geographical locations. Most of them are not influenced by gender or elevation. While all these differences have been described in different populations, this is the first time that we have been able to determine them as genetically controlled populations that share genetic, sociodemographic, and

TABLE 3 | Complete blood count (CBC) and blood biochemical analysis in low and high-altitude dwellers.

	Women		Men		
	Low altitude (230 m)	**High altitude (3,800 m)**	**Low altitude (230 m)**	**High altitude (3,800 m)**	***P*-value**
Lymphocytes	7.0 ± 2.0	6.0 ± 2.0	7.0 ± 2.0	6.0 ± 1.0	0.163
Neutrophiles	56.0 ± 8.0	55.0 ± 9.0	55.0 ± 7.0	52.0 ± 9.0	0.416
Lymphocytes	36.0 (32.0–42.0)	36.0 (31.0–40.0)	36.0 (32.0–40.0)	37.0 (32.0–46.0)	0.763
Monocytes	6.0 (5.0–7.0)	6.0 (5.0–7.0)	7.0 (6.0–9.0)	7.0 (6.0–8.0)	0.418
Eosinophiles	2.0 (1.0–2.0)	1.0 (1.0–3.0)	2.0 (2.0–3.0)	2.0 (1.0–3.0)	0.190
Hematocrit	41.0 (38.0–42.0)	47.0 (45.0–49.0)	45.0 (43.0–47.0)	52.0 (50.0–54.0)	0.515
Hemoglobin	13.45 ± 1.01	15.23 ± 1.10	15.31 ± 1.11	17.06 ± 1.01	0.897
RBC	4.0 ± 4.0–5.0	5.0 ± 5.0–5.0	5.6 ± 5.3–6.0	6.0 ± 5.0–6.5	0.363
Platelets	263.00 ± 52.00	276.00 ± 47.00	257.00 ± 53.00	257.00 ± 55.00	0.368
MCV	94.00 ± 4.00	92.00 ± 4.00	93.00 ± 3.00	91.00 ± 4.00	0.826
MCH	32.0 (30.0–32.0)	30.0 (29.0–31.0)	32.0 (31.0–32.0)	30.0 (29.0–31.0)	0.250
MCHC	33.0 (33.0–34.0)	33.0 (32.0–33.0)	34.0 (34.0–35.0)	33.0 (33.0–33.0)	**0.031**
Glucose	89 (83–95)	89 (84–92)	91.0 (83.0–97.0)	90.0 (84.0–95.0)	0.411
Cholesterol	174 ± 37	193.0 ± 28.0	167.0 ± 38.0	196.0 ±30.0	0.275
Triglycerides	127 (90–179)	90 (73–143)	133.0 (106.–180)	110.0 (78.0–146.0)	0.438
HDL	46.0 (40–55)	56.0 (46.0–71.0)	41.0 (38.0–47.0)	49.0 (44.0–60.0)	0.610
LDL	98.0 ± 32.0	113.0 ± 22.0	93.0 ± 34.0	117.0 ± 26.0	0.278
AHA Heart Risk	2.0 (1.0–5.0)	1.0 (1.0–5.0)	3.0 (2.0–5.0)	5.0 (2.0–9.0)	0.461

RBC, Red Blood Cells; MCV, Mean corpuscular volume; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration. Bold value is statistically significant difference at 95% confidence level.

economical similarities, and geographically distinct territories (GAD Oyacachi, 2019; GAG Limoncocha, 2019).

Some of the differences that we have found, especially anthropometric distinctions are probably due to the adaptive processes. These processes have been described in several investigations that have explained how humans chronically exposed to high altitudes become more fit to function under hypoxic conditions (Julian and Moore, 2019).

The results of our study compare anthropometric differences in a genotype-controlled indigenous adult population living at low (230 m) and high altitudes (3,800 m). When analyzing the data, we observe that in general, women from high altitudes are slightly lighter and slightly taller than women from the lowlands (Merrill, 2020); nevertheless, men from high altitudes are significantly shorter and lighter than men from low altitudes. Our findings are similar to those reported in Bolivia by Leatherman et al. (1984). This study conducted an anthropometric survey among 138 men from rural mountainous areas of Bolivia (3,700 m) and concluded that men from high altitudes are shorter and lighter than their low altitude counterparts (Leatherman et al., 1984). Among Quechuas, a similar native group from Peru, Toselli et al. (2001) found individuals shorter at high altitudes in relationship to their corporal mass (Toselli et al., 2001). In contrast to earlier findings, however, no evidence of these results was detected by Khalid (1995) when they showed that high altitude residents from Saudi Arabia were significantly heavier and taller than the low altitude control group. These differences between two populations (the Andean and the Saudis) could demonstrate differences in terms of adaptation, something that has been described extensively before (Moore et al., 1998, 2011; Beall, 2007; Tyagi et al., 2008; Moore, 2017a).

On the other hand, women from high altitudes have a higher proportion of obesity than their low altitude counterparts, possibly due to cultural conditions that force women to stay at home cooking while men leave their houses to work (Khalid, 2007; Lin et al., 2018).

It has been hypothesized that at least 5% of high-altitude natives from Peru possess a newly discovered gene named *FBN1*. This gene seems to be associated with favoring high altitude Andean natives with low stature and possibly thicker skin (Pennisi, 2018). It is well-known that high altitude dwellers and animals are often smaller, an evolutionary response to the shortage of food or oxygen and thicker skin, which may help shield the body from intense UV radiation in such places (West, 2012; Pennisi, 2018).

It is well-known that weight among newborns is significantly lower among high-altitude neonates than their sea-level counterparts (Al-Shehri et al., 2005; Hoke and Leatherman, 2019), a situation that might continue not only during pregnancy but during the 1st years of childhood and adolescence (Lichty et al., 1957; Iannotti et al., 2009; Moore et al., 2011).

The fact that newborns are smaller has to do with an adaptive process that aims to reduce oxygen consumption by the fetus, being more efficient to deliver oxygen to a smaller organism through a smaller placenta (Krüger and Arias-Stella, 1970; Zamudio, 2003; Dolma et al., 2021).

Besides anthropometric differences, high altitude residents had superior lung capacities, enhanced vascularity, a blunted ventilatory response to sustained hypoxia and lower exercise

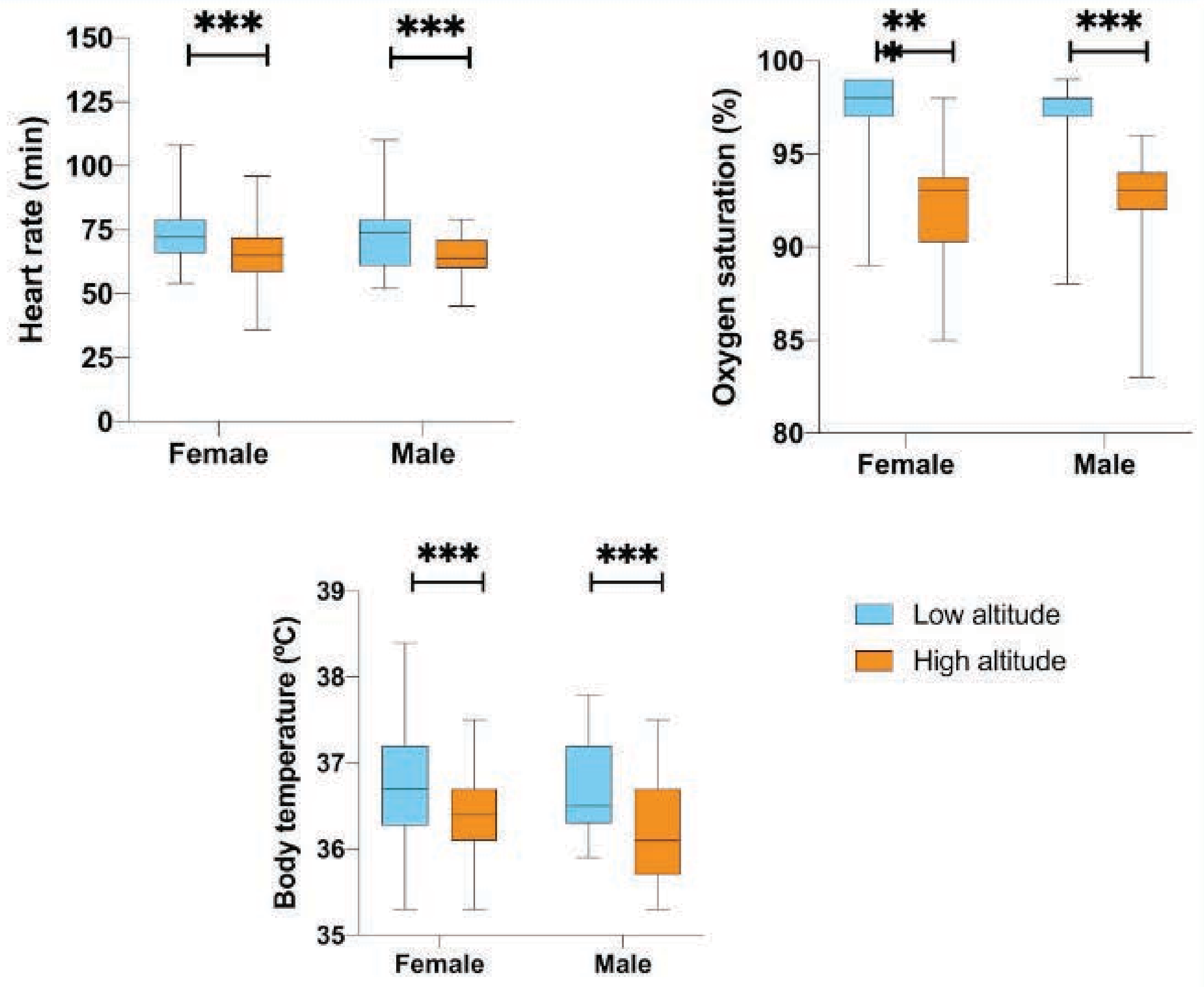

FIGURE 2 | The differences of Hematological parameter according to sex by altitude. **,***Represents outliers values.

ventilation, and overall superior efficiency of O_2 transport, utilization, and distribution (Zhuang et al., 1993; Brutsaert et al., 2005; Moore, 2017a; Ortiz-Prado et al., 2019). In the present study, we tried to identify whether there are physiological differences that are not necessarily due to sociocultural, social, economic, or differences in habit. According to the latest data from local governments in both Oyacachi and Limoncocha, the schooling rate, mortality rate, economic dependence, and access to health care services are similar in both parishes (GAD Oyacachi, 2019; GAG Limoncocha, 2019). Both parishes have only one health center provided regulated by the Ministry of Public Health (MoH).

In relation to high altitude lifestyle differences, habits, and endogenous preconditioning, gathering data is a complex task. Different populations have different eating habits, different lifestyles, and they usually subsist in a way different than their low-land counterparts (Westerterp, 2001; Lundby et al., 2006; Li and Zhao, 2015; Brutsaert, 2016). The data about risk factors available in Ecuador suggest that people living in provinces from the highlands consume more alcohol (17.1 vs. 9.1%) and smoke more (6.5 vs. 2.5%) than the people living at lower altitudes (Freire et al., 2015). In a general nationwide analysis, the National Institute of Statistics and Censuses of Ecuador (INEC) reported that people in the coast region seem to have a higher consumption of carbohydrates (36 vs. 30%) than those living in the highlands (INEC, 2018). Although these data on dietary variability could be extrapolated to the population living at high altitudes in Ecuador, it is well-known that people visiting high altitude locations have a significant loss in appetite and an accelerated metabolism that might speed up weight loss (Karl et al., 2018; Rausch et al., 2018).

The aforementioned similarities and some differences shared by both populations might not be fully responsible for our findings. We believe that physiological, hematological, and lipid

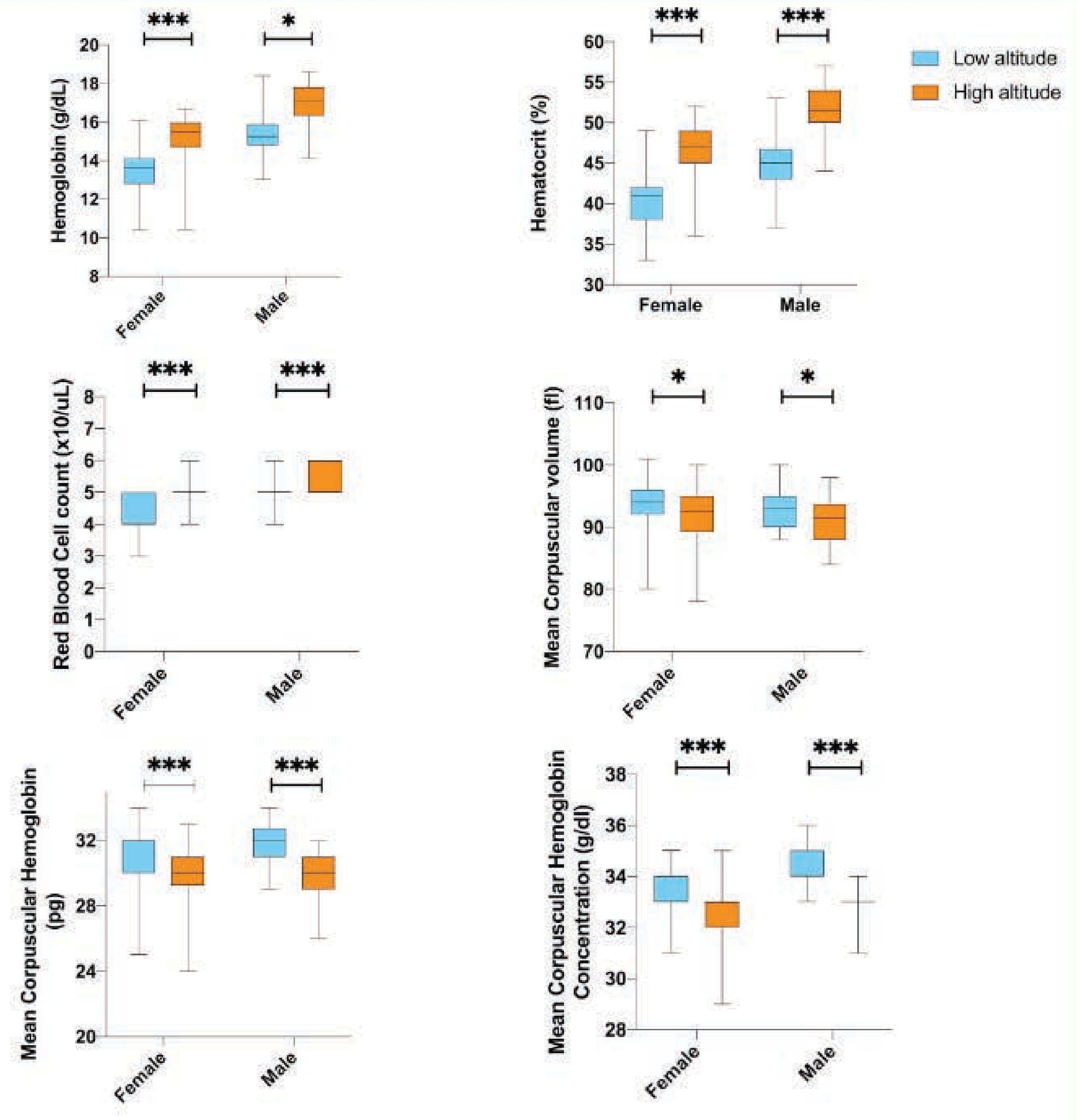

FIGURE 3 | Blood biochemistry and lipid profile difference value according to sex by altitude. **,***Represents outliers values.

profile differences have a genetic, respiratory, circulatory, and adaptive origin although most of them were not influenced by gender or elevation. For instance, we found that heart rate (HR') within the high-altitude population was 7 beats per minute slower than those at low altitudes and men always report lower MAP than women. This may be explained by the significantly high polycythemia described at high altitudes (Winslow, 1984). The higher the number of RBCs, the easier the oxygen transport, translating into a reduced cardiac output among adapted populations (West et al., 2007; Miggitsch et al., 2009). In a recently published analysis, Holmström et al., suggested that a lower metabolic rate and greater parasympathetic activity might be common among highlanders (Holmström et al., 2020).

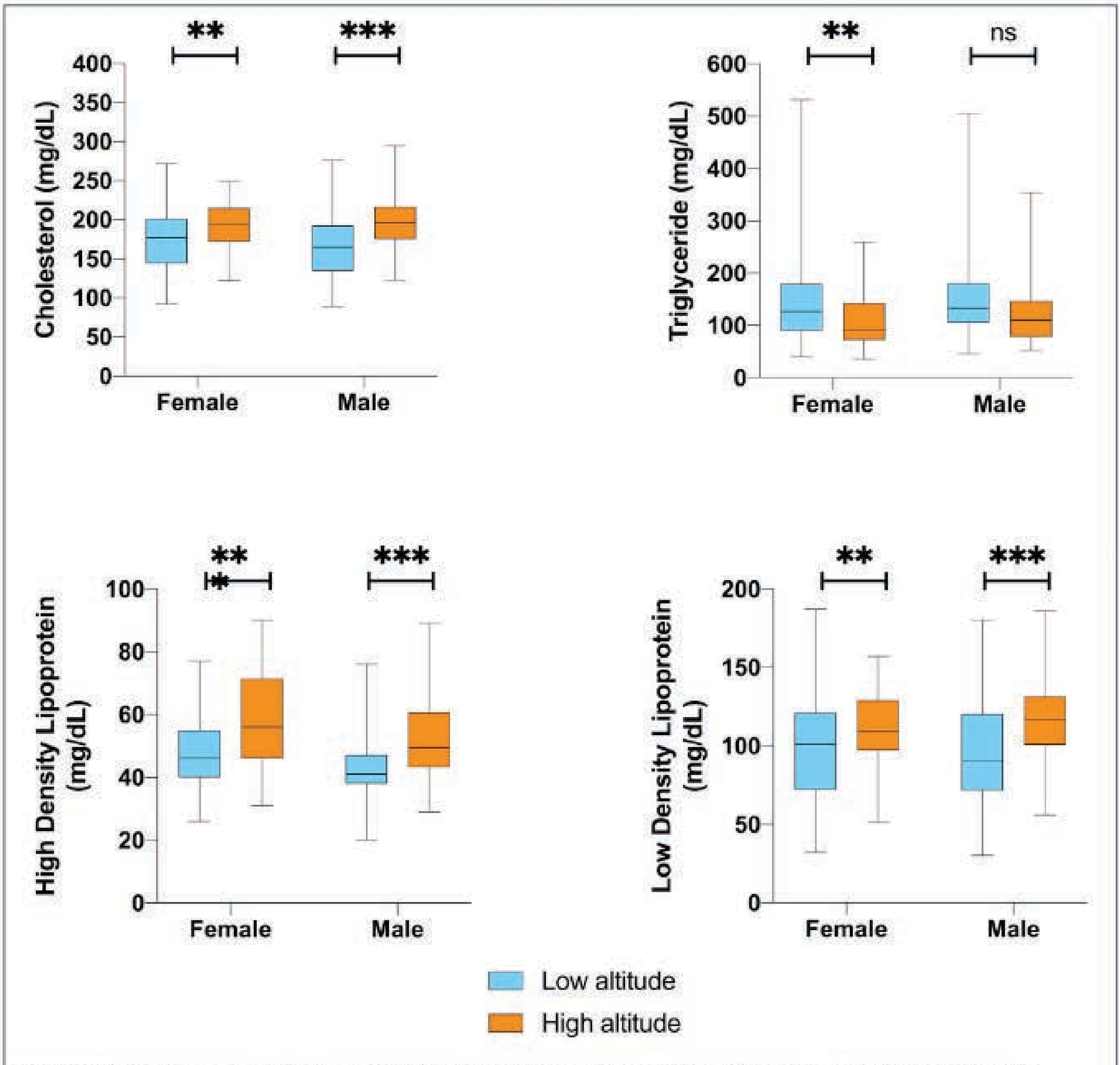

FIGURE 4 | Ancestry and main significant clinical and laboratory findings differences between low and high-altitude group. **,***Represents outliers values.

Having smaller RBCs, higher hemoglobin concentrations, lower MAP, and other differences might be, in part, attributed to their adaptational process experienced for centuries of living at different altitudes (Moore et al., 2011; Moore, 2017b). The Kiwcha population living at 230 m above sea level migrated further south centuries ago, while the Kiwcha group living above 3,800 m above sea level found a place to successfully thrive at a high altitude (Cardoso et al., 2012). When comparing the data obtained from both indigenous groups located at low and high altitudes, we did not find differences in the profile of their white blood cells; however, the size of RBCs and hemoglobin composition were found to be clinically different as expected and noted in several previous studies (Beall et al., 1998; Beall, 2006; Storz, 2007).

The difference in the number of RBCs and their size is expected since the low availability of oxygen at high altitudes due to the low barometric pressure causes a positive response on erythropoiesis and the subsequent production of RBCs (Zhong et al., 2015; Akunov et al., 2018; Ortiz-Prado et al., 2019).

The observed differences within the high-altitude population (**Figure 5**) might indicate an increased oxygen-carrying capacity (Samaja et al., 2003). The higher the production of the

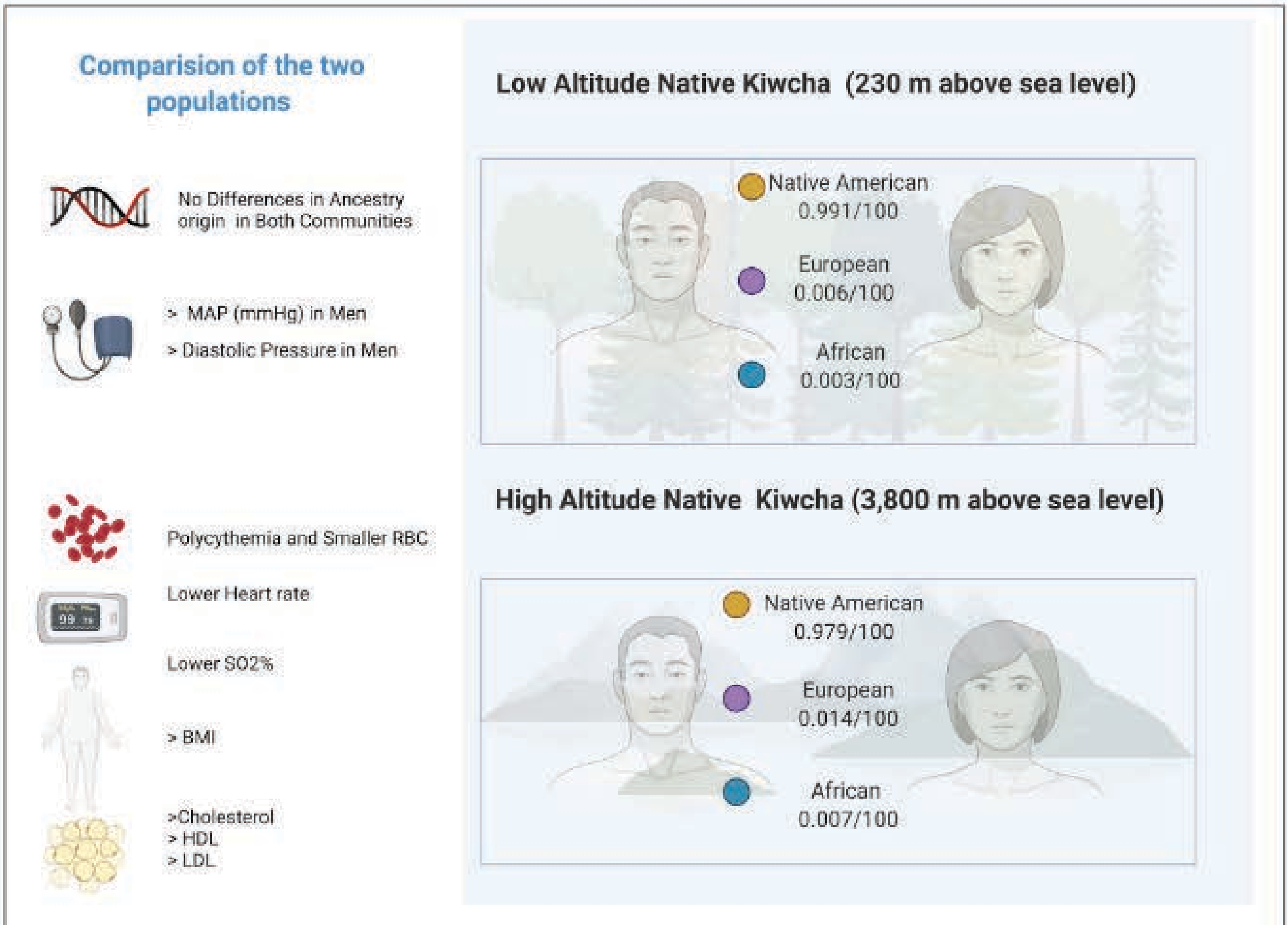

FIGURE 5 | Digital infographic showing the main clinical differences between the inhabitants of Limoncocha (low altitude) and Oyacachi (high altitude).

RBCs the thicker the blood, therefore, adaptative mechanisms based on a slightly reduced size of the RBCs and lower hemoglobin concentration within the erythrocyte might confer an evolutive advantage, reducing the risk of blood stasis (Stobdan et al., 2017).

Also noticeable are the differences in plasma lipid profile, as the group located at low altitude is more prone to having higher levels of triglycerides, especially among women, whereas the group located at a high altitude presents higher total cholesterol serum level and LDL and HDL levels which differ from men to women. Partially supporting these findings, high rates of hypercholesterolemia have been described in adult populations above 3,600 m that inhabit Peru and Tibet (Mohanna et al., 2006; Sherpa et al., 2011). However, the study of the influence of altitude on the lipid profile parameters has not been able to show causality due to the wide variability in the available data. A study by Ranhotra and Sharma, when comparing two populations of indigenous Khasis adults living at high and low altitudes, showed a decrease in total cholesterol and LDL of high-altitude residents, accompanied by a decrease in triglyceride levels at high altitudes (Ranhotra and Sharma, 2010). Similarly, a study by Siqués et al. carried out in natives of low altitudes who were exposed for 8 months at a height of 3,550 m did not reveal changes in total cholesterol levels and was accompanied by an increase in the concentration of triglycerides after altitude exposure (Siqués et al., 2007). Therefore, the influence of external factors such as physical activity, sedentary lifestyle, diet, and tobacco consumption has a considerable impact on the lipid profile of the altitude inhabitants.

These differences in habit patterns, lipid profile, and even in the ratio between obese and non-obese populations could be associated with lower mortality caused by cerebrovascular and cardiovascular diseases at high altitudes (Faeh et al., 2009; Burtscher et al., 2021).

Faeh et al. (2009) and Burtscher et al. (2021), provided data supporting the statement that living at a moderate altitude (1,000–2,000 m) elicits beneficial effects on all-cause mortality for both sexes, including diseases of the circulatory system in Switzerland and Austria, respectively (Faeh et al., 2009; Burtscher et al., 2021).

In the Kiwcha's case, the geographical isolation, and consequent sociodemographic and cultural factors that have been exposed over time, determine some behavioral differences between the Kiwcha inhabits of Oyacachi and Limoncocha living at different altitudes, which also may have an influence on our findings (GAD Oyacachi, 2019; GAG Limoncocha, 2019).

Despite not having found significant differences in the risk for the development of heart disease and stroke, lower rates of coronary heart disease and stroke have been observed in the European population living at moderate altitudes (Faeh et al., 2009; Burtscher, 2016), and a progressive decrease in mortality from coronary heart disease and stroke has been observed as the altitude increases. External factors such as hypoxia level and solar radiation can also play a role. However, these effects are mainly observed at moderate elevations (around 2,000 m) in contrast to higher elevations (above 3,000 m; Moore, 2001; Faeh et al., 2009; Burtscher, 2016).

The study of these Andean populations confers an interesting opportunity to explore differences in a well-controlled group. The Oyacachi Kiwcha population (high altitude) and the Limoncocha group have evolved differently thanks to their geographical differences. In our context, having two populations that are genetically similar but have adapted to their landscapes for more than 500 years may provide important information on the mechanisms that could be linked to adaptation. As the adaptation to chronic hypoxia is polygenic, molecular adaptations may differ from those found in other parts of the planet, as has been seen among people living in the Himalayas or the mountainous areas of Ethiopia (Moore, 2001; Azad et al., 2017).

For instance, a recently published study suggests that both genetic predisposition and environmental exposure determine the size and function of human organs such as the spleen (Holmström et al., 2020). Although this information has not been compared with Andean natives, the increased spleen size found among Sherpas might also be linked to an improved circulating hemoglobin function (Holmström et al., 2020).

In an extensive literature review by Azad et al. (2017), the authors described the genomic implications of the adaptation of different organisms to high altitude (Azad et al., 2017). They described how a series of genetic components gave rise to the different bio-molecular pathways that regulate oxygen transport, the circulatory system functioning or the overall erythrocyte, oxygen, and hemoglobin homeostasis (Azad et al., 2017).

We suggest that several molecular and physiological mechanisms that have yet to be revealed might play a direct role in explaining some of the differences described in this study. Although numerous factors and variables could not be controlled, the reported findings provide new insights about an understudied population.

LIMITATIONS

The main limitation of this study was the absence of a dietary and exercise assessment, as diet massively alters blood lipid profile. Another limitation was that despite obtaining a significant sample size to carry out this study, not the entire population belonging to these indigenous communities that met the inclusion criteria was willing to participate. So, even if it is a small probability, it cannot rule out that the inclusion of the data corresponding to those people who did not participate could produce variations in our results or even alter our interpretation. Another potential weakness is the gender asymmetry in the sample size because men were a lower number of participants than women.

CONCLUSION

Permanent life at both altitudes induced well-known adaptive responses in Kiwcha dwellers: increased number of erythrocytes, hemoglobin concentration, hematocrit level, and serum glucose level. Although we have found remarkable differences in the plasma lipid profile between the populations at the two altitudes, these alterations did not seem to be influenced by altitude, sex, or age.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Universidad de las Americas, CEISH. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EO-P was fully responsible for the conceptualization, data collection, and elaboration of the study. EO-P, DP, and JM-M participated in drafting the manuscript equally and are fully responsible for it. DP, JM-M, and DD visited indigenous communities and collected samples. KS-R, JI-C, and EO-P contributed to the data collection and the construction of figures and tables. EO-P, MC, EV, JI-C, and GV contributed to the descriptive statistical analysis and the discussion section of the manuscript. GB was responsible for DNA extraction and analysis of ancestry ratios. EO-P critically reviewed the entire manuscript and produced several comments prior to submission. All the authors have read and approved the final version of the manuscript.

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Best wishes,

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Optimism and health self-perception-related differences in indigenous Kiwchas of Ecuador at low and high altitude: a cross-sectional analysis

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ABSTRACT

Background: Living at high altitude causes adaptive responses at every physiological and molecular level within the human body. Emotional and psychological short or long-term consequences, including mood changes, higher mental overload, and depression prevalence as well as increased risk to commit suicide have been reported among highlanders.

Objective: The objective of the current report is to explore the differences in self-reported dispositional optimism and health perception among sex, age and genotype controlled indigenous Kiwcha natives living at two different altitudes.

Methodology: A cross-sectional analysis of the comparison of the means of the subscales and summary scores of the SF-36 self-reported questionnaire and the Life Orientation Test-Revised (LOT-R) was conducted among 219 adults Kiwchas living at low (230 m) and high altitude (3,800 m) in Ecuador.

Results: High-altitude dwellers presented lower scores in all the studied dimensions of SF-36 and the total score. Differences were found for the Role limitation sphere due to Vitality ($p = 0.005$), Mental Health ($p = 0.002$) and social functioning ($p = 0.005$). In all the cases, participants living at low altitudes scored higher than those living at high altitudes. Lowland women were more optimistic than their high-altitude counterparts.

Conclusions: We observe that populations located at high altitudes have more unfavourable self-reported health states. Although our results depict the existence of significant differences in the health status of indigenous peoples living at different altitudes, further studies are needed to explain in depth the sociodemographic and/or environmental factors that might underlie these differences.

Key words: SF-36; Emotional Health; Physical functioning; Body Pain; Optimism; High altitude

Introduction

Humans have settled in almost every region of the planet, including those high altitude mountainous regions around the world (West et al., 2007). These particular regions are often hostile, having colder temperatures and lower atmospheric pressure than places situated close to sea level. Currently, more than 5.7% of the population reside above 1,500 m of altitude and at least 140 million live above what is considered high altitude (2,500 m) (Burtscher, 2014). It has been difficult to define at which elevation the effects of high altitude become more severe and where the threshold is located in terms of mild or severe hypoxia (West et al., 2007). Imray in 2011 (Imray et al., 2011) used the classification of high altitude exposure according to the recommendations from the International Society of Mountain Medicine, a categorization that seems to be the most pragmatic. The author defined low altitude everything located below 1,500 m, moderate or intermediate altitude between 1,500 to 2,500 m, high altitude from 2,500 to 3,500 m, the very high altitude from 3,500 m to 5,800, more than 5,800 extreme high altitudes and above the 8,000 m is considered the death zone (Imray et al., 2011).

The effects of high altitude exposure on people have been described several times before (Burtscher, 2014; Moore, 2017; West et al., 2007). Acute exposure to hypobaric hypoxia, especially above 2,500 m triggers several physiological responses in the body, mainly driven by cardiorespiratory compensatory mechanisms (Gaur et al., 2021; Naeije, 2010). At the same time, chronic and long-term exposure to high altitude has been associated with genetic, anatomic and physiological compensatory mechanisms that create better-adapted organisms to live in high altitude locations (Beall, 2007; Julian and Moore, 2019; Moore, 2017).

The effects of long-term high altitude exposure on the central nervous system and cognitive development have been studied before (Aquino Lemos et al., 2012; Hu et al., 2016; Wehby, 2013; Yan, 2014). Most of the analysis have been conducted in animal models and have shown that neurological tissue maturation and cellular replication might be affected during simulated hypobaric hypoxia (Floyd et al., 2020). In humans, studies on neuropsychological functioning are scarce. In small cohorts, it has been reported that children born above 4,000 m of elevation are less attentive and responsive to visual and auditory stimuli than children born at lower altitudes (Saco-Pollitt, 1981). Neuropsychological assessment among high altitude children and adolescent indicated a minor reduction in psychomotor speed with increasing altitude (Hogan et al., 2010).

Despite this evidence, the long-term effects of chronic hypoxia on human behavior and attitudes towards life have rarely been studied (Kious et al., 2018). It has been hypothesized that living in at high altitude may have an effect on the serotonin metabolism, reducing the synthesis of the 5-hydroxytryptophan (5-HTP), thus decreasing serotonin levels within the central nervous system(Kious et al., 2018). The results published by Kious et.al 2018 might direct our understanding in how low serotonin levels might be linked to mood symptoms that are common among people residing at high altitude (Kious et al., 2018). It has also been reported that brain chemistry seems to be altered due to long term exposure to higher altitude (Hwang et al., 2019; Shi et al., 2014). Del Maestro, Ahmad, Dong and de Aquino also reported significant correlations between high altitude depression, anxiety-related symptomatology and sleep problems (DelMastro et al., 2011).

The time-lapse between the exposure to high altitude and the presence of measurable effects is still unclear. Some reports suggest that even short-term visits to high altitude locations might have a negative on impact mental health. For instance, Barbara Shukitt-Hale and Harris R. Lieberman in 1996 have described the effects of altitude on cognitive performance and mood states (Shukitt-Hale and Lieberman, 1996). They have reported that even one-month of high altitude exposure was sufficient to increase emotional instability (Shukitt-Hale and Lieberman, 1996). Psychotic symptoms have also been reported among healthy mountain climbers while reaching extreme altitudes even for relatively short periods of time (Hüfner et al., 2018).

Previous research has also described adverse effects in populations residing in harsh or unwelcoming climates (Kurlansik and Ibay, 2012; Melrose, 2015). Seasonal affective disorder is a condition in which life self-perception can be deteriorated in colder climates (Kurlansik and Ibay, 2012). The fact that living at higher altitudes is often associated with colder weathers could be associated with this negative response towards life among highlanders.

All these effects might be linked, at least partially, with the development of some psychiatric conditions. For instance, the role of high altitude hypoxia as a risk factor for major depression or suicide has also been reported (Gamboa et al., 2011; Ortiz-Prado et al., 2017; Reno et al., 2018a). Despite the availability of some evidence, it could be interpreted that chronic hypoxia exposure is associated with poor outcomes in mental health and pessimistic attitudes about the future. In this sense, we have conducted what we believe is the first comparative analysis of the differences in self-perception towards physical and mental health, emotional well-being, and dispositional optimism in two well-controlled populations located at low and high altitude.

We hypothesize that those living at high altitudes will show worse perception of their own physical and mental health than those living at low altitudes.

Methodology:

Study design

A cross-sectional analysis of the differences in self-reported physical, mental health status and dispositional optimism among Kiwcha natives living in low and high altitudes in Ecuador.

Setting

This study was carried out in two different cantons in Ecuador. Oyacachi located at 3,800 m of elevation in the province of Napo with a population of 570 adult Kiwchas living at high altitude and Limoncocha, a canton with 890 adults Kiwcha natives living at 230 m in the Amazonian province of Sucumbios.

Participants

This study included 219 adult Kiwchas, 135 women (61.5%) and 84 men (38.5%) who voluntarily agreed to participate in the study. In Oyacachi, a small Kiwcha community with 570 adults we recruited 96 participants and in Limoncocha, a community with 890 adults, we recruited 123 volunteers. In both communities, Spanish and Quechua are the only spoken languages. Because in some cases, there may be dwellers who speak one language better than the other, an official translator was included as part of the fieldwork in both communities.

Inclusion criteria

The study was carried out in otherwise healthy women and men that volunteered with their participation in the study. The age range included every person older than 18 years old that was legally able to participate in the study. We only included subjects that were raised and born in their communities and have not left their home for more than three months at once.

Exclusion criteria

Volunteers who were 18 years of younger, those who were born in a different canton but are currently living or residing in Oyachachi or Limoncocha were excluded.

Variables and outcomes

Health status: We evaluated health profiles among participants using the 36-item short-form health survey (SF-36) (Ware and Sherbourne, 1992), a well-known self-reported questionnaire used to assess perceived health status. The questionnaire evaluates eight dimensions of the physical and emotional well-being. The dimensions included in the questionnaire are physical functioning (PF), role functioning (RF), role emotional (RE), vitality (VS), mental health (MH), social functioning (SF), body pain (BP), general health (GH). In addition, the SF-36 includes a question addressing health change (HC) in relation to the last year. In the present study we used the Spanish version of the SF-36 (Prieto and Anton, 1995) which has demonstrated good psychometric properties (Vilagut et al., 2005) that are comparable with those found for the original version in English.

Optimism: This construct was assessed using the Life Orientation Test-Revised (Scheier et al., 1994), a 10-item scale that measure how optimistic or pessimistic feel the person about the future. We used the Spanish version of the scale (Otero et al.) which present good psychometric properties (Gustems-Carnicer et al., 2017)

Outcome

Significant differences in terms of self-perception, quality of life and optimism between the two groups.

Data sources

Individual-level socio-demographic information, place of residence and past medical history was obtained in-situ in both communities. Information on the SF-36 self-questionnaire and the LOT-R was deployed within the communities with the help of our research team members in case someone had any question. Both questionnaires were presented in Spanish, because the two communities are fluent in Spanish, while a continuing follow-up was provided during the entire process in case any doubt on word meaning arouse. In case someone could not fully understood some word or any part of the questionaries, a local translator (Spanish-Quechua) was present at any time to resolve any linguistic trouble.

Study size and sample size calculation:

In terms of the number of patients required to achieve significance the sample size (n) and margin of error (E) were given by the following formula:

$$x = Z({}^{c}/_{100})^2 r(100\text{-}r)$$

$$n = {}^{Nx}/_{((N\text{-}1)E^2 + x)}$$

$$E = \text{Sqrt}[{}^{(N - n)x}/_{n(N\text{-}1)}]$$

Where N is the population size (n=570 in Oyacachi and n=890 in Limoncocha), (r) is the fraction of expected responses (50%), and $Z(c/100)$ is the critical value for the confidence level (c). The total number of medical and physical evaluation required to achieve significance was 82 for the high altitude group and 96 for the low altitude control group.

Data analysis

Descriptive statistics were used to analyze and visualize differences between the two populations. Before to conduct any analysis, normality tests were conducted to choose the appropriate analyses to be performed. Mostly data did not meet the normal distribution, then non-parametric test were used. Unpaired Wilcoxon test was performed to test differences of continuous variables and Chi-squared test was used to test the association or independence of categorical variables. When the expected values were less than 5 in any of the categories, Fisher's exact test or Spearman's test were used when the variable had evident asymmetries with histograms prior to the selection of the test. All statistical analysis accepted significance with a p-value < 0.05. Bonferroni's correction was used to avoid family-wise error rate for each group of multiple comparisons $\alpha = 1 - (1 - \alpha)\ 1/k$. All calculations were completed using the R software (R Core Team, 2020)

Ethical consideration

A full ethical approval was obtained (MED.EOP.17.01) throughout the Universidad de las Americas bioethics committee (CEISH). All participants voluntarily signed an informed consent form accepting and fully understanding the objective of our study. A local Quechua-Spanish translator was hired in both communities in case anyone had problems understanding some parts of the informed consent or the questionnaires. To protect the identity and autonomy of every subject, all personal or identifiable information was anonymously coded to guarantee their individual rights.

Results

A total of 219 persons fully completed the self-reported questionnaires, 56% (n = 123) were part of the low altitude group and 44% (n = 96) from the high-altitude group.

Age and Sex differences

In the low altitude (Limoncocha) group, 37.5% (n = 44) were men and 63.5% (n = 79) were women, while in the high-altitude group (Oyacachi), 41.6% were men (n = 40) and 58.4 % (n=56) were women. No significant differences were found regarding the distribution of participants by sex (p value: 0.54).

In the lowland group, the mean age was 43 year (SD = 17) while in the high-altitude group was 42 y (SD = 17). These differences were not statistically significant (p = 0.8)

SF-36 self-administered questionnaire

The overall scores for the SF-36 questionnaire shows a significant difference between the low and high-altitude group [Table 1 here].

The median and the interquartile range of the scores for each domain and for the total score of the SF-36 by the altitude (low vs. high) shows differences in most subscales [Figure 1 insert here.

Unpaired Wilcoxon tests, for comparing the scores by altitude, indicated that the scores were significantly different for the dimensions, after using a Bonferroni's correction the significance level was set up at $p = 0.0051$: Vitality ($p = 0.005$), Mental Health ($p = 0.002$), Social functioning ($p = 0.005$).

Perceived health by sex

For males, the results after Bonferroni correction ($p = 0.0051$) indicate no significant differences between, men living at low altitude and those living at high altitude. Also, no significant differences were found for the scores of women living at low altitude compared to those living at high altitude. No significant differences were found between men and women within the same location (Table 2) [Table 2 insert Here].

Perceived health by age group

Figure 2 shows the median scores for each dimension and the whole SF-36 for each age group (Young adults, Adults, and Elderly) by living altitude. For young adults, after Bonferroni correction ($p = 0.0051$) , significant differences were found regarding, Mental Health ($p = 0.002$) and General Health ($p = 0.004$). Table 3 shows median and IQR for each age group by altitude they were living [Table 3 insert here].

Young adults living at low altitude presented higher scores than those living at high altitude. For adults and elderly no significant differences were found in relation to the scores of the dimensions of the SF-36, neither for the total score [Figure 2 – Insert Here].

Optimism and Pessimism using The Life Orientation Test Revised (LOT-R)

The LOT-R results in the lowland people had a median of 16.0 (IQR:14.00-18.00) the same as the high-altitude group 16.0 (IQR: 13.00-17.50). No significant difference was found in the overall comparisons ($p = 0.37$).

When comparing the results by sex, women scored 16.0 in the low altitude group (IQR: 15.0-18.0) and 15.0 (IQR: 13.0-17.0) in the high-altitude group, showing a statistically significant difference ($p = 0.029$), which indicates that women living at low altitudes are more optimistic than those living at high altitude. For men, the low altitude group had a median score of 16.0 (IQR: 14.0-18.0) while the high-altitude group had a median of 18.0 (IQR: 14.9-19.0) although men living at high altitude scored higher in the LOT-R test, this difference was not statistically significant ($p = 0.15$). Also, no significant differences were detected when comparing into each age group regarding to the altitude of residence, young adults (low altitude = 16, IQR= 14.00 - 18.00; high altitude = 15, IQR = 13.00 - 18.00), adults (low altitude = 15, IQR= 14.00 - 18.00; high altitude = 16, IQR = 13.00 - 17.00), elderly (low altitude = 17, IQR= 15.00 - 18.00; high altitude = 17, IQR = 15.50 - 18.00).

Sociodemographic differences between communities

In terms of socio-demographic differences, we recognize that high altitude inhabitants have A greater share of economically active population than the low altitude group (Table 4).

[Insert table 4 Here]

Although more people work at Oyacachi, education attainment is lower among highlanders, despite this, accessing to running water, electricity and garbage collection is easier for highlanders (Table 4).

Discussion

This is the first study that aims to evaluate the level of optimism among people living at different elevations and one of the very few studies analyzing health status self-perception at different altitudes (Gonzales et al., 2013). We have used the SF-36 scale, which is one of the most widely used quality of life scales related to general health (HRQOL) in the world (Alonso et al., 1995; Lima et al., 2009). This tool has been widely validated in different languages as well as being reliable for clinical and research uses. An additional advantage of the SF-36 is the generation of eight domain scores, which give doctors and nurses a quick overview of the different aspects of HRQL of their patients (Abbasi-Ghahramanloo et al., 2020; van der Meulen et al., 2020)

When analyzing the data obtained from both indigenous groups located at a high and low altitude, we found significant differences in SF-36 dimensions related to physical symptoms such as Vitality. A dimension that assess behaviors related with energy and fatigue, which is a common body responses to the exposure of high altitude (Gaur et al., 2021; Naeije, 2010). Unsurprisingly, and in line with our hypothesis, those living at high altitude present less vitality. In fact, it seems that this perception is also supported by the presence of psychological symptoms, represented by worse mental health and social functioning in indigenous people from high altitude than those living in low altitude. The presence of these psychological difficulties in the population living in high altitude could be probably due to the alteration of serotonin metabolism and brain bioenergetics in this population due to permanent hypobaric hypoxia exposure (Kious et al., 2018). Bradwell et al. found a significant deterioration in the mood of marines exposed to training in high altitude locations and stress stimuli (cold, physical activity, decreased oxygen availability) characterized by increased fatigue, anger and depression, which may persist even 90 days after exposure to those conditions. This may be due to an increase in the levels of stress hormones that could cause a bad mood (Bardwell et al., 2005). When evaluating the alterations in the hypothalamic pituitary adrenal axis, in the face of exposure to high altitude among hikers and natives, discovering an increase in cortisol levels when exceeding 3,000 meters above sea level, however, the cortisol levels of natives (Sherpas) did not change (Park et al., 2014). Also, the results might be explained in light of the possibility of development of chronic mountain sickness, an incapacitating syndrome due to lifelong exposure to hypoxia experienced by people living at high altitude (Villafuerte and Corante, 2016). Patients with this syndrome complain about difficulty in exercising and presenting bone and join pain, which can aggravate performance in job and the perception of fatigue, and less vitality as indicated by our participants living at high altitudes. It is clear that altitude produce changes in the organism that might lead to mood changes, but at the same time mood changes can cause physical symptoms, like psychomotor retardation in depression (Buyukdura et al., 2011), which reduce behavioral components, that might explain the perception of fatigue and lees vitality in high altitude inhabitants.

Other sociodemographic and environmental factors might be involved in the origin of these differences. Certainly, people living at high altitude face up different situations that those living at low altitude (e.g., weather conditions, steep locomotion, access to natural resources, etc.) that might explain their divergent social functioning. Then, it is not possible yet to assert that geographical altitude 'per se' is the only factor that explain the presence of such psychological affectations.

In this sense, geographical, climatological, and environmental factors are significantly different in both communities(GAD Oyacachi, 2019; GAG Limoncocha, 2019). Oyacachi is located at very high altitude (2,500 m to 3,500 m) according to The International Society of Mountain Medicine, while Limoncocha is located at low altitude (< 1,500 m)(Imray et al., 2011) [Figure 3 Insert Here].

Oyacachi has an average range that goes from – 2° to 17 ° C degrees, while in Limoncocha, temperature varies from 18 to 26° C degrees. Living in colder weather as well as living in harsh weathers has been associated with behavioral changes that are linked to depression(Øverland et al., 2020; Wirz-Justice et al., 2019).

The effects of altitude on mood are evidenced from another point of view from multiple studies that have found higher rates of suicide in residents of altitude, however these are studies developed from a database with limitations (Brenner et al., 2011; Reno et al., 2018b). Betz et al. conduced an individual analysis of cases, it found that individuals who suffered suicide were more likely to have relatives with a history of depression, in the same way, several factors such as age, gender and residence can influence access to health care in high-altitude populations (Betz et al., 2011). Also, Sabic et al. reported a link between altitude and suicide among US Army veterans, thus demonstrating that even in well developed countries, presumably with minor interlocal sociodemographic differences, altitude is associated to a higher mental overload(Sabic et al., 2019).

By segregating the groups by gender, no significant difference were found by gender. Also, no significant differences were reported between adult and elderly populations of the two study groups. Probably explained by the presumption that elderly populations are often less likely to articulate mental health problems due to the concerns of stigma, shame, cultural and religious misconception(Jang et al., 2009).

Geographical altitude and weather conditions can certainly affect cultural habits and specifically how people socialize. Persons living at high altitude spend more time within their homes due to harsher weather which certainly affects socialization. It seems that in our studied populations the effect of altitude is different according to gender, probably due to differences in tasks performed day by day, especially because women tend to stay at home most of the day and also can have less interest or access to information about opportunities to development, which can result in a more pessimistic view of the world.

When separating the groups by age, differences between the two locations were only found in young adults. Most of the differences were observed in dimensions related with psychological distress. Young adults living at high altitudes were more prone to, mental health distress when compared with their counterparts living at low altitude. Apparently, this could be due to different degrees of cultural influence in different age groups, Jang et al. It showed that older adults are more exposed to altered cultural concepts and stigmas regarding mental illnesses that are evidenced as a negative attitude towards mental health services, this could translate into difficulties to express alterations in the mood of elderly populations in our study (Jang et al., 2009).

In terms of optimism, we only found that women have a less optimistic view towards the future among the high-altitude dwellers, while among men we found no statistically significant differences. We speculate that men due to social pressure may choose to report that they feel better and have a better view of their future regardless of where they live, while women often being more realistic than men report more accurately than men(Brenner and DeLamater, 2016). Chang et al. found statistically significant gender differences in reporting psychological outcomes: men were more likely to report more positive psychological outcomes for themselves rather than for others, and women were more likely to report more negative and realistic psychological outcomes for themselves(Chang et al., 2010).

In relation to the effects of chronic hypoxia on people's optimism, it can be speculated that living in conditions with a generally more hostile climate, colder, rainier and with less available partial pressure of atmospheric oxygen may cause people to feel more vulnerable towards their future.

Although we know that the level of education can be linked to a person's perception of his or her own reality and emotional situation. The high altitude group has 13.7% of illiteracy while the low altitude group 5.43% (Table 4), nevertheless, both parishes have 5 schools per every 1,000 inhabitants (GAD Oyacachi, 2019; GAG Limoncocha, 2019). In view of the differences in terms of sources external income, having oil and gas production in Limoncocha (Low altitude) might interfere with major access and better quality in terms of education.

At the same time, access to health care in both parishes is similar, both having only one primary health center for their entire population, assuming that there are more similarities than differences between these two populations.

These results are the first one in the world reporting optimism levels among high-altitude dwellers, and while more definitive information and results are needed, opening the door for future studies is always necessary.

Limitations:

First, one limitation is a scarcity of data in the literature directly addressing the influence of altitude on mental health and well-being. Another limitation of the present study is that, despite obtaining a significant sample to carry out this research, not all the people belonging to these indigenous communities who met the inclusion criteria were willing to participate. Whether the inclusion of these subjects who did not participate would have produced variations in our data or even induced changes in some results is impossible to elucidate.

We are also aware that the SF-36 questionnaire is not well validated in the elderly; therefore, we have been cautions to emit definitive conclusions. A minor problem related with questionnaires is that we required applying the translation to Spanish and the intervention of a Spanish-Quechua translator to clarify some word meaning in the forms. Anyway, all the participants were able to complete the questionnaire with no help once possible meaning troubles were solved.

The lack of regression and correlation analyses, not employing variables that could predict well-being variables such as income, education level, socio-economic status, medical comorbidities reduce the power of our conclusions since these data was not collected. In that sense, we recommend further analysis to try to better understand the complex link between optimism and health related self-perception at high altitude.

Conclusion:

We observe that age-sex and genotype matched Kiwcha indigenous populations located at different elevations have differences in terms of how they perceive their own health status. High altitude natives are more likely to report unfavorable health states represented by lower scores in all dimensions of the SF-36, when compared with their counterparts at low altitude. Indigenous people living at high altitude are significantly more prone to report alterations in vitality, mental health, and social functioning than those living at low altitude. When comparing age groups, differences were only found among young adults mostly in dimension related to psychological distress. Although our results reveal the presence of significant differences in health status of indigenous peoples of Kiwcha lineage living at different altitudes, no significant within-sex differences were found. Further studies are needed to explain in depth the sociodemographic and environmental factors that could underlie such differences.

List of abbreviations

5-HTP: 5-hydroxytryptophan
PF: Physical functioning
RF: Role functioning/emotional,
RE: Role functioning/emotional
VS: Vitality (energy/fatigue)
MH: Mental Health (Emotional well-being)
SF: Social functioning
BP: Body pain
GH: General health
HC : Health change
LOT-R test: Life Orientation Test-Revised.
Y: Young Adults
A: Adults
E: Elderly.
HRQOL: Qualities of life scales related to general health

Declarations

Ethics approval and consent to participate

All data were collected from the patient's medical records after obtaining written informed consent. The study was approved by the Universidad de las Americas review board (CEISH). All data was anonymized, and all identifiable information and biological samples were stored according to the local guidelines.

Consent to publish

Written informed consent was obtained from every patient in the study.

Availability of data and materials

All data is available upon reasonable request. Since information from indigenous communities were studied, only anonymized and not identifiable data can be shared. If you need further detail, please contact us at: e.ortizprado@gmail.com

Competing interests

The authors declare that they have no competing interests

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Authors' Contributions

EOP was fully responsible for the conceptualization, data collection and elaboration of the study. EOP, CP and KSR participated in drafting the manuscript equally and are fully responsible for it. DD, IO, JIC visited indigenous communities and applied the questionnaire.

IO, JIC and EOP contributed with the data collection and the construction of figures and tables. EOP, CP, MC, EV, and GV contributed with the descriptive statistical analysis and the discussion section of the manuscript. EOP, GV and CP critically reviewed the entire manuscript and produced several comments prior to the submission. All authors have read and approved the manuscript.

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4.*3 Analysis of excess mortality data at different altitudes during the COVID-19 outbreak in Ecuador.*

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Scientific Article

AU1►
Analysis of Excess Mortality Data at Different Altitudes During the COVID-19 Outbreak in Ecuador

AU2► Esteban Ortiz-Prado,[1,2,i] Raul Patricio Fernandez Naranjo,[1] Eduardo Vasconez,[1] Katherine Simbaña-Rivera,[1] Trigomar Correa-Sancho,[1,ii] Alex Lister,[3] Manuel Calvopiña,[1] and Ginés Viscor[2,iii]

Abstract

Ortiz-Prado, Esteban, Raul Patricio Fernandez Naranjo, Eduardo Vasconez, Katherine Simbaña-Rivera, Trigomar Correa-Sancho, Alex Lister, Manuel Calvopiña, and Ginés Viscor. Analysis of excess mortality data at different altitudes during the COVID-19 outbreak in Ecuador. *High Alt Med Biol.* 00:000–000, 2021.
Background: It has been speculated that living at high altitude confers some risk reduction in terms of SARS-CoV-2 infection, reduced transmissibility, and arguable lower COVID-19-related mortality.
Objective: We aim to determine the number of excess deaths reported in Ecuador during the first year of the COVID-19 pandemic in relation to different altitude categories among 221 cantons in Ecuador, ranging from sea level to 4,300 m above.
Methodology: A descriptive ecological country-wide analysis of the excess mortality in Ecuador was performed since March 1, 2020, to March 1, 2021. Every canton was categorized as lower (for altitudes 2,500 m or less) or higher (for altitudes >2,500 m) in a first broad classification, as well as in two different classifications: The one proposed by Imray et al. in 2011 (low altitude <1,500 m, moderate altitude 1,500–2,500 m, high altitude 2,500–3,500 m, or very high altitude 3,500–5,500 m) and the one proposed by Bärtsch et al. in 2008 (near sea level 0–500 m, low altitude 500–2,000 m, moderate altitude 2,000–3,000 m, high altitude 3,000–5,500 m, and extreme altitude 5,500 m). A Poisson fitting analysis was used to identify trends on officially recorded all-caused deaths and those attributed to COVID-19.
Results: In Ecuador, at least 120,573 deaths were recorded during the first year of the pandemic, from which 42,453 were catalogued as excessive when compared with the past 3 years of averages (2017–2019). The mortality rate at the lower altitude was 301/100,000 people, in comparison to 242/100,000 inhabitants in elevated cantons. Considering the four elevation categories, the highest excess deaths came from towns located at low altitude (324/100,000), in contrast to the moderate altitude (171/100,000), high-altitude (249/100,000), and very high-altitude (153/100,000) groups.
Conclusions: This is the first report on COVID-19 excess mortality in a high-altitude range from 0 to 4,300 m above sea level. We found that absolute COVID-19-related excess mortality is lower both in time and in proportion in the cantons located at high and very high altitude when compared with those cantons located at low altitude.

Keywords: COVID-19; Ecuador; excess deaths; high altitude; hypoxia; statistical bootstrapping

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Introduction

THE COVID-19 PANDEMIC continues to create unprecedented pressure in countries around the world and their health systems. Up to September 2021, more than 220 million cases have been reported worldwide, and at least 4.5 million deaths have been officially registered as COVID-19 (Bashir et al., 2020; Coccia, 2020; JHU, 2020).

Several environmental and social factors have been associated with lower or higher COVID-19-related mortality rates and transmissibility of the SARS-CoV-2 virus (Bashir et al., 2020; Coccia, 2020). Among the environmental factors, high-altitude exposure has generated controversy and intrigued the scientific community in its possible benefits through hypoxia in terms of infection, prevalence, and mortality due to COVID-19 (Millet et al., 2021).

One of the main questions surrounding the role of hypobaric hypoxia and COVID-19 is to recognize when a population is located at high altitudes. It has been difficult to define at which elevation the effects of high altitude become significant on a human body and where this threshold lies in terms of mild or severe hypoxia (West et al., 2007). Imray et al. (2011) proposed a classification of high-altitude exposure based on the study by Pollard and Murdoch (1997) "The High Altitude Medicine Handbook", a categorization that seems to be the most pragmatic and has been widely adopted for mountain medicine.

According to this categorization, low altitude is defined as everything located below 1,500 m, moderate or intermediate altitude from 1,500 to 2,500 m, high altitude from 2,500 to 3,500 m, the very high altitude from 3,500 to 5,800 m, more than 5,800 m extreme high altitude, and finally above the 8,000 m is considered the death zone (Pollard and Murdoch, 1997). In 2007, after several concerns raised about playing football under harsh environmental conditions (including geographical altitude), the FIFA Sports Medical Committee and the FIFA Medical Assessment and Research Centre (F-MARC) invited 12 international scientists and clinicians to review the scientific body of literature and to reach a consensus.

As a result of this discussion, the following altitude classification was proposed: "Near sea level" (0–500 m); "Low altitude" (above 500–2,000 m) where minor impairment of aerobic performance becomes detectable; "Moderate altitude" (above 2,000–3,000 m) where acute mountain sickness starts to occur and acclimatization gets increasingly important for physical performance; "High altitude" (above 3,000–5,500 m) where mountain sickness and acclimatization to altitude become clinically relevant and sports performance is considerably impaired; and "Extreme altitude" (above 5,500 m) where prolonged exposure leads to progressive physical deterioration (Bärtsch et al., 2008a, 2008b). Nevertheless, if we need to take into consideration permanent human settlements instead of transitory climbing feats, or sport competition, several authors worldwide have classified altitude exposure in two simplified categories: below 2,500 m is considered low altitude and above 2,500 m is thought high AU0► altitude (Bailey et al., 2019).

Within this context, several authors have tried to determine the potential relationship between the mortality generated by SARS-CoV-2 virus and its transmissibility and living in regions located at high altitudes (Arias-Reyes et al., 2020; Woolcott and Bergman, 2020; Ortiz-Prado et al., 2021; Zubieta-Calleja et al., 2021).

Some research groups have established that living at high altitudes could be related to reduced mortality, morbidity, and improved survival rate related to patients confirmed with SARS-CoV-2 infection (Arias-Reyes et al., 2020; Kong et al., 2020; Zubieta-Calleja et al., 2021).

Although living at high altitude may be associated with lower incidence of COVID-19 and apparently lower mortality, the physiopathology or environmental factors behind this association are still being studied (Pun et al., 2020). For example, the effect of living at high altitude and ACE-2 receptor expression has been hypothesized, but there is no definitive evidence to support this claim (Joyce et al., 2020). However, adaptation to high altitude, the increased resistance to hypoxia, as well as environmental influence (ultraviolet [UV] radiation, ozone, or cold) as protective factors have not been linked to better survival yet (Cardenas et al., 2021).

Despite not having additional information on other factors and cofactors, studying excess mortality at different altitudes adds novelty to the current literature. Additionally, using excess all-cause mortality will provide a powerful tool to quickly assess unbiased estimates of the real COVID-19 mortality burden in Ecuador. We propose an innovative approach that uses average values in bootstrapped simulations to replicate the data generation mechanism of death time series and thus obtain more solidly built estimations of expected deaths to quantify the excess mortality in Ecuador in function of altitude. This would be the first study using such an extensive altitude range, based on a broad classification of lower and elevated altitudes (2,500 m as cutoff) as well as two classifications widely accepted by high-altitude physiology and mountain medicine experts.

Methods and Data ◄AU3

Study design

An ecological study of all-cause mortality recorded in Ecuador from March 1, 2020, to March 1, 2021, was performed. All deaths recorded within the national registry database in Ecuador were used to compute COVID-19-related and non-COVID-19-related deaths during the first year of the pandemic in Ecuador.

Setting

The study was carried out in Ecuador, one of the smallest Latin American countries, located in the equatorial line and bordering the Pacific Ocean. Ecuador shares borders with Peru and Colombia, and its current population is estimated to be 17,577,116 inhabitants. The country has four regions (Coastal Lowlands, the Andean Highlands, the Amazonian Basin, and the Galapagos Islands) organized into 24 provinces and 221 political subdivisions called cantons (cities). The population density in Ecuador is 71/km^2 (184 people per mi^2), the total land area is 248,360 km^2 (95,892 mi^2), 63% of the population is urban (11,123,641 people in 2020), and the median age in Ecuador is 27.9 years (Worldometer, 2021).

Population

Our study included all nationwide recorded deaths from 2017 to 2020. A total number of 115,070 deaths in 2020 were analyzed, with 42,453 recorded as excess deaths.

Variables

The database retrieved regarding deaths in Ecuador contains the following variables: jurisdiction (canton, province, and region), date, total absolute, and the relative number of deaths from 2017 to 2020. Total deaths represent the number of deaths in each specific period considered in the analysis. For other complementary analysis, variables such as region or registered contagious cases were used, which were obtained from the same official websites.

We have designed a daily time series for deaths across 221 cantons in Ecuador. Furthermore, we divided cantons according to their elevation (in meters) considering two classifications according to their altitude: lower and upper broad altitude classification (<2,500 and >2,500 m) and two of the most used stratified high-altitude classifications:

- The one proposed by Imray et al. (2011) (low altitude <1,500 m, moderate altitude 1,500–2,500 m, high altitude 2,500–3,500 m, or very high altitude 3,500–5,500 m).
- The one proposed by Bärtsch et al. (2008b) (near sea level 0–500 m, low altitude 500–2,000 m, moderate altitude 2,000–3,000 m, high altitude 3,000–5,500 m, and extreme altitude 5,500 m).

To compute excess deaths, we used as reference the data from 2020 and calculated the deviations against stable trends using the daily average for the same days in the years 2017, 2018, and 2019. We display results daily since the start of pandemics on March 1, 2020, and we extended our analysis until March 1, 2021.

Data sources/measurement

Data for this study were obtained using the free information available over historical databases of the National Institute of Statistics and Census (INEC, 2020) and the National Civil Registry of Ecuador with data from January 2017 to March 2021 (INEC, 2020).

The excess deaths were computed with built-in algorithms applied to the official data using R software version 3.6.1. Algorithms were developed for each time stage at daily, weekly, and monthly levels. The mean values for deaths in cantons, provinces, and regions were calculated at the different time periods, and then, the difference of values between deaths in the year 2020 was calculated against the average deaths in years 2017–2019. The same method was applied for the bootstrapped model. However, in the last case, we simulate deaths' behavior considering what would happen in the previous years if an extreme event such as a pandemic occurred to model the mechanism of data generation for 2020.

Bias

To reduce the risk of bias or involuntary errors, two researchers retrieved the data separately. Once data were downloaded, both investigators analyzed the data set separately. The researchers resolved any questions or doubts after reaching a consensus with a third researcher included in the analysis. The mean values and confidence intervals were computed independently, instead of using the same R data code used for the entire analysis, as a control quality mechanism to confirm the homogeneity of the data set used by both researchers.

Study size

Excess deaths were calculated with daily, weekly, and monthly resolution. Data of death cases at the monthly level was composed of a time series of 1,152 observations across 24 provinces and 221 cantons in Ecuador. At the weekly level, the time series of deaths was composed of 5,088 observations for 24 provinces. At the daily level, the time series of deaths was composed of 35,064 observations for 24 provinces. The time series starts on January 1, 2017, and ends on March 1, 2021. For cantons, the time series of deaths had 323,611 observations.

Statistical methods

Descriptive statistics were applied to outline the differences among provinces and cantons. To analyze the evolution of deaths, we initially applied dynamic statistical tests to the daily death series in each province as well as across the whole country of Ecuador to identify on which days, there were changes in the behavior of the number of reported cases by elevation.

In all provinces, we have n daily observations. Each i observation from 2 to n was used as a change point. With this reference point, the previous and subsequent observations constitute different data sets. Then, a variance test was applied to identify the variability and test the following hypothesis:

$$H_0 : \textit{Deaths before } i \textit{ are equal to Deaths after } i$$

$$H_1 : \textit{Deaths before } i \textit{ are different to Deaths after } i$$

As it is not possible to consider data before the first day (at the risk of going back indefinitely in the analysis), we started from $i = 2$. We obtained a series of p-values for each i and therefore selected the minimum of those values where H_0 is rejected. This point highlights where an important change of trend occurred.

The Poisson adjustment makes it possible to identify how the trend in the evolution of the causes of death will be (Karian and Dudewicz, 2016). Based on the Poisson distribution, it measures the daily death rate increase or decrease.

To calculate the excess deaths at the country and province level, we developed a bootstrapping procedure. The bootstrap method is a statistical technique for estimating quantities about a population by averaging estimates from multiple small data samples. We used a model based on central tendency measures and sample means, which is frequently used to calculate excessive mortality (Rodrigues et al., 2019; Modig et al., 2021).

Statically, the mean value of a sample is used for exploratory analysis, but this calculation is sensitive to extreme values (Verzani, 2018). Consequently, the presence of outliers might negatively impact the quality of the results. Moreover, due to the current pandemic, all countries are having more deaths per day and comparing them with the values of the death's series of previous years could expand the excess deaths indicator.

So, to avoid extreme estimates in the expected deaths, we use a bootstrapping approach. The essential concept of bootstrapping is to emulate the repetition of specific experiments by simulating new data, followed by a statistical measure's recalculation using such simulated data (Efron and Tibshirani, 1994).

The bootstrap emulates the sampling distribution of our expected deaths estimator $\hat{\mu}_{deaths}$ by simulating the data generation and model fitting processes. It does this by generating artificial data $y^{(b)} = \left(y_1^{(b)}, \ldots, y_n^{(b)}\right)$ from a distribution that approximates the true unknown sampling distribution of the actual data. This is repeated several times, B, resulting in an extensive collection of bootstrap estimators $\mu_{deaths}^{(b)}$, $b = 1, \ldots, B$. The distribution of these artificially generated bootstrap estimators can be used to infer the sampling distribution of $\hat{\mu}_{deaths}$.

As the true sampling distribution of the death time series is unknown, we will use nonparametric bootstrapping. Suppose the death data y_i, $i = 1, \ldots, n$, are independent and have an identical distribution. In that case, the empirical cumulative distribution function can be used as a discrete approximation of the true cumulative function.

$$\hat{F}_{ecdf}(y) = \frac{1}{n}\sum_{i=1}^{n} I(y_i \leq y)$$

We define the general algorithm as follows:

1. Calculate $\mu_{deaths}^{(b)}$ using $y^{(b)} = \left(y_1^{(b)}, \ldots, y_n^{(b)}\right)$.

With the results of simulations, we obtained $\hat{\mu}_{deaths}$ and defined bootstrap confidence intervals at $\alpha = 0.05$ using the percentile method. We completed 1,000 bootstraps to retrieve robust estimates (Efron and Tibshirani, 1994). Because data are available at the daily level, we produced monthly, weekly, and daily timescale estimates for the country and its provinces.

Results

In Ecuador since March 1, 2020, at least 120,573 people have died, an increase of 64% when compared with the 73,431 deaths reported during the same period in 2019. During 2020, at least 49,279 people have died in excess when compared with the previous 3 years of averages (2017, 2018, and 2019).

Maximum number of deaths per day and per region

During the initial wave of the pandemic, between March and April 2020, at least 1,120 deaths were reported in one single day. The coastal province of Guayas and the city of Guayaquil reported the deadliest impact of the pandemic with 795 and 678 deaths, respectively, in one single day.

During the second COVID-19 wave in Ecuador, the highlands reported the maximum number of deaths in 1 day, being the Province of Pichincha during July 2020, the province with the highest excessive mortality for a single day (107 deaths in 1 day), and Quito, the city with the highest excessive mortality within the highlands with at least 98 deaths in 1 day (Fig. 1). ◀F1

The overall excessive mortality per day within the coastal towns and provinces was on average 591% greater than the ◀AU4 excessive mortality reported within the highlands.

Excessive mortality comparison between low- and high-altitude cantons

When categorizing every 1 of the 221 cantons in the lower (<2,500 m) and upper (>2,500 m) altitude, we found that the total number of deaths in the lower altitude group was 86,170, being 47,631 excess deaths, whereas at the upper altitude group, we found 34,403 deaths, being 15,778 of them reported as excess deaths (Fig. 2). ◀F2

Excessive mortality by low, moderate, high, and very high altitude stratified classification

When categorizing every 1 of the 221 cantons by altitude, according to four categories: low altitude (<1,500 m), moderate altitude (1,500–2,500 m), high altitude (2,500–3,500 m), and very high altitude (>3,500 m), we found that the highest peak of the pandemic in the low-altitude group caused at least 1,027 deaths in one single day, from which 929 of them were excessive COVID-19 related deaths. At

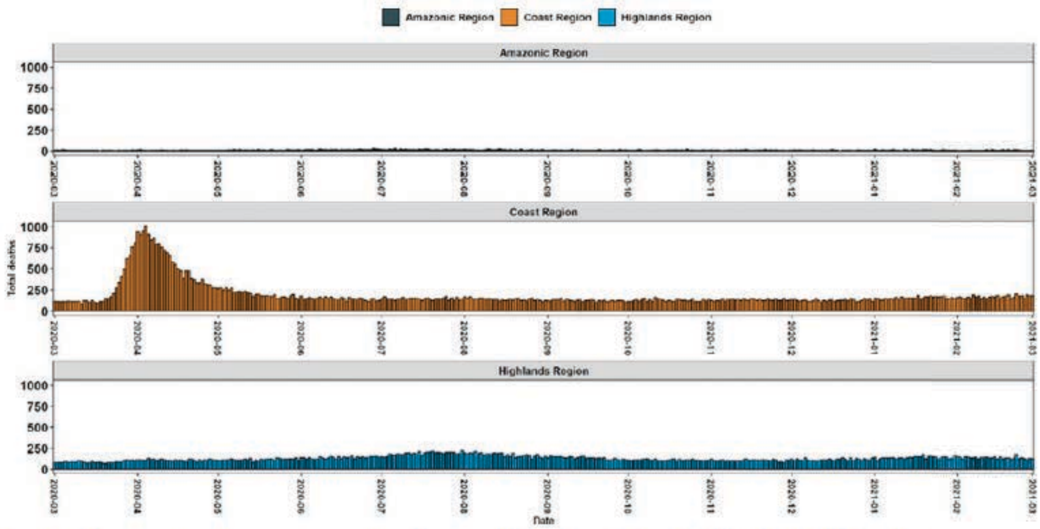

FIG. 1. Daily comparison between expected and excess deaths during March 2020–March 2021 in the Coastal Lowlands, Andes highlands, and Amazonian regions of Ecuador.

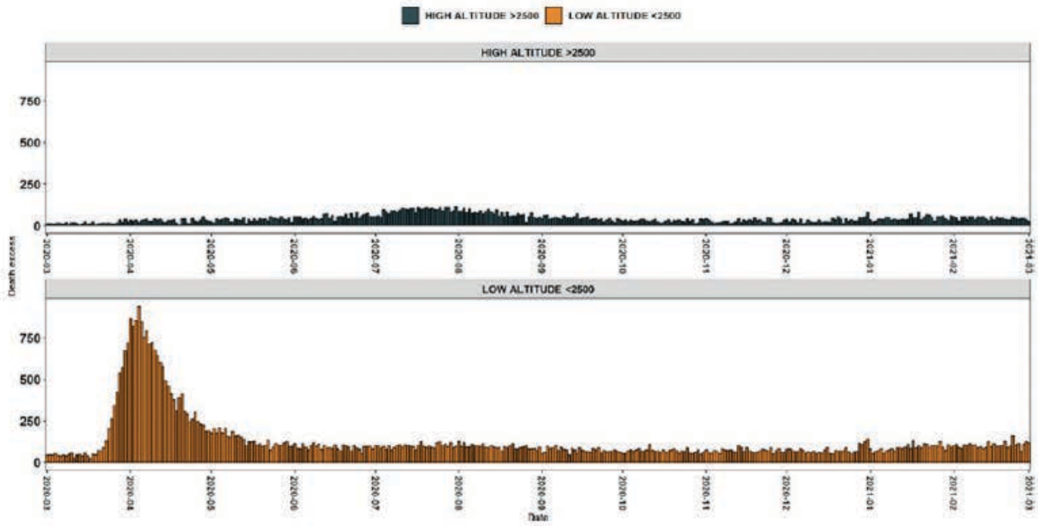

FIG. 2. Daily evolution of excess deaths within lower (<2,500 m) and upper altitude (>2,500 m) in 221 cantons in Ecuador.

moderate altitudes, we found a peak of 58 deaths in 1 day, being 38 of them recorded as excessive mortality. When compared with the high-altitude group, we found 157 deaths in 1 day, being 101 of them recorded as excessive. Within the highest locations, categorized as very high altitude, we found 16 deaths in one single day, and 14 of them were excessive mortality (Fig. 3). F3

Excessive mortality by near sea level, low, moderate, high, and extreme altitude stratified classification

As a sensibility analysis, we observed excess deaths are more frequent in the near sea level category with at least 31,429 excess deaths with a rate of 346/100,000 people, whereas the high- and extreme altitude groups have 14,621 and 945 excess deaths, respectively (Fig. 4). F4

Confirmed deaths against daily excess deaths rates by province

Guayas is the province with the highest absolute excessive mortality in the country with 19,208 deaths, representing an increase of 94% over the expected deaths in comparison to previous year. This represents an excess mortality rate of 438/100,000 inhabitants. However, considering the variability of population density, the province of Santa Elena had the highest excess mortality rate with 443/100,000 inhabitants (Table 3). T3

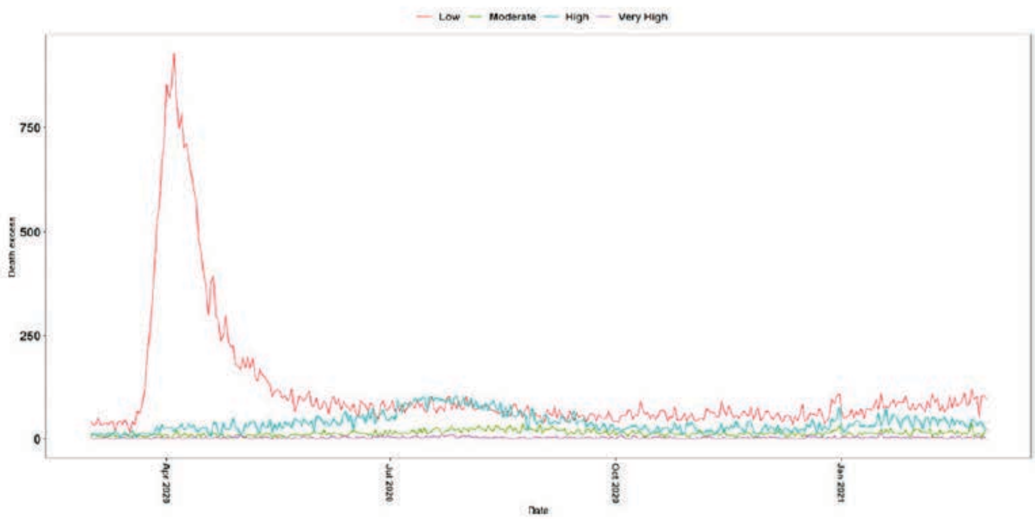

FIG. 3. Excessive mortality in Ecuador at four elevation ranges: low altitude (<1,500 m), moderate altitude (1,500–2,500 m), high altitude (2,500–3,500 m), and very high altitude (>3,500 m).

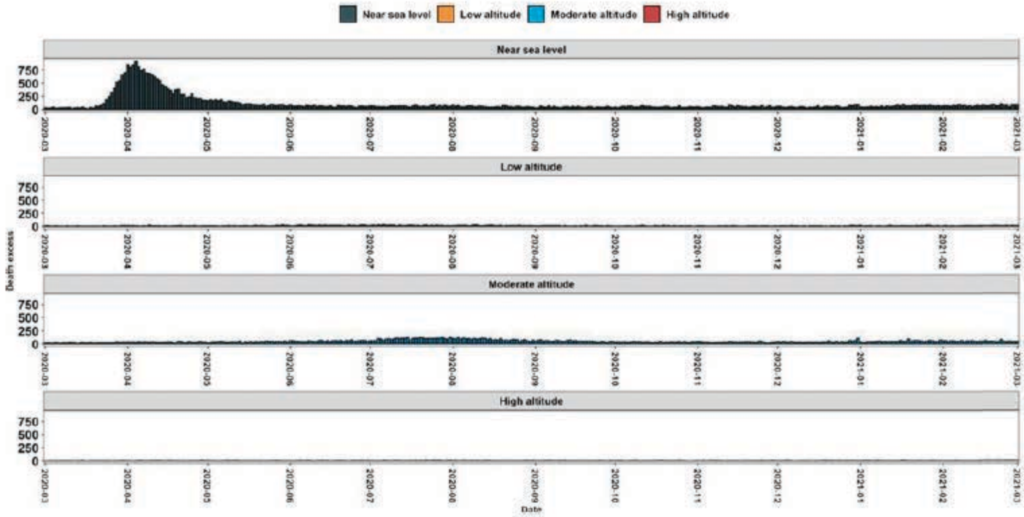

FIG. 4. Excessive mortality in Ecuador at four elevation ranges: Near sea level (0–500 m), low altitude (500–2,000 m), moderate altitude (2,000–3,000 m), high altitude (3,000–5,500 m), and extreme altitude (5,500 m). The number of excess deaths in the low-altitude group using the Bärtsch et al. (2008) classification by provinces is displayed in Table 1.

Discussion

In Ecuador, more than 120,000 people have died during the first year of the COVID-19 pandemic. It is important to emphasize that most of these deaths hit areas located near sea level. Most per capita deaths have occurred in places located below 2,500 m of elevation.

Our study revealed that the coastal region was the most affected region in terms of excess deaths in Ecuador. Although this area is where most people live, when we adjust for population, we confirm that the average rate is significantly higher than the one reported at high altitude.

The main highlight from our article is the fact that cantons located at low altitude are always those with the highest COVID-19 mortality rates. Our analysis included three elevation categories, which offer peculiar results when compared.

We found that below 2,500 m of altitude, mortality rates are 24% higher than cantons located above 2,500 m. Using a wider altitude category, we found that the cantons located at high altitude are the second in reporting the highest mortality, whereas those cantons located at moderate and very high altitude are the ones with the lowest mortality. These variations could be related to other factors different from geographical altitude, such as the population density and mobility of each of these regions. Nevertheless, the two classifications coincide in the fact that higher mortality occurred at lower altitudes.

This could go hand in hand with previously published reports from other parts of the world in which researchers have shown that living at high altitude appears to be associated with lower mortality rates.

This appreciation seems plausible since the first published research about altitude and its relationship with COVID-19 or SARS-CoV-2 infection was available. Arias-Reyes et al. (2020) undertook a descriptive analysis of high altitude and COVID-19 mortality. They described a lower proportion of SARS-CoV-2 infections and lowered COVID-19-related deaths in populations located on the Tibetan plateau and the Ecuadorian and Peruvian Andes (Arias-Reyes et al., 2020). Unfortunately, the prevalence of infection, demographic density and human mobility, and factors that might interfere with higher transmissibility (Kadi and Khelfaoui, 2020; Bhadra et al., 2021) were not included in the analysis.

Since then, a full hand of studies have emerged and have offered somehow conflicting results. For instance, Woolcott and Bergman (2020) have concluded that in the United States and Mexico, those populations residing above 2,000 m have a higher total cumulative number of COVID-19 cases and a higher mortality rate attributed to COVID-19 than those located at lower altitudes. These results sparked a back-and-forth discussion between the authors and Zubieta-Calleja et al. (2021) who have argued that the published results might overestimate the mortality risk due to underdiagnosis, a problem that is also present in lowland dwellers due to the high proportion of asymptomatic infected subjects. Zubieta-Calleja et al. (2021) also suggested that case fatality rate should decrease with altitude based on a report of a higher proportion of asymptomatic COVID-19 cases at higher altitude based on the study of Kong et al. (2020).

Most of the available information points out that living at high altitudes may be associated with lower mortality and lower transmissibility rates in mountainous areas (Accinelli and Leon-Abarca, 2020). The mechanisms associated with this apparent phenomenon remain unclear. Two current opinions describe this potentially favorable effect of high altitude: in the first place, the role of the environment found in high-altitude locations, and second, the physiological traits that humans chronically exposed (and adapted) to high altitude can develop to reduce the impact of COVID-19.

Some theories have been proposed to justify the altitude protective effects from a physiological point of view. For instance, Choquenaira-Quispe et al. (2020) have suggested that people living in high-altitude areas would have a lower expression of ACE-2 receptors. They have also pointed out

TABLE 1. EXCESS MORTALITY AT NEAR SEA LEVEL, LOW, HIGH, AND EXTREME ALTITUDE IN ECUADOR

Range	*Province*	*Canton*	*Canton population*	*Total deaths*	*Expected deaths*	*Excess deaths*	*Rate/100,000*
Near sea level	Guayas	Guayaquil	2,723,665	30,469	15,931	14,538	534
	El Oro	Machala	289,141	3,069	1,527	1,542	533
	Manabí	Manta	264,281	2,730	1,466	1,264	478
	Manabí	Portoviejo	321,800	2,961	1,737	1,224	380
	Santa Elena	Santa Elena	188,821	1,875	722	1,153	611
	Guayas	Milagro	199,835	1,920	1,033	887	444
	Guayas	Durán	315,724	1,339	469	871	276
	Los Ríos	Quevedo	213,842	1,759	934	825	386
	Guayas	Daule	173,684	1,168	521	647	372
	Los Ríos	Babahoyo	175,281	1,530	1,079	451	257
Low altitude	Sto. Domingo Tsáchilas	Santo Domingo	458,580	3,113	1,951	1,162	253
	Napo	Tena	79,182	389	224	165	208
	Pastaza	Pastaza	84,377	356	265	91	107
	Morona Santiago	Morona	58,281	254	186	68	116
	El Oro	Piñas	30,206	230	205	25	84
	Loja	Calvas	29,565	196	124	73	245
	Loja	Catamayo	35,961	165	107	58	162
	Loja	Paltas	23,471	164	118	46	194
	El Oro	Zaruma	25,654	139	109	30	117
	Zamora Chinchipe	Zamora	32,761	117	73	44	134
Moderate altitude	Pichincha	Quito	2,781,641	19,093	11,926	7,167	258
	Tungurahua	Ambato	387,309	3,466	2,039	1,427	369
	Azuay	Cuenca	636,996	4,242	3,076	1,166	183
	Chimborazo	Riobamba	264,048	2,253	1,497	756	286
	Cotopaxi	Latacunga	205,624	1,665	955	710	345
	Imbabura	Ibarra	221,149	1,717	1,118	599	271
	Loja	Loja	274,112	1,782	1,400	382	139
	Cañar	Azogues	86,276	751	496	255	295
	Carchi	Tulcán	102,395	670	407	263	257
	Pichincha	Rumiñahui	115,433	569	289	280	242
High altitude	Pichincha	Mejía	108,167	419	272	147	136
	Chimborazo	Colta	44,838	326	179	147	328
	Cotopaxi	Salcedo	67,100	302	204	98	146
	Chimborazo	Guamote	58,291	256	166	90	154
	Tungurahua	Píllaro	43,371	230	173	57	132
	Chimborazo	Guano	48,395	211	142	69	143
	Bolívar	San Miguel	29,004	192	118	74	254
	Cotopaxi	Pangua	24,612	107	64	44	177
	Cotopaxi	Saquisilí	31,426	116	80	37	116
	Tungurahua	Quero	20,627	94	63	31	149

that high-altitude dwellers have higher expression of the hypoxia-inducible factor (HIF-1α); thus, a subsequent gene overexpression on EPO production and angiogenesis is seen within their tissues (Ortiz-Prado et al., 2010; Dunn et al., 2012).

The data of ACE-2 expression in hypoxia and altitude are very conflicting (see Pun et al., 2020), and even if true with the modest suppression that hypoxia might cause, it is nowhere near zero and there is no evidence that a slightly lower expression of ACE-2 would materially affect virus uptake and disease evolution (Pun et al., 2020). Beside those presumptions, Khera et al. (2021) reported that angiotensin receptor blockers appear to have no effect on hospitalization or COVID-19-related deaths; additionally, there is currently no evidence that highlanders have lower ACE-2 expression.

It has also been suggested that anatomical, molecular, and physiological long-term adaptations found among high-altitude dwellers might have a protective role, reducing the impact of COVID-19-related systemic hypoxia (Choquenaira-Quispe et al., 2020; Canales-Gutiérrez et al., 2021). The process of high-altitude adaptation (hypobaric hypoxia) could be associated with a reduced oxidative state and a reduced inflammatory response (Carmody et al., 2020; Millet et al., 2021). Living under hypoxic conditions could increase endogenous antioxidant capacities through an improved oxygen supply. This antioxidant status may confer some protection in relation to the severe inflammatory state encountered during SARS-CoV-2 infections, condition that is associated with acute respiratory distress syndrome and COVID-19 deaths (Millet et al., 2021; Montenegro et al., 2021).

From the clinical point of view, it is more difficult to demonstrate the physiological implications on COVID-19 survival. Jaramillo et al. (2021) have evaluated survival rates among severely ill COVID-19 patients. They analyzed the differences in two cohorts of patients, treated in similar hospitals but located at different altitudes, one placed at low altitude (10 m) and the other one at high altitude (2,830 m). They reported that living at high altitude was associated with

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Table 2. Excessive Mortality per Region and per Province in Ecuador

Region	*Province*	*Population 2020*	*Total deaths*	*Expected deaths*	*Excess deaths*	*% Increase*	*Rate/100,000*
Amazonian Basin	Morona Santiago	196,535	659	487	172	35%	87
	Napo	133,705	587	370	217	59%	162
	Orellana	161,338	592	393	199	50%	123
	Pastaza	114,202	415	306	109	36%	95
	Sucumbíos	230,503	979	605	374	62%	162
	Zamora Chinchipe	120,416	387	249	138	55%	114
	Subtotal	956,699	3,619	2,411	1,208	50%	126
Coastal Lowlands	El Oro	715,751	5,378	2,952	2,426	82%	339
	Esmeraldas	591,083	2,296	1,563	733	47%	124
	Guayas	4,387,434	39,652	20,444	19,208	94%	438
	Los Ríos	921,763	5,453	3,560	1,893	53%	205
	Manabí	1,562,079	10,902	6,329	4,573	72%	293
	Santa Elena	401,178	3,078	1,303	1,775	136%	443
	Sto. Domingo Tsáchilas	511,151	3,291	2,085	1,206	58%	236
	Subtotal	9,090,439	70,050	38,236	31,814	83%	350
Galapagos	Galápagos	33,042	61	46	15	33%	46
	Subtotal	33,042	61	46	15	33%	46
Andes Highlands	Azuay	881,394	5,456	3,940	1,517	38%	172
	Bolívar	209,933	1,166	817	349	43%	166
	Cañar	281,396	1,601	1,074	527	49%	187
	Carchi	186,869	1,083	692	391	56%	209
	Chimborazo	524,004	3,581	2,367	1,214	51%	232
	Cotopaxi	488,716	2,810	1,711	1,099	64%	225
	Imbabura	476,257	2,874	1,978	896	45%	188
	Loja	521,154	3,066	2,342	724	31%	139
	Pichincha	3,228,233	20,761	12,980	7,781	60%	241
	Tungurahua	590,600	4,445	2,699	1,746	65%	296
	Subtotal	7,388,556	46,843	30,600	16,243	53%	220
	Total	17,468,736	120,573	71,294	49,279	69%	282

a substantial improvement in survival rates, severity-of-disease classification system scores at 72 hours, and better respiratory and ventilatory profiles than the low-altitude group (Jaramillo et al., 2021).

It seems that some physiological traits-based theories reported by some groups go hand in hand with the biological plausibility that implies being exposed to high altitudes for long periods of time and may cause adaptation of the organism to overcome hypoxia and hypoxemia better. In other words, populations chronically living at high altitudes may be better suited to withstand tissue hypoxia in vital organs in the case of SARS-CoV-2 severe infection and therefore have lower mortality.

Another important aspect to consider that has not been discussed yet is the fact that lower prevalence of different comorbidities in populations located at high altitudes has been reported. For instance, stroke, cardiovascular diseases, hypertension, diabetes, and obesity have been reported to be less prevalent at high altitude (Faeh et al., 2009, 2016; Hirschler et al., 2012; Aryal et al., 2017; Narvaez-Guerra et al., 2018). Although the relationship between comorbidities and morbidity attributed to COVID-19 has been well described, the role of chronic diseases at high altitude and lower mortality has not yet been explored. Nevertheless, these preconditioning may be a factor to consider in relation to the lower COVID-19 mortality reported at high altitude when compared with lower altitude locations.

Table 3. Comparison of COVID-19-Related Deaths in Ecuador According to the Two Different Altitude Classifications

	Observations	*Population 2020*	*Total deaths*	*Expected deaths*	*Excess deaths*	*% Increase*	*Rate*
Lower altitude	172	12,196,744	86,170	49,484	36,686	74	301
Upper altitude	48	5,206,227	34,403	21,810	12,593	58	242
	Total	17,402,971	120,573	71,294	49,279	69	283
Low altitude	141	10,369,446	75,171	41,608	33,563	81	324
Moderate altitude	32	1,827,298	10,999	7,876	3,123	40	171
High altitude	36	4,824,326	32,705	20,694	12,011	58	249
Very high altitude	12	381,901	1,698	1,116	582	52	153
	Total	17,402,971	120,573	71,294	49,279	69	283

The standard and most recognized classification (lower vs. upper) and a stratified classification commonly accepted by mountain medicine experts.

In addition to this potential hypoxic tolerance and lower prevalence of comorbidities, atmospheric and environmental conditions at high altitudes could also be implicated. Researchers worldwide have listed a handful of environmental factors that may be linked to reduced SARS-CoV-2 activity at high-altitude locations. For instance, the current literature suggests that abrupt variations in temperature within hours and days, air quality including ozone (O_3) atmospheric concentrations, and increased exposure to UV light radiation might play a role in reducing viral activity at high altitude (Arias-Reyes et al., 2020; Semple and Moore, 2020).

Other social repercussions and practices at a community or individual level might play a key role with the proposed lower COVID-19 mortality found at high altitude. For instance, lower population density and reduced human mobility might be linked to a reduced spread of the virus (Kadi and Khelfaoui, 2020; Bhadra et al., 2021). For obvious reasons, remote and harsh terrains (like the ones found at high altitude) are difficult to inhabit. Geographical isolation and vast areas are often the rule at higher grounds, generating lower population density areas than low-altitude areas (Huamaní et al., 2020).

We speculate that cold and rainy climate may have shaped the behavior of high-altitude dwellers for centuries. They often spend more time indoors and socialize more within their households rather than with other members of their communities as those living at low altitudes (Rehdanz and Maddison, 2005).

Another factor to consider may be access to health services at high altitudes. During the COVID-19 pandemic, while many health services collapsed worldwide, thousands of people could have fled their usual places of residence to find better health care at lower altitudes, generating a reporting bias within most of the published analysis. Although in developed countries interregional differences are not often marked, in places such as the Tibetan plateau, the Ethiopian highlands, or the Andes mountainous region, differences in health care access and quality might be observed and need to be acknowledged.

Finally, we suggest that living in remote and hardly accessible locations may confer some protection against SARS-CoV-2 infection and COVID-19 disease regardless of geographic elevation. It appears that a combination of social, environmental, cultural, physiological, and molecular factors may come together to enhance the protective effect of living at high altitude in relation to SARS-CoV-2 virus infection. The role of education, the presence of comorbidities, hygienic and dietary habits, interpersonal distancing, and other social determinant factors should be further discussed and analyzed to find a cause–effect relationship between high altitude and COVID-19.

Limitations

The main limitation of this study is the use of one dimension to track excess deaths and bootstrapped excess deaths. A vast array of research has been conducted recently where excess deaths are also analyzed for other factors, such as age ranges, gender, population density, and other social data stratifications (Kadi and Khelfaoui, 2020). Unfortunately, the lack of data management in the official statistics database of Ecuador has produced all deaths cases at an aggregated level, so there is not an official source to find more details about the impact of deaths across multiple strata.

Another limitation related to data quality is the uncertainty in the level of death underreporting. After detailed data analysis, we quantified in 3–5 days the delay to register a death case at the official statistics. Using the common mean as the base for excess deaths tracker, and considering this situation, the results could be distorted because of extreme values that can appear on specific days. On the other side, using the bootstrapped mean helps to control the phenomenon of underreporting since this measure infers the data generation mechanism for the death cases series, thus better discriminating and buffering the effect of outliers.

Additionally, having only the death cases series for the country and provinces can impact the distribution of excess deaths below traditional mean and bootstrap mean. Despite having data from 2017 to 2020 in terms of death cases, the absence of covariates such as age or gender can influence the results profoundly. It could produce large aggregated values, as our results show a difference of almost 9,000 cases between traditional excess and bootstrapped excess.

This is related to how the distribution of excess deaths is affected because of necessary elements such as sociodemographic variables and classification of death cases in reporting. This means that additional information is needed, such as for the case of illnesses such as influenza and the contribution of effects from lockdown such as the reduction of atmospheric pollution or the use of facial masks (Torres and Sacoto, 2020). Further work is needed to determine the relative importance of these different factors on the overall estimates of excess deaths.

Conclusions

To the best of our knowledge, this is the first study to analyze excess deaths in relation to altitude using two different elevation range categories. Our study shows that the cantons located at low altitudes have the highest mortality rate and highest number of excess deaths in a single day reported. However, the lowest mortality rate was found in those cantons located at high altitudes, and in relation to time, the number of excess deaths per day was 50% lower in high-altitude cantons than those located below 2,500 m of altitude.

Ethical Approval and Consent to participate

According to the local and international regulation, this study did not require ethical approval.

Availability of Supporting Data

All the information used for this analysis can be found online throughout the national databases available in the corresponding websites.

Authors' Contributions

E.O.-P. is responsible for the conceptualization of the study. R.P.F.N. and K.S.-R. contributed to data collection, ◄AU7 data extraction, and data visualization. E.O.-P., R.P.F.N., and K.S.-R. were responsible for the elaboration of the first draft of the article. E.O.-P., R.P.F.N., and K.S.-R. contributed with the descriptive statistical analysis. E.O.-P., A.L., T.C.-S., and G.V. were responsible for the elaboration of the discussion section of the article. G.V. and M.C. were responsible for editing the final version of the article.

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__4.__4 Stroke Related Mortality at Different Altitudes: A 17-Year Nationwide Population-Based Analysis from Ecuador

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Stroke-Related Mortality at Different Altitudes: A 17-Year Nationwide Population-Based Analysis From Ecuador

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Introduction: Worldwide, more than 5.7% of the population reside above 1,500 m of elevation. It has been hypothesized that acute short-term hypoxia exposure could increase the risk of developing a stroke. Studies assessing the effect of altitude on stroke have provided conflicting results, some analyses suggest that long-term chronic exposure could be associated with reduced mortality and lower stroke incidence rates.

Methods: An ecological analysis of all stroke hospital admissions, mortality rates, and disability-adjusted life years in Ecuador was performed from 2001 to 2017. The cases and population at risk were categorized in low (<1,500 m), moderate (1,500–2,500 m), high (2,500–3,500 m), and very high altitude (3,500–5,500 m) according to the place of residence. The derived crude and direct standardized age-sex adjusted mortality and hospital admission rates were calculated.

Results: A total of 38,201 deaths and 75,893 stroke-related hospital admissions were reported. High altitude populations (HAP) had lower stroke mortality in men [OR: 0.91 (0.88–0.95)] and women [OR: 0.83 (0.79–0.86)]. In addition, HAP had a significant lower risk of getting admitted to the hospital when compared with the low altitude group in men [OR: 0.55 (CI 95% 0.54–0.56)] and women [OR: 0.65 (CI 95% 0.64–0.66)].

Conclusion: This is the first epidemiological study that aims to elucidate the association between stroke and altitude using four different elevation ranges. Our findings suggest that living at higher elevations offers a reduction or the risk of dying due to stroke as well as a reduction in the probability of being admitted to the hospital. Nevertheless, this protective factor has a stronger effect between 2,000 and 3,500 m.

Keywords: stroke, high altitude, mortality, angiogenesis, adaptation, Ecuador

INTRODUCTION

Cerebrovascular disease or stroke is the second leading cause of death worldwide; affecting more than 16 million people each year (Hankey, 2017). Around one in six men and one in five women will have a stroke in their lifetime, In 2016, the global lifetime risk of stroke from the age of 25 years onward was approximately 25% among both men and women (Global Burden of Disease group, 2018). Stroke is the third leading cause of disability worldwide and affects people of all ages, though the causes of stroke at a younger age are very different from those at older ages (Fullerton et al., 2003; Seshadri and Wolf, 2007; Johnson et al., 2016; deVeber et al., 2017). The risk of developing stroke increases with high blood pressure, atrial fibrillation, cigarette smoking, hyperlipidemia, and diabetes mellitus (Hankey, 2017). Other modifiable factors are obesity, chronic kidney disease, excessive alcohol use, cocaine consumption, sedentarism, psychological stress and depression (Everson et al., 1998; Cheng et al., 2016; Guzik and Bushnell, 2017). The list of non-traditional factors linked to stroke includes some environmental conditions such as high altitude exposure. Hypobaric hypoxia due to living in mountainous regions may play a role in stroke incidence and mortality; nonetheless, this environmental factor has been poorly investigated (Jha et al., 2002; Niaz and Nayyar, 2003; Pilz et al., 2008; Szawarski et al., 2012; Gürdal et al., 2018).

Worldwide, at least 5.7% of the population live above 1,500 m, with millions of people chronically exposed to high altitude (Tremblay and Ainslie, 2021). There are regions of the world with millions of people living above 2,500 m, including the South American Andes, the Indochinese Himalayas and the Ethiopian Plateaus (Tremblay and Ainslie, 2021). The association between high altitude exposure and stroke is still unknown and the very few investigations available are still inconclusive (Jha et al., 2002; Niaz and Nayyar, 2003; Ezzati et al., 2012; Burtscher, 2014; Mallet et al., 2021). It has been difficult to define at which elevation the effects of high altitude become more severe and where the threshold is located in terms of mild or severe hypoxia (West et al., 2007). The International Society of Mountain Medicine defines low altitude everything located below 1,500 m, moderate or intermediate altitude between 1,500 and 2,500 m, high altitude from 2,500 to 3,500 m, the very high altitude from 3,500 to 5,800 m, more than 5,800 extreme high altitude and above the 8,000 m is considered the death zone (Imray et al., 2011).

Anecdotal evidence suggest that acute exposure to high altitude (>2,500 m) might increase the risk of thrombosis secondary to short-term hypoxia, which has been associated with the development of ischemic stroke (Kotwal et al., 2007; Gupta and Ashraf, 2012; Zangari et al., 2013). Most of these studies found a significant association between living in high altitude and having a higher risk of stroke, especially among younger populations (<45 years of age) (Jaillard et al., 1995; Jha et al., 2002; Niaz and Nayyar, 2003; Faeh et al., 2009). Contrasting results were published by Faeh et al. (2009) who found a decreased risk of cardiovascular diseases (CVD) and stroke-related mortality among those living in high altitude locations in Switzerland (Faeh et al., 2009). This study reported a 12% decreased risk of cardiovascular diseases and stroke-related mortality per 1,000 m of elevation according to mortality data from the year 1990 to 2000. The dataset included sociodemographic information, place of birth and place of residence as well as the median elevation of each city, ranging from 259 to 1,960 m (Faeh et al., 2009).

Faeh et al. (2016) conducted a well-controlled analysis in Switzerland during 2016 through investigating whether changes in temperature, terrain characteristics, and built environment muddled the relationship between living at a moderately higher altitude and having a decreased risk of IHD. After accounting for all other environmental parameters, they revealed that the inverse altitude-IHD relationship maintained, and probably physical environment factors appear to have an independent effect on cardiovascular health (Faeh et al., 2016).

Although this offers a new perspective of the potential protective effect of living at higher altitudes, the elevation range did not surpass 2,000 m, making it difficult to extrapolate the results to other mountainous regions of the world. To further explore the relationship between high altitude and stroke, we conducted a nationwide ecological study in Ecuador with data from 2001 to 2017, including more than 100,000 stroke patients living at different elevations, ranging from 0 m at sea level to 4,300 m within the Ecuadorian highlands.

MATERIALS AND METHODS

Study Design

This is an ecological analysis of the geographical distribution of stroke using hospital admissions as a proxy for incidence and stroke mortality in Ecuador from 2001 to 2017. The analysis included all the stroke cases and fatalities reported in every city (cantons) of Ecuador as the unit of analysis with a yearly resolution. Stroke cases included all the hospital admissions and deaths according to the patient's place of residence reported to the National Institute of Census and Statistics (INEC).

Sample and Setting

A country-wide comparison of the total number of strokes from the 24 provinces and the 221 cantons in Ecuador was performed from 2001 to 2017. Ecuador with an area of more than 283,000 km^2 is the smallest country in the Andean mountainous region in South America. The country is divided into four geographical regions, the coast, the highlands, the Amazon region, and the Galapagos Islands. The political division encloses 24 provinces, 10 from the highlands, seven from the coast, six from the Amazon region, and one from the insular region of Galapagos. Every province has several political divisions called cantons and they are comparable to cities elsewhere. The country has 141 cantons at low altitude, 28 at moderate altitude, 41 at high altitude, and 11 at very high altitude (**Figure 1**).

Population

According to the 2017 National Institute of Census and Statistics (INEC) data projections, Ecuador has a population of 17,082,730, 51% women and 49% men. In terms of ethnicity, most of

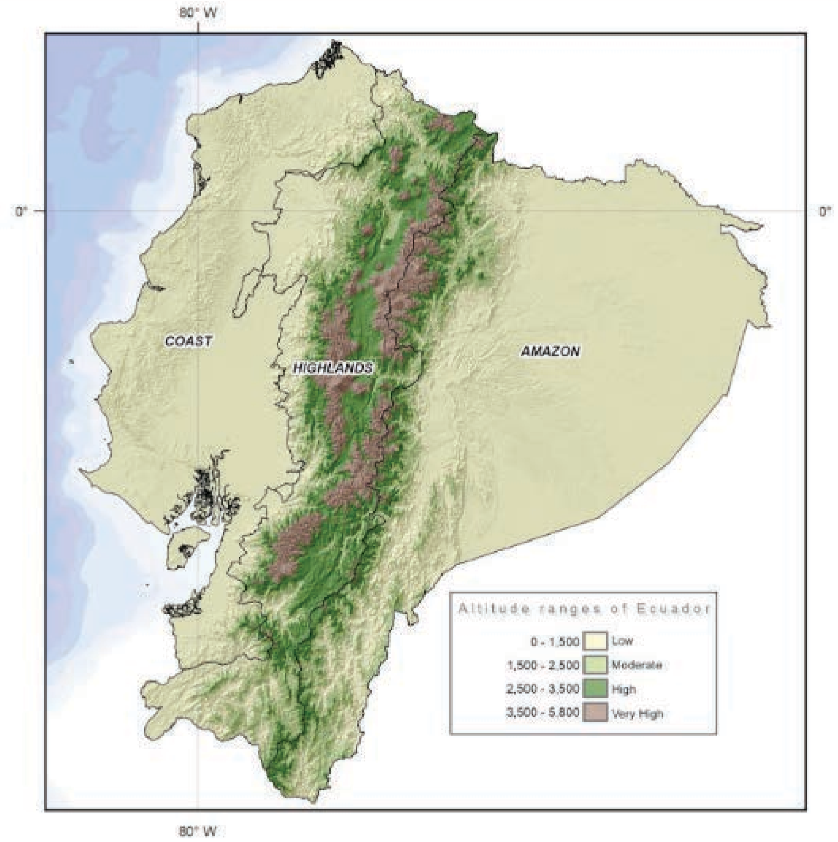

FIGURE 1 | Topographic map of Ecuador using elevation contour lines to show the shape of the country's surface. Map created by the Authors.

people are Mestizo (79.3%), followed by Afro-Ecuadorians (7.2%), indigenous (7.1%), white or Caucasian descendants (6.1%) and other groups (0.4%) (INEC, 2010). By elevation, Ecuador has 60% of its population residing at low altitude (<1,500 m), 10% at moderate altitude (1,500–2,500 m), 27% at high altitude (2,500–3,500 m) and 3% at very high altitude (3,500–5,500 m) (**Figure 2**).

Exposure

The association between altitude exposure and stroke incidence and mortality was analyzed. The classification of low altitude <2,500 m and high altitude >2,500 m was used as a cut-off point for elevation exposure, while the classification offered by the International Society of Mountain Medicine (low altitude (<1,500 m), moderate altitude (1,500–2,500 m), high altitude (2,500–3,500 m) and very high altitude (3,500–5,500 m) was used to assess prevalence odds ratios by different elevations (Imray et al., 2011).

Outcome

Stroke age-sex and altitude adjusted incidence and mortality rates were calculated using the total number of stroke hospital admissions and all the stroke-related deaths in Ecuador.

Data Source

Data were retrieved from the National Institute of Census and Statistics (INEC) using the general hospital admission and the mortality databases from the last 17 years of available data on discharges and death certificates according to the patient's place of residence within the public and private health system in Ecuador. The databases included the latest International Classification of Diseases 10th Revision (ICD-10) coding system and the information concerning stroke was retrieved from the INEC public domain at https://aplicaciones3.ecuadorencifras.gob.ec/sbi-war/.

Data concerning hospitals beds, doctors, and hospital per capita were obtained from the health-related activities database from 2018, available from the following public domain at https://www.ecuadorencifras.gob.ec/actividades-y-recursos-de-salud/.

Inclusion Criteria

Using the International Classification of Diseases 10th Revision (ICD-10) the following subtypes of stroke cases and deaths were included: I60 subarachnoid hemorrhage (SAH), I61 intracerebral hemorrhage (ICH), I63 ischemic stroke, I64 Stroke not specified, and the combination of all of them in a new variable called "all strokes".

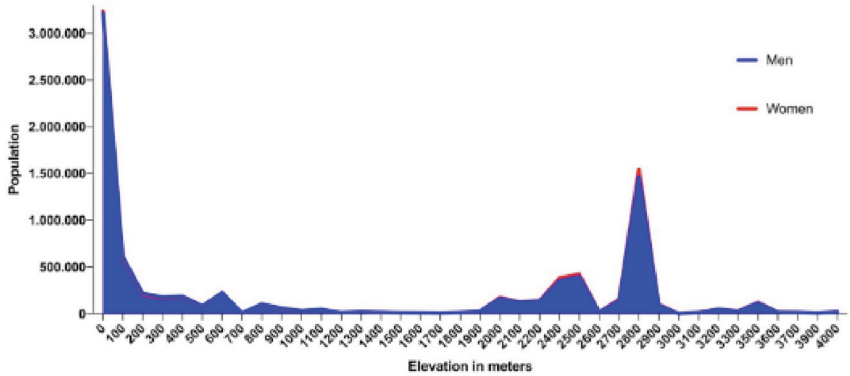

FIGURE 2 | Population by elevation in Ecuador by sex.

Exclusion Criteria

Patients without an ICD-10 diagnosis of major stroke were not included as Kokotailo and Hill defined "major" stroke types to those described as I60, I61, I63, and I64 (Kokotailo and Hill, 2005). The following ICD-10 codes including transient ischemic attack (TIA) were excluded: I65 Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction, I66 Occlusion, and stenosis of cerebral arteries, not resulting in cerebral infarction, I67 Other cerebrovascular diseases, I68 Cerebrovascular disorders in diseases classified elsewhere and I69 Sequelae of cerebrovascular disease.

Bias

To reduce the possibility of incurring in some degree of selection bias and due to the nature of the data, two researchers (EOP and KSR) downloaded the dataset and ran the analyses independently. To ensure that the data pertained to persons residing at different altitudes, the variable "place of residence" was used instead of the variable "place of medical attention".

Statistical Analysis

Incidence and mortality crude and age-sex adjusted rates were calculated using the population at risk for every altitude location. The 2010 Ecuadorian census data were used as the standard population for the direct standardization (INEC, 2010). We have used the 2010 census data as the standard population since no real door-to-door data has been collected in subsequent years. Measurements of frequency (counts, absolute, and relative percentages), central tendency (mean and median), and dispersion (range and standard deviation), as well as absolute differences were performed for age, sex, and the canton's elevation.

To reduce the impact of age-sex population distribution's differences at different altitudes, a direct standardization method was applied to calculate expected incidence and mortality rates. The age-specific mortality rates (observed) for each age group in a given population was used to compute the age-specific expected mortality rates. By this method, we obtained the expected deaths for each age group of each elevation range to later add the number of expected deaths from all age groups and divide the total number of expected deaths by the standard population (Naing, 2000). A Poisson regression was used to find the altitude effect on incidence/mortality after adjusting for age and sex. For association, we obtained OR for the total number of expected cases by the population at risk in all the groups to obtain the likelihood of death due to stroke hospital admissions. Poisson regression models were used to quantify the association between sex, altitude, age, and the risk of stroke. Relative risks were obtained from the exponents of the coefficients of the corresponding models.

The analysis of the data employed SPSS statistics software for Macintosh (IBM Corp., 2014, version 24.0, Armonk, NY, United States) and the Poisson analysis was done in R version 3.6.2. Figures and graphs were performed in Prism 8 GraphPad Software version 8.2.0 (San Diego, CA, United States). The basic cartography maps were generated using QGIS Development Team 2.8 (Creative Commons Attribution-ShareAlike 3.0 license CC BY-SA).

Ethical Consideration

This secondary data analysis of publicly available, anonymized data received ethical approval from the University of Southampton with the Faculty of Medicine Ethics Committee ERGO 51422.R3 number. None of the data used can be identified with any personal information as the dataset did not include names, addresses, e-mails, GPS locations, or telephone numbers. Since this secondary data is available on the government official websites, no individual codes or numbers were given, making it impossible to re-assess or reverse any data toward an individual.

RESULTS

From 2001 to 2017, a total of 38,201 deaths and 75,893 hospital admissions due to stroke (I60, I61, I62, and I64) were reported to INEC. The sex distribution for the deceased was 19,163 deaths for men and 19,038 for women. In terms of hospital admissions, men accounted for 52% (n = 39,569) and women 48% (n = 36,324) of hospital stroke admissions. Sex was not a risk factor for stroke when female is used as a reference [OR: 1.01 (0.99–1.028), *p*-value: 0.434].

We found that patients who reside at high altitude develop stroke at a later age than the low altitude dwellers (**Table 1**).

Pooled Age and Sex-Adjusted Stroke Death Rates (2011–2017)

In terms of mortality, when the age-sex adjusted, rates were applied to the low (<2,500 m) and high (>2,500 m) altitude population, the results demonstrate that the mortality rate is greater for the low altitude group in men [16.5/100,000 (CI 95% 11.5–21.4)] and women [16.2/100,000 (CI 95% 11.7–20.8)] versus [10.6/100,000 (CI 95% 6.9–14.3)] and women [12.3/100,000 (CI 95% 8.45–16.9)]. After computing the differences of proportions, men living at high altitude (>2,500 m) have 35.7% lower mortality rates than those living at lower altitudes (<2,500 m) and that this difference is greater in men than women (**Figure 3A**). When using the four-categories classification we found that men living at low altitude [56.7/100,000 (CI 95% 54.9–58.6)], moderate altitude [54.6/100,000 (CI 95% 52.7–56.4)], high altitude [43.7/100,000 (CI 95% 42.3–45.3)] and very high altitude [51.8/100,000 (CI 95% 49.7–53.8)] have higher stroke mortality than women at low altitude [53.3/100,000 (CI 95% 51.4–55.1)] and very high altitude [43.4/100,000 (CI 95% 42.2–44.7)]. In relation to the four altitude categories, we found that men residing at high and very high altitude have 24.1% and 10.7% lower mortality rates than their low altitude peers, and that these differences hold for both men and women (**Figure 3B**).

Age and Sex-Adjusted Stroke Mortality and Stroke Admission Rates by Age Groups

Stroke hospital admission rates by age groups are significantly lower among younger population (<40 years of age) (**Figure 4**).

Differences among elevations groups did not yield statistically significant diffidence ($p > 0.05$) (**Figure 5**).

Age-sex adjusted rates at different elevations demonstrated that mortality and admission hospital rates per 100,000 people are greater for the low and moderate altitude groups in men and women when compared to the high and very high altitude groups (**Table 2**).

Age-Specific and Sex-Specific Stroke-Related Hospital Admission and Mortality Risk in Ecuador

In the last 17 years of available data, we can observe that hospital admission is less likely to occur in the highlands for men OR: 0.69 CI 95% (0.68–0.71) and women OR: 0.83 CI 95% (0.83–0.86), while at 2,500 m of elevation and above, mortality risk was only reduced among men OR: 0.84 CI 95% (0.81–0.87) but no among women 1.08 CI 95% (1.05–1.12).

Stroke Mortality and Hospital Admission Relative Risk at Four Different Elevation Ranges

Populations from very high altitude are less likely to die due to stroke in both, men [OR: 0.91 (0.88–0.95)] and women [OR: 0.83 (0.79–0.86)]. Getting admitted to the hospital is also less likely to occur in the high altitude group [OR: 0.55 CI 95% (0.54–0.56)] when compared with the low altitude group OR: 0.65 CI 95% (0.64–0.66) (**Figure 6**). Using the International Society of Mountain Medicine classification, the probability of being admitted to the hospital was lower for the high [OR: 0.64 CI 95% (0.61–0.67)] and very high altitude group [OR: 0.55 CI 95% (0.50–0.59)] (**Figure 6**). While the probability of dying due to stroke was lower for men living at moderate [OR: 0.96 CI 95% (0.92–0.99)], high [OR: 0.76 CI 95% (0.73–0.79)] and very high altitude [OR: 0.91 CI 95% (0.88–0.95)] and lower for women living at very high altitude [OR: 0.83 CI 95% (0.79–0.86)] (**Figure 6**).

Burden of Diseases Analysis

In terms of years of life lost prematurely (YLL), stroke predominantly caused mortality among older adults, especially men. From 2001, at least 109,759 years of life were lost prematurely due to stroke, 57,521 (52%) among men and 52,238 (47%) in women. Computing differences in rates yielded a lower burden of stroke at high and very high measured in YYL per 100,000 people (**Table 3**).

Access to Health Services at Different Elevations

The number of doctors, beds and hospital per population living at every single category of elevation is displayed in **Table 4**. In the four categories classification, the very high altitude range has 334

TABLE 1 | Descriptive analysis of age median (in years) between deaths and hospital admission due to all-causes of stroke in Ecuador at different elevation ranges.

	Mortality				Hospital admission			
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
	Men		Women		Men		Women	
<2,500 m	72	(72–74)	76	(76–77)	66	(66–67)	68	(68–69)
>2,500 m	76	(76–78)	79	(78–81)	69	(69–70)	71	(71–72)
Low altitude	71	(71–72)	75	(75–76)	66	(66–67)	68	(67–68)
Moderate altitude	77	(76–79)	78	(77–81)	68	(67–70)	73	(73–74)
High altitude	75	(74–79)	79	(78–81)	69	(69–70)	71	(71–72)
Very high altitude	78	(74–82)	77	(73–83)	67	(65–71)	71	(69–74)

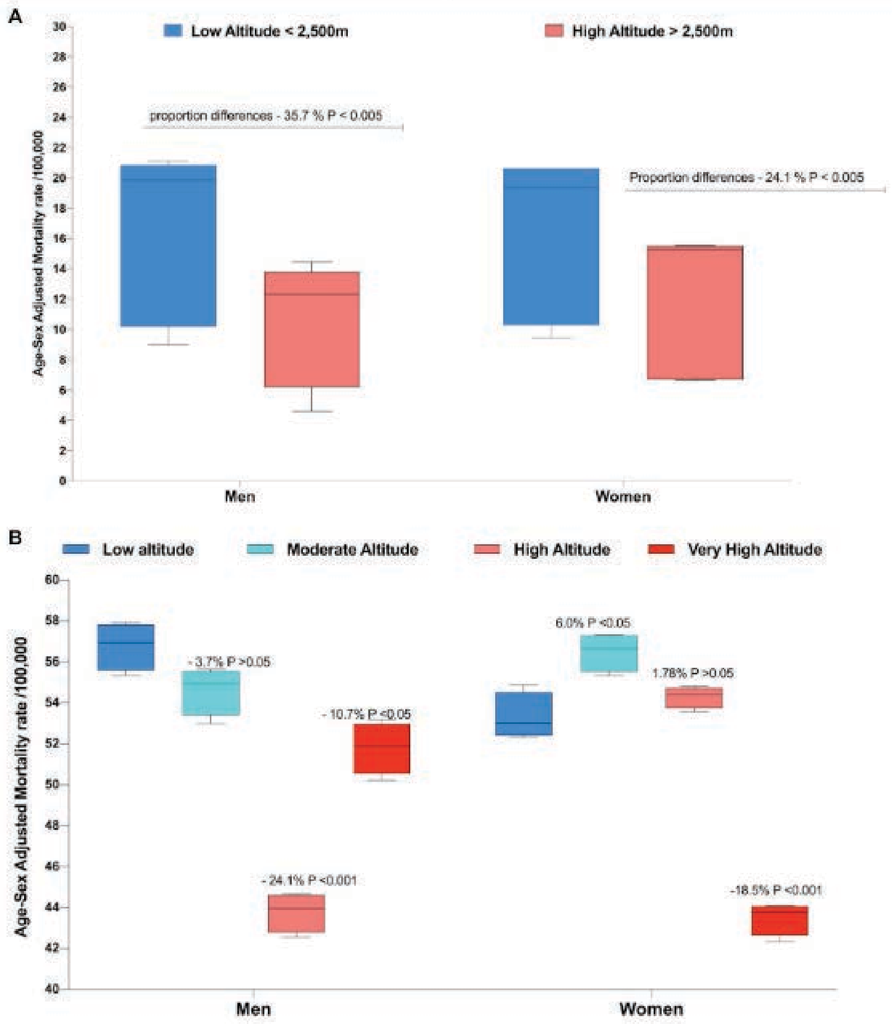

FIGURE 3 | Overall age and sex-adjusted mortality rate by sex and elevation exposure. **(A)** Low altitude (<2,500 m) and High altitude (>2,500 m) Classification and **(B)** Low altitude (<1,500 m), Moderate altitude (1,500 – 2,500 m), High altitude (2,500 m – 3,500 m) and Very High altitude (3,500 m – 5,500 m).

doctors per 100,000 people living at that elevation and 24 beds per 100,000 which is 86% less beds per capita that the high altitude group, 85% less than de moderate altitude group and 81% less than the low altitude group (**Table 4**).

In terms of doctors per capita, we found that at moderate elevation, the number of doctors per every 100,000 people is 518 per 100,000, having the low altitude group 12.7% less doctors per 100,000 people, followed by the high altitude group with 15.8% and the very high altitude group with 35.5% less doctors per 100,000 than the moderate altitude group (**Table 4**).

DISCUSSION

To our best knowledge, our study is the first to describe the burden of stroke at four different elevation ranges including low-moderate, high, and very high altitude. Ecuador is unique for this type of analysis since it has populations residing from sea level to very high altitude (4,300 m) (**Figure 2**). Understanding the country-wide distribution of stroke in Ecuador has already important implications in terms of evaluating the burden of this condition in a country where it has been poorly described before. Significant epidemiological differences in terms of stroke incidence and mortality were found when compared to the population settled at lower altitudes. Our results suggest that living at higher altitudes is associated with a reduction in the probability of developing ischemic stroke. The nationwide data from all the 221 elevations show that both men and women have fewer hospitalizations and lower incidence rates of stroke than their low-altitude controls. Stroke-related deaths are also lower within the high altitude group and the burden of stroke measured in years of life lost (YLL) due to premature mortality is also lower at higher altitudes.

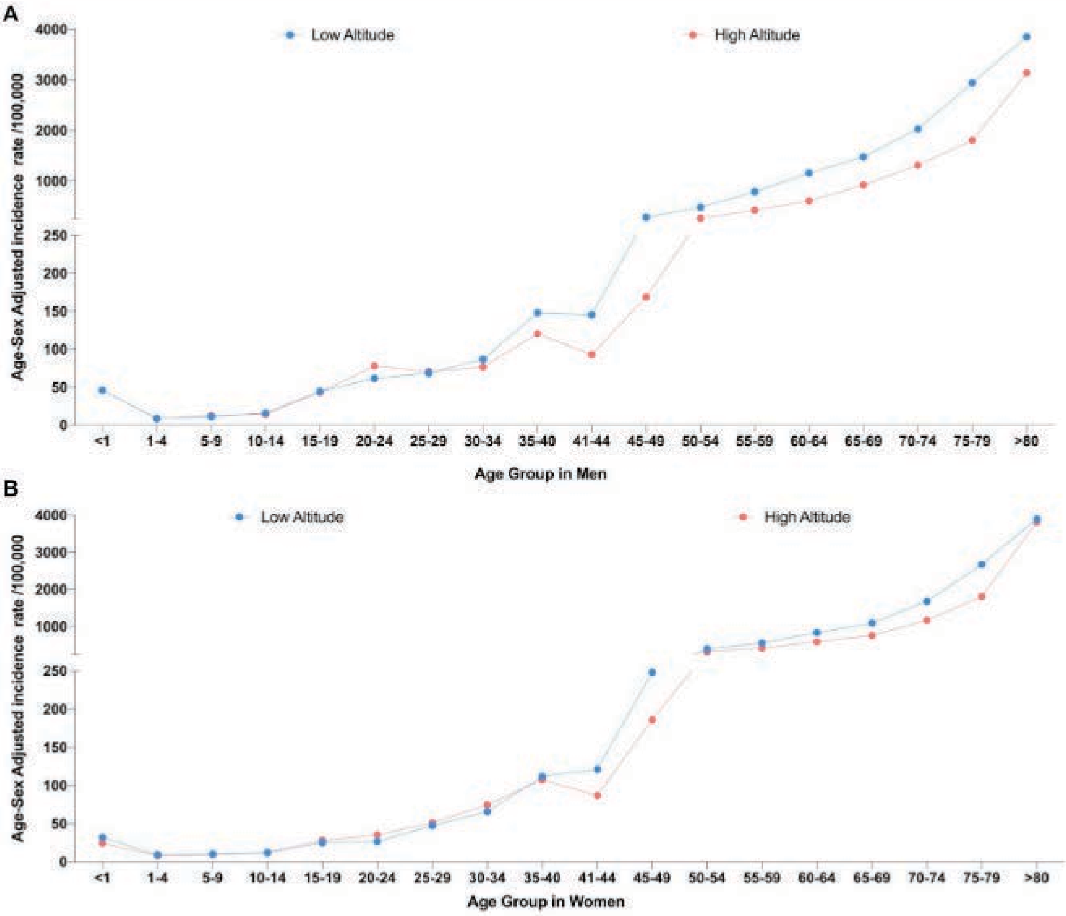

FIGURE 4 | Age-sex adjusted incidence rates due to stroke by age group using the two elevation categories. **(A)** Incidence rates in men at low altitude (<2,500 m) and high altitude (>2,500 m) and **(B)** Incidence rates in women at Low altitude (<2,500 m) and High altitude.

Our results suggest that living at higher altitudes is associated with a risk reduction of developing stroke, evidenced by the significant lower rates of stroke admissions and mortality rates among the high altitude group, despite having similar access to health services. This results are similar to those reported in Switzerland in 2009, that study longitudinally compared stroke mortality at high altitude (Faeh et al., 2009). With increasing altitude, they found an almost constant decline in CHD and stroke mortality in Switzerland within a range of 259–1,960 m. These findings were more evident in men than in women, and the negative association between altitude and disease was stronger for CHD than for stroke (Faeh et al., 2009). Another epidemiological study recently published by Burtscher et al. (2021b), provided additional data supporting the statement that living at moderate altitude (1,000–2,000 m) elicits beneficial effects on all-cause mortality for both sexes, including diseases of the circulatory system in Austria. They found that cardiovascular diseases were main contributors to lower mortality rates at higher altitude within a 10-years period within this country (Burtscher et al., 2021b).

In terms of our findings, we observed a consistent dose-response relationship between high altitude and a reduced risk of developing stroke between 2,000 and 3,500 m of elevation. Beyond this point, other factors might be involved in a reduction of this hypothesized protective effect. For instance, it seems evident that living at certain elevation confers some risk reduction in terms of stroke incidence and stroke-related mortality (Faeh et al., 2009, 2016; Burtscher et al., 2021b).

Additionally, a well-performed comprehensive review, recently published by Burtscher et al. (2021a,b), emphasizes the relationship between hypoxia and brain aging, another important factor that might play a neuroprotective role (Burtscher et al., 2021a). For instance, they described cellular and physiological adaptations during intermittent hypoxia conditioning (IHC), rendering organisms more resistant to subsequent hypoxic or ischemic insults (Mayfield et al., 1994; Dudnik et al., 2018; Burtscher et al., 2021a). They also explored the facts around whether hypobaric or normobaric hypoxia could act as a neuroprotective factor, improving brain aging at high altitude. It seems that despite the importance of O_2 in

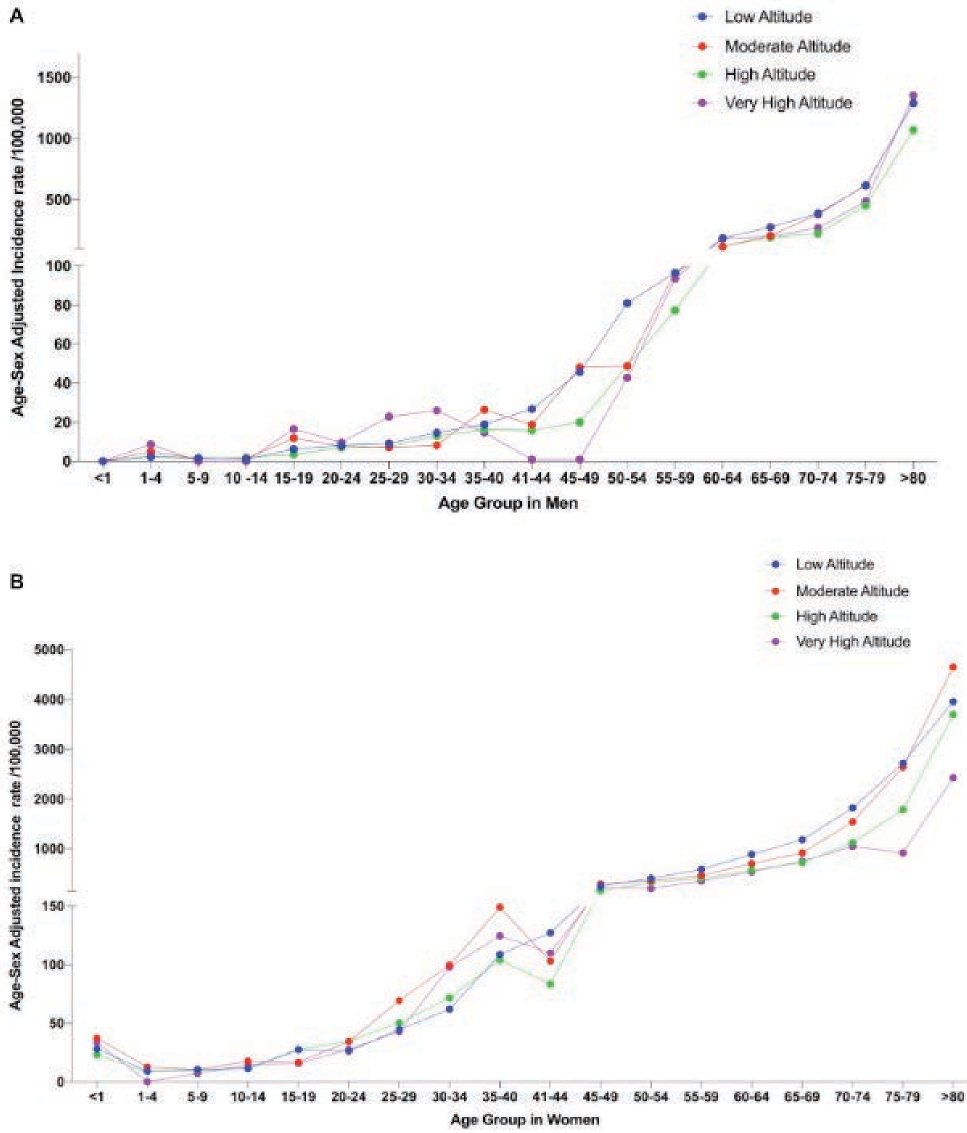

FIGURE 5 | Age-sex adjusted incidence rates due to stroke by age group using the four elevation categories. **(A)** Incidence rates in men at Low Altitude (<1,500 m), Moderate Altitude (1,500 – 2,500 m), High altitude (2,500 m – 3,500 m) and Very High altitude (3,500 m – 5,500 m) and **(B)** Incidence rates in women at Low Altitude (<1,500 m), Moderate Altitude (1,500 m – 2,500 m), High altitude (2,500 m – 3,500 m) and Very High altitude (3,500 m – 5,500 m).

oxidative metabolism, aged organisms can profit from modestly hypoxic environments (Kim et al., 2011). They also described molecular pathways that might oppose aging, mainly driven by the Hypoxia-inducible factor 1 (HIF-1) that mediates the metabolic adaptation to hypoxia and ischemia, including the transition from oxidative to glycolytic metabolism as well as behaving as a positive modulator of aging (Leiser and Kaeberlein, 2010; Cerychova and Pavlinkova, 2018; Burtscher et al., 2021a).

Despite the vast amount of biomedical information related to high altitude hypoxia, ischemia and stroke, is still difficult to distinguish a relationship between biological protective factors (i.e., increased capillary vascularity and capillary perfusion per mm^3 of brain tissue), better lifestyle habits or due to lower occurrence of well-known risk factors (i.e., smoking, obesity, hypertension) (Ortiz-Prado et al., 2010; Hill et al., 2011; Dunn et al., 2012; Hirschler et al., 2012; Voss et al., 2014; Steinback and Poulin, 2016; Beaudin et al., 2017; Liu et al., 2021).

For instance, brain angiogenesis is a common finding among acclimatized and adapted brain to high altitude (Ortiz-Prado et al., 2010; Dunn et al., 2012; Corante et al., 2020). This is the postulated most important protective factor when reducing the size of a stroke and when improving recovery after an ischemic episode at high altitude (Yang et al., 2010; Dunn et al., 2012;

TABLE 2 | Age-sex adjusted mortality and hospital admission stroke rates in Ecuador and the absolute differences in rates when compared to the reference elevation (Low altitude).

	Deaths			Hospital admission		
	(*n*)	Age-adjusted rates	Differences	(*n*)	Age-adjusted rates	Differences
Men						
Low altitude (<1,500 m)	11,241	57.9	Ref	25,003	305.4	Ref
Moderate altitude (1,500–2,500 m)	1,887	55.6	−2.3	4,412	255.9	−49.4
High altitude (2,500–3,500 m)	5,674	44.4	−13.5	9,921	196.8	−108.6
Very high altitude (3,500–5,500 m)	361	53.1	−4.8	233	170.0	−135.4
Total	19,163	N/A	−7	39,569	N/A	−98
Low altitude (<2,500 m)	13,344	56.3	Ref	29,652	291.6	Ref
High altitude (>2,500 m)	5,819	47.4	−8.9	9,917	204.3	−87.3
Total	19,163	N/A	−8.9	39,569	N/A	−87.3
Women						
Low altitude (<1,500 m)	9,770	53	Ref	20,371	251.6	Ref
Moderate altitude (1,500–2,500 m)	2,222	57.2	4.2	4,657	259.2	7.6
High altitude (2,500–3,500 m)	6,690	54.8	1.8	11,096	200.7	−50.9
Very high altitude (3,500–5,500 m)	356	44.1	−8.9	200	164.5	−87.1
Total	19,038	N/A	−1	36,324	N/A	−43.5
Low altitude (<2,500 m)	12,183	52.6	Ref	25,312	246.5	Ref
High altitude (>2,500 m)	6,855	56.9	4.3	11,012	208.5	−38.0
Total	19,038	N/A	4	36,324	N/A	−37.9

Hayakawa et al., 2017; Belayev et al., 2018). Nevertheless, above this point, high hematocrit levels due to a significant polycythemia causing thicker blood overcome this protective factor, reducing blood flow, and causing stasis as well as thrombogenesis (Tohgi et al., 1978; Meifang et al., 2000; Stavropoulos et al., 2017; Warny et al., 2019). Although no data from human studies are available, our results support the plausible relationship of a "protective window" that lays between 2,000 and 3,500 m of elevation, we suggest that anything below this point progressively loses the hypothesized protective effect that causes higher stroke incidence. On the other hand, anything above 3,500 m confronts angiogenesis and vascular remodeling with significant polycythemia, blood stasis and reduced blood flow, progressively triggering thrombogenesis.

It is well described that thrombogenesis is triggered by endothelial damage, blood stasis and increased coagulation (Gupta et al., 2019). When humans are exposed to altitudes greater than 3,500 m, the standard barometric pressure is 67 kPa (505 mmHg) and keeps getting low as we ascend (Ortiz-Prado et al., 2019). At this point, there is 66% of the oxygen available at sea level and the degree of hypoxia experienced relies on our adaptation (Frisancho, 1975; Beall, 2006). Nevertheless, and despite adaptation or acclimatation, either systemic or local hypoxia are inevitable at some point. Thrombosis and embolism at high altitude has been reported several times (Kotwal et al., 2007; Abeysekera et al., 2012; Parsehian et al., 2015; Singhal et al., 2016). The mechanisms related to this proposed prothrombotic state are numerous. Hypoxia is not only a consequences of vascular occlusion but also stimulates thrombogenesis (Tyagi et al., 2014). Polycythemia triggered by chronic high altitude exposure is an independent risk factor for thrombosis as well as for reducing and altering blood flow and cytokine-mediated inflammation in polycythemia (Brill et al., 2013; Zavanone et al., 2017; Jain et al., 2021; Jiang et al., 2021). At high altitude, other risk factors might also increase as elevation is gained. At high altitude, physical activity is reduced due to harsh conditions, reducing mobilization, and increasing hyperventilation (Sherpa and Shrestha, 2020; Uno et al., 2020). Dehydration aggravating blood stasis, hyperventilation aggravating dehydration and a proposed increased platelet adhesiveness might counteract some of the protective effects related to a reduced stroke incidence found at moderate or high altitude (Sharma et al., 1980; Tyagi et al., 2014). Although we do not know the elevation threshold at which high altitude becomes a stroke risk factor, we suggest that above 3,500 m, especially in unacclimatized individuals the protective effect starts to fade.

In relation to high altitude lifestyle differences, habits, and endogenous preconditioning, gathering data is a complex task. Different populations have different eating habits, different lifestyles and they usually subsist in a different way than their low-land counterpart (Westerterp, 2001; Lundby et al., 2006; Li and Zhao, 2015; Brutsaert, 2016). The data about risk factors available in Ecuador suggest that people living in provinces from the highlands consume more alcohol (17.1% versus 9.1%) and smoke more (6.5% versus 2.5%) than the people living at lower altitudes (Freire et al., 2015). These behaviors might contradict the paradoxically lower mortality of stroke among highlanders (INEC, 2015). People from the coast seem to have higher consumption of carbohydrates (36% versus 30%) and have inferior access to health services (24 versus 32 health centers per every 100,000 people) than the persons in the highlands (INEC, 2018). Although these data on dietary variability could

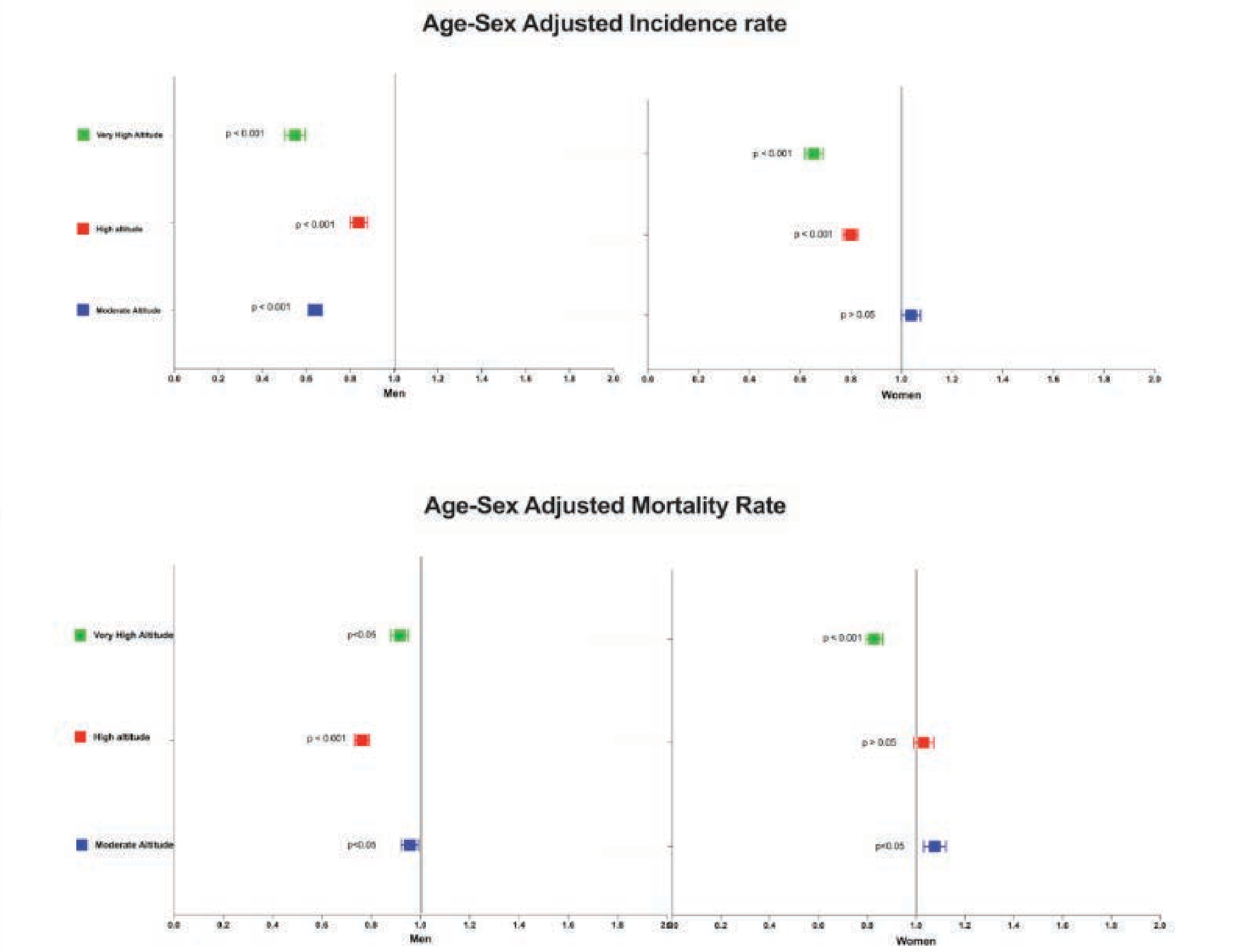

FIGURE 6 | Cumulative risk for mortality and hospital admissions in men and women living at four different elevation in Ecuador from 2001 to 2017. Low altitude was used as a reference variable.

TABLE 3 | Burden of stroke and years of life lost (YLL) prematurely due to stroke in Ecuador from 2001 to 2017.

Altitude	Population	Deaths	Death's rate/1,000 pop.	YLL	YLL per 1,000 pop.
Low altitude (<1,500 m)	8,941,296	3,543	0.40 (0.38–0.41)	75,823	8.48 (8.42–8.54)
Moderate (1,500 – 2,500 m)	1,424,273	537	0.38 (0.35–0.41)	11,004	7.73 (7.58–7.87)
High altitude (2,500 m – 3,500 m)	4,360,711	1,249	0.29 (0.27–0.30)	21,698	4.98 (4.91–5.04)
Very high altitude (3,500 m – 5,500 m)	252,194	84	0.33 (0.27–0.41)	1,234	4.89 (4.62–5.17)
Total	14,978,474	5,413	0.36 (0.35–0.37)	109,759	7.33 (7.28–7.37)

The most likely value at 95% confidence level (<95% less likely >95% less likely).

be extrapolated to the population living at high altitude in Ecuador, it is well-known that people visiting high altitude locations have a significant loss in appetite as well as an accelerate metabolism that might speedup weight loss (Karl et al., 2018; Rausch et al., 2018).

In terms of diabetes, there is no published information about the differences for high and low altitude population in Ecuador, nevertheless, the crude mortality rate according to the INEC database. We found only one study that showed that diabetes in the coastal provinces is more prevalent (388/100,000) than in the highlands (236/100,000), situation that is similar to other studies (Santos et al., 2001; Lopez-Pascual et al., 2018). The available literature suggests that short-term exposure to high altitude leads to transient hyperglycemia, primarily triggered by activation of the sympathetic system, while long-term exposure results in lower plasma glucose concentrations, mediated by better

TABLE 4 | Number of hospital's beds, number of doctors, and number of hospitals per 100,000 people living in Ecuador by different elevation range.

Altitude ranges	Hospital beds per 100,000	Doctors per 100,000	Hospitals per 100,000
Low altitude (<2,500 m)	130	452	3.0
Moderate altitude	162	518	2.5
High altitude (>2,500 m)	177	436	3.4
Very high altitude	24	334	2.6
Low	128	438	2.8
High altitude	173	435	3.2

insulin sensitivity and increased clearance of peripheral glucose (Koufakis et al., 2019). An inverse relationship between altitude, diabetes, and obesity has been well documented. Woolcott in their study showed that living at high altitude (1,500–3,500 m) is associated with a lower likelihood of having diabetes than living between 0 and 499 m in the same way those living at high altitude were 25% less likely to be obese (Woolcott et al., 2014). Several hypothesis have been raised about weight loss at high altitude, including those briefly discussed above (increased resting metabolic rate), as well as the possible role of endocrine molecules such as neuropeptide Y (NPY), ghrelin, galanin, cholecystokinin (CCK), and interleukin-6 (IL-6) stimulating weight loss (Duraisamy et al., 2015). In addition, the negative energy balance in hypoxia seems to be largely due to a reduction in energy intake due to lack of appetite and probably due to a reduced carbohydrate and lipids intake (Díaz-Gutiérrez et al., 2016).

Other risk factors such as hypertension and sedentarism have been showed to be less prevalent among high altitude dwellers according to some of the available published data (INEC, 2009; Ortiz-Prado and Dunn, 2011; Narvaez-Guerra et al., 2018). Although a cause-effect relationship between high altitude and stroke cannot be established with ecological studies, our results suggest that milder chronic hypoxia could play a protective role for the development of stroke, and more severe long-term hypoxia (>3,500 m) might be linked to a higher burden of cerebrovascular diseases (Pilz et al., 2008; Faeh et al., 2009; Kent et al., 2013; Lopez et al., 2018).

The observed results show an apparent protective effect of residing at high altitude in relation to stroke. In that sense, there are some biases that we cannot control due to limitations of the data itself. For instance, the healthy user effect bias is one that we could not controlled. There is no mechanism to discern if one patient represents two cases receiving medical attention in two different places at two different times. We have already discussed about the differences in terms of exercise, diet, or habits between the two populations and although we have information available, not all variables can be controlled with an observational study design such as this. Despite these limitations, we believe that the impact of these biases in a setting such as ours should not have a major effect. Similar results have been obtained in well- controlled studies, suggesting important insights into the role that chronic hypoxia and stroke-associated survival at high altitude.

LIMITATIONS

The main limitation of this analysis is that some residual risk factors such as educational attainment, socioeconomic status, BMI, BP, smoking, diabetes, and polycythemia were not controlled since data is not available. Another limitation is the lack of information needed to run a proportional hazards model to estimate survival rates. The data available in the country do not refer to the time that passed before any of the events occurred (in this case stroke related deaths) and we only have information on how many of those events were recorded on a giving year.

Observational epidemiological studies, especially ecological ones, cannot conclude a cause-effect relationship, however, they are very valuable for identifying associations and relationships for further investigations.

CONCLUSION

This is the first epidemiological study that attempt to explore the association between stroke and the burden of cerebrovascular disease at different elevations, ranging from 0 to 4,300 m above sea level. Our findings suggest that living at higher elevations might offer a reduction of the risk of dying due to stroke as well as a reduction in the probability of being admitted to the hospital. Nevertheless, this finding has the strongest epidemiological repercussions between 2,000 and 3,500 m and beyond this point, the hypothesized protective effect starts to fade. It could be hypothesized that high altitude residents, probably due to their increased cerebral microvasculature have better perfusion, thus protecting the brain in some degree against the hypoxic insult. Although the results of this ecological study support a previously proposed theory, more investigation is needed to understand the complex relationship between hypobaric hypoxia, time of exposure and stroke.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are publicly available. This data can be found here https://github.com/covid19ec/StrokeData.

ETHICS STATEMENT

This secondary data analysis of publicly available, anonymized data received Ethical Approval from the University of Southampton with the Faculty of Medicine Ethics Committee ERGO 51422.R3 number.

AUTHOR CONTRIBUTIONS

EO-P contributed toward the conception and design of the whole project, obtained full access to the data from the National

Institutes of Statistic in Ecuador, was primarily accountable for all aspects of work, and ensuring integrity and accuracy of the research as well as of the drafting of the manuscript. SC, JV, and AB-G contributed toward data acquisition and revision of the available literature. KS-R, LG-B, and MC-A contributed to the statistical analysis, internal validity of the study, and initial drafting of the manuscript. AH-T undertook the burden of disease analysis and economic impact of stroke at different altitudes in Ecuador. PE, AB, GV, and PR critically reviewed and edited the manuscript, and providing input toward the reporting of the data and its interpretation. All authors contributed to the article and approved the submitted version.

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__4.__5 The disease burden of suicide in Ecuador, a 15 years' geodemographic cross-sectional study (2001-2015)

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The disease burden of suicide in Ecuador, a 15 years' geodemographic cross-sectional study (2001–2015)

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Abstract

Background: Suicide affects people from different backgrounds, ethnical groups, socio-economic status and geographical locations. In Latin America, suicide reports arescarce, specially in Andean countries. In Ecuador, very few reports have partially described this phenomenon, nonetheless, estimation of the burden of disease (BoD) hasnever been reported in the country.

Methods: A country-wide comparison was performed using the Ministry of Public Health's national databases of overall mortality, Hospital Discharges Database, and the Population Census of the National Institute of Census and Statistics (INEC). The study variables analyzed were age, geographical distribution to provincial level, sex, means of suicide, educational attainment, marital status and mortality. Linear Regression and relative Risk analysis were used to predict outcome and the likelihood that suicide occur among study variables.

Results: In the last 15 years, 13,024 suicides were officially reported. Men were 3 times more likely than women to die by suicide. The overall age-adjusted suicide ratio in Ecuador corresponds to 7.1 per 100,000 per year. The sex-specific rates were 5.3 in women and 13.2 in men. The primary mean of suicide was hanging X70 (51.1%), followed by self-poisoning X68-X69 (35.2%) and firearms X72-X74 (7.6%). Provinces located at higher altitude reported higher rates than those located at sea level (9 per 100,000 vs 4.5 per 100.000). The total economic loss due to suicide was estimated to be $852.6 million during the 15 years' analysis.

Conclusions: This is the first geodemographic study exploring the complete burden of suicide in Ecuador and one of the very few in Latin-America. In the last 15 years of available data, Ecuador ranks above the regional average with an adjusted suicide rate of 7.1 per 100,000 inhabitants. An important finding is that Suicide affects rather younger populations, adding more than 10,000 years of premature years of life lost (YYL) between 2001 and 2015, becoming the first and fourth leading cause of death among adolescent women and men respectively.
Suicide affects people from different backgrounds, socioeconomic status and educational attainment. The mean of suicide changed over time showing that gun and pesticides related deaths decreased significantly since 2001, while hanging and suffocation increased in more than 50%.

Keywords: Suicide, Self-inflicted injury, Pesticides, Hanging, Firearms, Ecuador, DALY

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Background

Suicide affects people from different backgrounds, ethnical groups, socio-economic status and geographical locations [1–3]. Suicide can be defined as any deliberated act by which an individual's death results directly or indirectly from a self-inflicted injury or poisoning [4, 5]. Suicide is a global health problem, ranking between 4th to 20th cause of mortality for any given region in the world [6, 7]. According to the World Health Organization (WHO),a person commits suicide every 40 s [1]. In 2012, suicide accounted for 1.4% of all deaths worldwide, the majority occurring in low- and middle-income countries [8, 9].

Suicide rates vary across countries, ranging from less than 1 per 100,000 deaths in Saudi Arabia and Belize to more than 40 per 100,000 deaths per year in Guyana or Lithuania [1, 10]. The Global Burden of Disease Group (GBD) reported that in 2013, more than 840,000 people died from self-harm worldwide [7]. According to this report, suicide was the 14th leading cause of years of life lost in the world [7].

Suicide is a multifactorial problem influenced by genetic, psychological, cultural and environmental factors [11].

Several risk factors for suicide have been clearly documented, e.g. male sex, younger age, having a psychiatric disorder such as depression and schizophrenia, hopelessness, marital status, white race, low income, owning firearms, incarceration, job loss and drug abuse [12–18]. Recently, a positive association between altitude gradient and suicide has been described [19].

It is estimated that about 30% of suicides in the world are committed by poisoning with pesticides, hangings or firearms, and the means of suicide depend greatly on the availability and access to the lethal object used by the person [20, 21].

In Latin America, the highest mortality rate comes from Uruguay; a small country with a little more than three million people reported more than 15 per 100,000 deaths per year from suicide in 2012 [6, 22]. Other countries like Guatemala (2.5/100.000), Venezuela (3/100.000) or Peru (5.8/100.000), reported more lower rates, averaging 3.7 per 100,000 deaths in 2012 [6].

In South America suicide rates change according to cultural, behavioral and socioeconomic factors, however, data availability and under-ascertainment might also contribute to these differences. Adding up all the regional reports, it was estimated that more than 45,800 people commit suicide every year in this region [23].

Data about suicide is still scarce in Latin America, especially in smaller countries like Ecuador. In the last 20 years just very few reports have partially described this phenomenon in the country [24–26].

The Observatory for Citizen Security in Quito carried out a study on the subject and determined that in 2014 in Ecuador there were 9 suicides per 100,000 inhabitants with similar results in 2015 [27]. The most recent scientific reports on Ecuadorian suicide epidemiology comes from 2011, with two descriptive analyses that offer an interesting demographic analysis of the problem, however, none of those reports included a detailed geodemographic and economic analysis of suicide, years of life lost, disability-adjusted life years (DALY) or risk analysis [24, 26].

In this sense, this document responds to the lack of data about the economic and public health impact of suicide in Ecuador, adding new insights about a problem that has been poorly described in Latin American countries will improve the capacity of policy makers to correctly approach this health problem.

Methods

Study design and population

The present study is an observational cross-sectional analysis of suicide data and the burden of disease in Ecuador in the last 15 years of available data, from 2001 to 2015.

Ecuador is situated in South America and according to national census data, the total population surpassed 16.4 million people in 2015 [28].

A country-wide comparison of the data from the 24 provinces was performed using the complete dataset from the Ministry of Public Health's national databases on overall mortality and hospital discharge data from 2001 to 2015, as well as 2010 population census data from the National Institute of Census and Statistics (INEC). The study variables analyzed were age, geographical distribution at the provincial level, sex, means of suicide, educational attainment, marital status, mortality and high altitude exposure.

Data sources and description

All cases of suicide were classified according to the International Classification of Diseases 10th Revision (ICD-10). ICD-10 codes reflecting intentional self-harm (X60-X84) were identified through autopsy reports provided by INEC. Data on demographic variables such as sex, province elevation, educational attainment and marital status for all cases of suicide were included.

The burden of disease attributable to deaths by suicide in Ecuador was measured in disability-adjusted life years, or DALYs. [29]. DALYs are the sum of years lived with disability (YLDs) and years of life lost due to premature mortality (YLLs). In the case of suicide, only YLLs were considered for the calculations. YLLs were computed as the number of deaths multiplied by life expectancy at the age of death for specific age and sex strata considering a life expectancy at birth of 80 years for men and 82.5 years for women. A standard time discounting of 3% without age weighting was used. All calculations were made in the "DALY" package for R [30].

Data analysis

The demographic variables, suicide method (X60-X84), place and date of suicide as well as the DALY data was analyzed using descriptive statistics. Data are presented as mortality rates, absolute values and proportions. The mortality rate was adjusted by age, sex and geographic location. Linear Regression and relative Risk analysis were used to predict outcome and the likelihood that suicide occur among variables. The calculations were completed using the IBM SPSS statistics version 24.0. References, citation and retrieval were managed by Zotero Open Source Software version 4.0.11. Spatial analysis was performed using QGIS 2.8 and the graphics were designed using the Piktochart infographic online app.

Ethical considerations

According to the international guidelines of good clinical practices (GCP) and the Helsinki Declaration, anonymous databases can be used when no harm or confidentiality can be guaranteed [31]. According to the national guidelines we have complied and met the criteria described above and the study approval was exempted by the BioEthics Committee for Human Research at Universidad de las Americas (CEISH-UDLA) [32]. The deidentified non- biological data is freely available to the public at the following link www.inec.gob.ec and is owned by the Government of Ecuador, through the National Institute of Statistics and Census of Ecuador (INEC).

Results

In Ecuador, over a period of 15 years from 2001 to 2015, a total of 13,024 deaths were attributed to self-inflected injuries. Over this time period, suicide rate fluctuated between 4.3 to 7.1 per 100.000. The overall national suicide mortality rate in private and public healthcare systems averaged 7.5 per 100,000 deaths. Men were 3 times more likely than women to die by suicide. The highest rate of suicide was recorded in Carchi province (12.7 per 100,000) and the highlands provinces had higher rates than those located at sea level (9 vs 4.5 per 100.000). For the first time in history, the rate of suicide in 2015 (7.9 per 100,000) surpassed the homicide rate (6.3 per 100,000).

Age distribution

Suicide in Ecuador affects all age groups, but adolescents and young adults are the most likely group to commit suicide (Fig. 1). During the 15 years of analysis, 262 children younger than 12 years old committed suicide; Azuay province had the highest cumulative percentage reported for this group (4%).

Among adolescents, suicide ranked first among all the causes of death in women aged 13 to 20 years old and 4th in men in the same age group, accounting for more than 17% and 10% of mortality, respectively (Table 1.).

The proportion of suicide by age groups in relationship with all other causes of death from 2001 to 2015 was 2.9% in children (6–12 years), 12.0% in adolescents (13–20 years), 5.8% among young adults (21–39 years) 1.5% in adults (40–65 years) and 0.2% among the elderly (>65 years old).

Sex differences

In Ecuador, men account for a majority of suicides, 71.5%. The overall sex-specific rates in Ecuador is 5.3 for women and 13.2 for men (Fig. 2) and the men to women ratio is 3:1. The proportion of suicide in comparison with all other causes of death is 1.9 in men and 1.0 in women.

Means of self-inflicted injury

The means used by persons who committed suicide in Ecuador differs according to sex and location of the victim. The principal means of self-inflected injury reported in the last 15 years is the X70: Intentional self-harm by hanging, strangulation and suffocation (ICD-10 X70), followed by Intentional self-poisoning by exposure to pesticides (ICD 10 X68) and then firearms (ICD 10 X72–74). (Fig. 3).

Women are more likely to use less violent means, such as poisoning and drug abuse, while men are more likely to use hanging, firearms or intentional self-harm with sharp objects (Fig. 4).

Self-inflicted deaths by firearms accounted for almost 15% of the of means of suicide s in 2001 and 5% in 2015. Hanging increased from 33% in 2001 to 69.3% in 2015 and pesticide self-poisoning decreased from 43% to 20% in the same time period (Fig. 5).

Geographical differences

The provinces with the highest suicide rate per 100.000 in Ecuador are Carchi (12.7/100,000), Napo (11.6/100,000), Cañar (11.3/100,000) and Azuay (11.0/100,000) (Fig. 6).

The lowest recorded suicide rate was reported in the coastal province of Santa Elena with 1.4 per 100.000. The highlands region of the country had the highest suicide rate (9 per 100,000), followed by the Amazonian region (8.1 per 100,000), the insular region of Galapagos (5.6 per 100,000) and finally the coastal region (4.5 per 100,000).

When the average elevation was analyzed, higher altitude locations (>2500 m) had a rate of 9.4 per 100,000 while lower altitude locations (<2500 m) had a rate of 6.3 per 100,000) (Table 2). We performed a logistic regression and a relative risk analysis for elevation (in meters) and suicide. The results show that living at high altitude has a very low chance to predict the occurrence

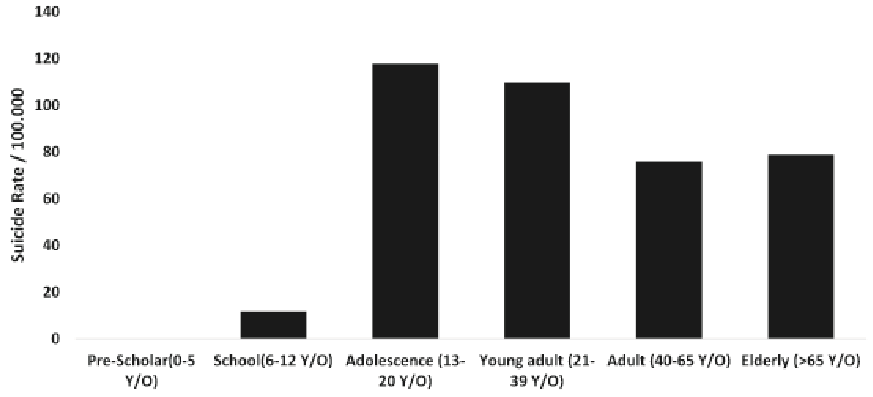

Fig. 1 Suicide rate per 100.000 by age in Ecuador from 2001 to 2015 Source INEC

of suicide (R^2 = 0.0232, p = 0.477), however the relative risk (RR) analysis showed a slightly high increment in the risk of committing suicide when living above 2500 m (RR = 1.545, 95% CI: 1.4890 to 1.6055, $p < 0.0001$).

DALYs and YLLs analysis

During the period 2001–2015 in Ecuador there were 13,024 deaths registered as self-inflected injuries causing death. These deaths are equivalent to 135,731 years of life lost due to premature mortality. 93% of YLLs are attributable to deaths in the economically active population. 73.6% of the burden generated by premature mortality occurred in men (Table 3).

Sociodemographic characteristics

In Ecuador, the majority of people committing suicide are single, followed by married and common law couples. Educational attainment was found to be another important factor related with suicide in Ecuador. In the last 15 years, people who did not finish primary or high school had the highest suicide rates among Ecuadorians. Urban communities have almost triple the suicide rates of rural communities. The overall suicide rate by race shows that mestizos or mixed race has the highest rate (9/100.000), followed by indigenous (7/100.000) and all the other ethnic groups (2/100.000). Suicide rates tend to be higher during January, March and October as described in Table 4.

Discussion

The results from this investigation demonstrate that suicide is one of the most important health issues in Ecuador. Adequate public policy needs to be pursued in order to generate effective public health prevention programs. The results in Ecuador accompany and support the WHO global epidemics [10, 33]. Nearly 13,500 deaths were attributed and officially reported as suicide in the last 15 years in Ecuador, averaging almost 890

Table 1 Main causes of mortality among men and women adolescents between 2004 and 2015

Adolescent Men 13–20 years			Adolescent Women 13–20 years		
Cause of death	N	%	Cause of death	N	%
096 Road traffic injuries	3376	22%	101 Intentionally Injured Injuries	1217	17%
102 Aggression	2564	17%	096 Road traffic injuries	788	11%
103 All other external causes	1574	10%	103 All other external causes	541	7%
101 Intentionally Injured Injuries	1501	10%	094 Other findings not elsewhere classified	511	7%
098 Accidental drowning and submersion	776	5%	102 Aggression	352	5%
094 Other findings not elsewhere classified	702	5%	061 Rest of diseases of the nervous system	290	4%
045 Leukemia	465	3%	045 Leukemia	288	4%
061 Rest of diseases of the nervous system	407	3%	074 pneumonias	271	4%
074 pneumonias	397	3%	089 Other direct obstetric deaths	252	3%
068 Other heart diseases	322	2%	068 Other heart diseases	215	3%
Other causes	3197	21%	Other causes	2872	36%
Total	15,224	100%	Total	7365	100%

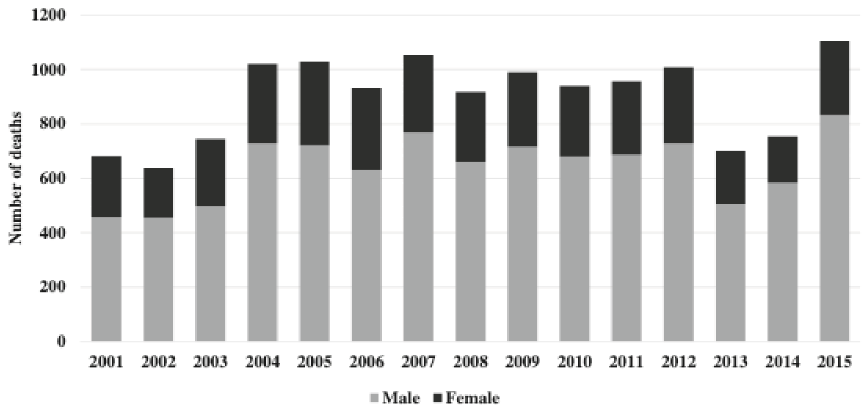

Fig. 2 Sex Distribution of suicide in Ecuador from 2001 to 2015 Source INEC

deaths per year, with an average suicide rate of 7.1 per 100,000. In Ecuador, men are three times as likely to commit suicide than women; this relationship of 3:1 seems to be within the range described worldwide [10, 22, 34].

Suicide rates vary from region to region, affecting provinces located in the Andean region of Ecuador more than those located at lower altitudes. It is not well understood why this relationship is present in Ecuador, however, other reports have also suggested the positive relationship between altitude and suicide rates [19, 35].

The differences between highland and lowland communities have been well documented and include cultural, physical or socioeconomic variances [27, 36]. Although there is not much research on this subject it is speculated that altitude can increase psychiatric disorders, mood changes, risk of depression and risk to develop stroke [37–40]. Greater access to firearms, isolation or reduced income have also been implicated as possible causes [35]. In Ecuador, high altitude provinces have more presence of indigenous groups than those provinces located at the coast. According to the latest National Census, this vulnerable population has less access to proper housing, education and health care [41]. The World Report on Violence and Health in 2002 found that suicide rates have increased among indigenous people [42]. Among the proposed risk factors, cultural differences, discrimination, poor adaptation to urban lifestyles, poverty and limited health access were identified [42, 43]. In this sense, Carchi and Azuay, two of the provinces with the highest suicide rates experienced a massive emigration from their young adults to the US and Europe in the year 2000 [44]. Immigration patterns are variables that increase the risk of suicide due to the apparition of broken families and children that were raised alone, make this group particularly vulnerable to depression, drug abuse and probably higher risk of suicide [45–47]. On the other hand our results might indicate that living at high altitude could be considered a non-traditional risk factor, although the effect of hypoxia on suicidal thoughts or behavior has not been demonstrated yet, a slightly higher relative risk of committing suicide was demonstrated among high altitude dwellers when compared to those located at lower altitudes [19, 35].

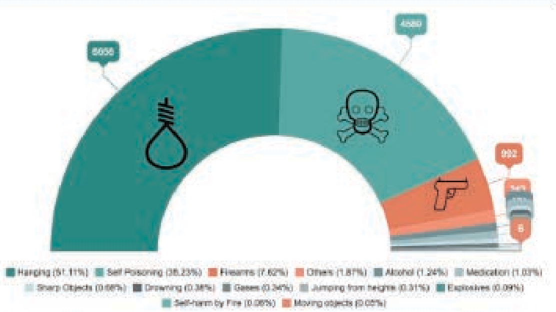

Fig. 3 Means of Self-inflected injury from 2001 to 2015 Source INEC

Among Andean countries, Ecuador has the second highest suicide rate, ahead of Colombia (6.1/100.000) and Peru (5.8/100.000) and behind Bolivia (18.7/100.000) [6, 22]. The reasons of this situation are not well understood; multifactorial risk factors might contribute to these differences among similar countries, and there may also be methodological differences in data collection and registering death causes.

It is not clear why some countries within the same region have significantly different suicide rates [6]. The World Health Organization reports that from the 800,000 people committing suicide each year, 50% are from China and India, and the highest rates reported were from Guyana, Lithuania, Hungary and South Korea [21, 33, 48]. Other countries including Saudi Arabia, Syria, Jordan, Nepal and Jamaica reported some of the lowest rates worldwide [49, 50].

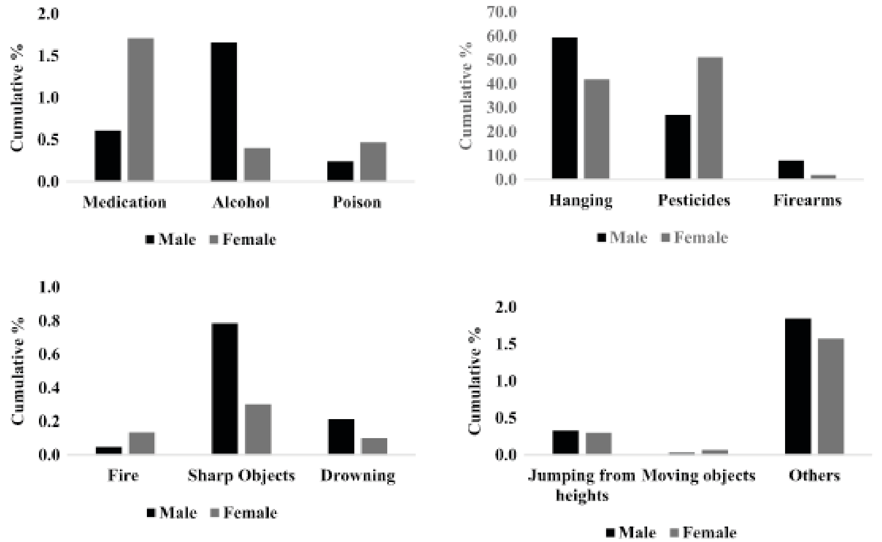

Fig. 4 Means of Self-inflected injury from 2001 to 2015 Source INEC

The data from rural and urban areas showed different characteristics regarding the means of the suicidal act [51]. The incidence of suicide between rural and urban areas varies around the world due to their cultural, socioeconomic and geographical particularities [52]. In Ecuador, most of the reports come from the cities, more than doubling the cases from rural communities. Social stress factors such as high unemployment rates, social isolation, divorce, drug abuse, excessive working and negative chronobiological or physical working conditions have been identified as risk factors in the urban area [53–56]. Emotional conflicts occur in both rural and urban areas, but due to cultural and economic features, divorce as a reason for suicide is less frequent among the rural communities [57]. It has also been hypothesized that longer night shifts and busier lifestyles in urban areas can increase the risk of suicide [58]. There has been very little research on the effect of urbanization on the incidence of suicide. It has been identified that women perform more suicidal acts in urban areas than men, which may be due to job-related factors (quality, opportunity for promotions, etc.) and also vulnerability living in large cities [59].

It is not yet clear why men commit suicide more than women, despite knowledge that suicidal thoughts are more common in women than men, this proportion is observed across cultures. Certain factors have been identified that influence the suicide rate in men [60, 61]. For instance, the gender gap and the social pressure that is exerted on men because the image is generally linked to family support, which can cause economic failure to have a stronger negative impact on men. In Ecuadorian culture, men are commonly perceived or expected to be the primary head of household or even the family's

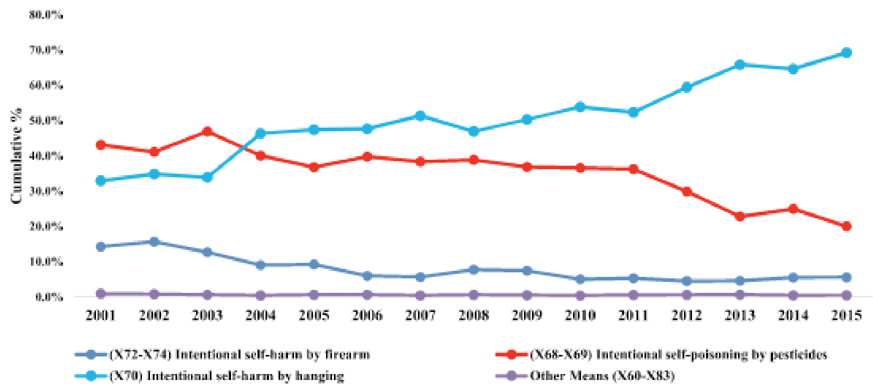

Fig. 5 Cumulative percentage of the mean of suicide in Ecuador in the last 15 years 2001–2015

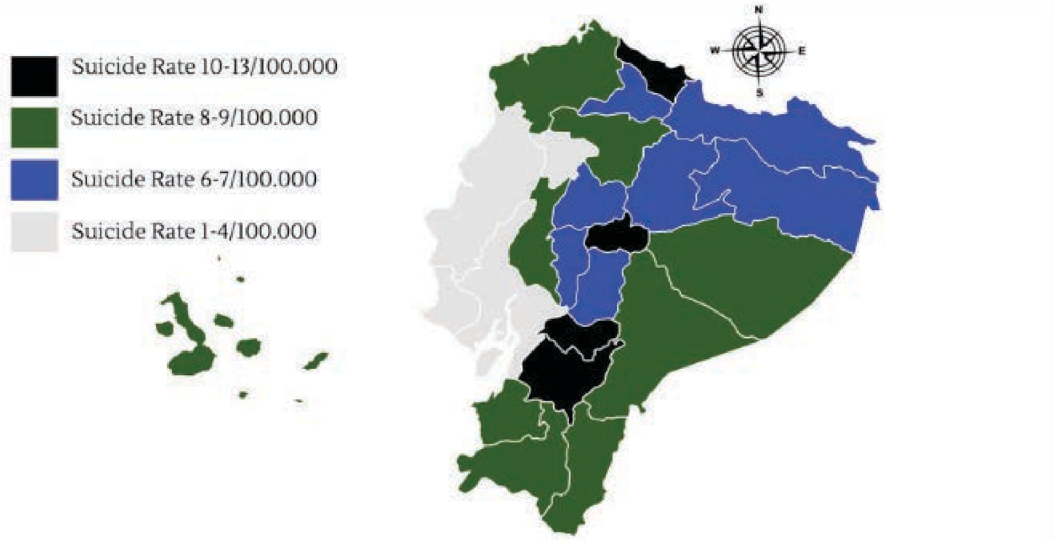

Fig. 6 Geographic distribution of suicide rate in Ecuador from 2001 to 2015 Source INEC

Table 2 Suicide Rate by province, region and elevation from 2001 to 2015 * deaths per 100,000

	Suicide rate	Region	Average Elevation/m	Altitude Classification
Azuay	11.0	Highlands *9/100,000	2560	High altitude > 2500 m *9.4/100,000
Bolívar	8.9		2668	
Cañar	11.3		2518	
Carchi	12.7		2980	
Cotopaxi	8.5		2800	
Chimborazo	8.3		2754	
Pichincha	5.9		2800	
Tungurahua	8.6		2577	
Imbabura	8.6		2225	Low Altitude < 2500 m *6.3/100,000
Loja	5.8		2060	
El Oro	5.4	Coast *4.5/100,000	6	
Esmeraldas	5.6		15	
Guayas	4.1		4	
Los Ríos	6.2		8	
Manabí	4.7		6	
Santo Domingo de los Tsáchilas	4.2		635	
Santa Elena	1.4		45	
Morona Santiago	6.8	Amazonia *8.1/100,000	940	
Napo	11.6		598	
Pastaza	6.1		790	
Sucumbíos	9.6		297	
Orellana	9.7		300	
Zamora Chinchipe	5.1		920	
Galápagos	5.6	Galapagos *5.6/100,000	6	

Table 3 Years Life Lost (YLL) due to suicide in Ecuador, years 2001–2015*

Year	YLL Males	YLL Females	Total YLL	per 10,000 pop.
2001	4306.62	1927.21	6233.82	4.86
2002	4332.90	1853.19	6186.10	4.72
2003	4975.93	2249.54	7225.47	5.42
2004	6069.33	2379.26	8448.59	6.23
2005	7430.72	2669.09	10,099.81	7.36
2006	6564.18	3057.33	9621.51	6.89
2007	7939.52	2826.75	10,766.27	7.57
2008	7248.46	2676.84	9925.30	6.86
2009	7834.41	2542.20	10,376.62	7.04
2010	7173.49	2627.56	9801.06	6.53
2011	7108.09	2707.92	9816.01	6.43
2012	7657.87	2734.28	10,392.15	6.70
2013	5207.05	1903.13	7110.18	4.51
2014	6322.19	1787.59	8109.78	5.06
2015	8784.75	2834.24	11,618.99	7.14
Total	98,955.53	36,776.12	135,731.65	6.22 (±1.03)**

*Years Life Lost computed as the number of deaths times the life expectancy at the age of death for specific age and sex strata, considering a life expectancy at birth of 80 years for males and 82.5 years for females. A standard time discounting of 3% without age weighting was used
**Average YLL rate per 10,000 population (±SD)

unique livelihood. They are expected to earn more than women counterparts so often times economic failure and feelings of inability to support one's family can create an insurmountable pressure [62].

According to available literature, the means by which a man takes his own life appear to be more violent than those means utilized by women [17, 63]. In Ecuador, men use more violent methods than women, including death by firearms, hanging and sharp objects (Fig. 4). Interestingly, the landscape of means of suicide in Ecuador have changed in the last 15 years. Firearms used to account for 15% of the total causes of suicide in 2001, however in 2015, this number dropped to 5% (Fig. 5). This important reduction might be a consequence of better gun control and stronger national safety policy in Ecuador in the last 10 years [64]. For the first time ever in 2015 homicide rate dropped below the suicide rate, This trend might also be related with an important reduction in crime reported in Ecuador in the last years since suicide did not changed dramatically in the last 15 years. [65, 66].

An alarming discovery is that among adolescent women, suicide is the main cause of death, including all violent and non-violent causes. In the last years suicide has become a major public health problem among adolescents, specially in developed countries like the US [67]. Data from other countries shows that men adolescents are 2.6 times more likely to commit suicide than adolescent women [68]. In Ecuador, the proportion of suicide among adolescents account for more than 12% of the total causes of deaths, being this number higher in women (17%) than in men (10%). Similar reports have been published in other countries, showing that proportions are useful tools when estimating the impact of suicide among all other causes of the unnatural Death [69].

Suicide is usually preventable, especially in health systems where mental health services are readily available [70]. These preventable deaths need to be addressed to public health policy makers in order to plan and implement suicide prevention programs with a special focus on high-risk groups such as young adolescents women and single young men. Despite the fact that from 2001 to 2015 suicide rates in Ecuador were fairly stable, the health system and economic impacts are highly concerning due to premature mortality. Ecuador reported 4421 deaths registered as suicide, and the total years of healthy life lost exceeded 135,731 years. Using the human capital method, in 2001–2015 period, the total economic loss due to suicide was estimated to be $852.6 million international dollars (year 2010 base), almost 1% of the Ecuadorian gross domestic product (GDP) for 2015 [65].

Limitations

The main limitation of our study is that data from suicide attempts was not available. In addition, the lack of data to assess confounding factors in order to better understand some of the observed associations and the possible causes of suicide is inexistent.

Conclusions

This geodemographic study is the first of its kind in exploring the complete burden of suicide in Ecuador and its economic impact over the local health and productive system. In the last 15 years of available data, nearly 13,500 deaths were officially registered as suicide, putting the country above the regional average with a suicide rate of 7.1 per 100,000. Suicide largely is taking the life of younger people; especially adolescent women signifies that gender inequality may be a contributing factor. Some of the possible causes of higher suicide rate among younger people can be explained by chronic stressors such as family dysfunction, school failure, sexual abuse, alcohol, drug use and immigration patterns.

Despite the fact that some of the means of suicide has changed over time, the annual rate of suicide has not varied significantly in the last 15 years. In fact, while other means like firearms and pesticide consumption decreased in the last few years, hangings have increased over time.

Table 4 Sociodemographic and monthly variation of suicide in Ecuador from 2001 to 2015

Civil Status	Cumulative %	Suicide Count	Month	Suicide Count	Cumulative %
Common-law	17.50%	2283	January	1292	9.9%
Single	48.00%	6248			
Married	23.20%	3025	February	970	7.4%
Divorced	1.90%	245			
Separated	1.90%	248	March	1087	8.3%
Widower	2.20%	291			
Unknown	5.30%	684	April	996	7.6%
Total	100%	13,024			
			May	1079	8.3%
Educational Attainment	Cumulative %	Suicide Count	June	1008	7.7%
illiteracy	5.70%	737			
Preschool	1.00%	130	July	1043	8.0%
School	48.50%	6323			
High School	31.40%	4087	August	1024	7.9%
Undergraduate	4.70%	611			
Graduate	0.10%	8	September	1066	8.2%
Unknown	8.70%	1128			
Total	100.00%	13,024	October	1105	8.5%
			November	1030	7.9%
Rural/Urban	Cumulative %	Suicide Count			
Urban	69.90%	9098	December	1016	7.8%
Rural	25.10%	3269			
Unknown	5%	657	Unknown	308	2.4%
Total	100%	13,024	Total	13,024	100%

Suicide seems to be more prevalent in high altitude provinces when compared to provinces at lower altitudes, however, this relationship does not demonstrate causality and further research is needed. Although this data is important, the analysis of risk factors and behavioral problems need to be addressed at a deeper level future studies.

The results of this study will provide an insight into the needs of authorities with regard to prevention programs and contributed to our understanding of suicide in Andean countries where information is scarce. Furthermore, it contributes to create the baseline data in order to publish guidelines for those involved in the medical practice of suicide specially those who are in charge of adolescents' school-based education programs and gender inequality policies.

Abbreviations
DALY: Disability-Adjusted Life Year; GBD: The Global Burden of Disease Group; ICD-10: International Classification of Diseases 10th revision; INEC: National Institute of Census and Statistics; IRB: Institutional Review Board; WHO: World Health Organization

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Availability of data and materials
All the datasets analyzed during the current study are available from the INEC repository and the online tool Redatam. The data is freely available to any scientist wishing to use it for non-commercial purposes, without breaching subject confidentiality.

Authors' contributions
EOP designed methodology and collected all the data. He is responsible for the acquisition of information and interpretation. He is the primary author of the manuscript and is fully responsible for this work. KS and LGB were fully responsible for acquiring the data in XLS format and transformed into CVS format for all the descriptive statistical analysis. They have also collaborated to write with the results section of the manuscript. AHT was fully responsible for the DALY and burden of disease analysis and provided a critical analysis of our manuscript prior to submission. FCL a well-known psychiatrist, added his expertise within the discussion section and throughout the entire manuscript during final revision and approval. EV and DC were fully responsible for downloading the data from INEC and performing the first descriptive analysis of the full data set. GV added a very important point of view regarding high altitude and suicide. He also critically reviewed the entire

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__4.__6 Partial pressure of oxygen in the human body: a general review

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Review Article

Partial pressure of oxygen in the human body: a general review

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Abstract: The human body is a highly aerobic organism, in which it is necessary to match oxygen supply at tissue levels to the metabolic demands. Along metazoan evolution, an exquisite control developed because although oxygen is required as the final acceptor of electron respiratory chain, an excessive level could be potentially harmful. Understanding the role of the main factors affecting oxygen availability, such as the gradient of pressure of oxygen during normal conditions, and during hypoxia is an important point. Several factors such as anaesthesia, hypoxia, and stress affect the regulation of the atmospheric, alveolar, arterial, capillary and tissue partial pressure of oxygen (PO_2). Our objective is to offer to the reader a summarized and practical appraisal of the mechanisms related to the oxygen's supply within the human body, including a facilitated description of the gradient of pressure from the atmosphere to the cells. This review also included the most relevant measuring methods of PO_2 as well as a practical overview of its reference values in several tissues.

Keywords: Hypoxia, gradient of pressure, pressure of oxygen, altitude acclimation, barometric pressure

Introduction

The human body is a highly aerobic organism that consumes oxygen according to its metabolic demand [1]. During aerobic respiration the presence of oxygen in addition to pyruvate, produces adenosine triphosphate (ATP), thus yielding energy to the entire organism [2]. To maintain homeostasis, the amount of oxygen within the tissues should respond to a gradient of pressure that pushes oxygen by diffusion throughout the membranes into the tissues [3]. The amount of dissolved oxygen within the tissues and the cells depends on several factors including: barometric pressure (BP), climatological conditions (temperature, relative humidity, latitude, altitude), as well as physiological, pathological, and physical-chemical processes within the organism itself [4, 5].

The composition of gases within the troposphere is constant at approximately the following ratio: 78.08% nitrogen, 20.95% oxygen, 0.93% argon and finally less than 0.038% for carbon dioxide and other gases [6].

Dalton's law establishes that within a combination of any given gases, the total pressure is the same as the sum of the partial pressures of each individual gas present in that mixture [7]. Thus, the partial pressure of oxygen (PO_2) depends mainly on the atmosphere's barometric pressure (BP) and its fractional concentration [8]. Geographical altitude is an important factor affecting BP, because as altitude increases, the amount of gas molecules in the air decreases, so the air becomes less dense than at sea level. At sea level BP is about 760 mmHg, although can be affected not only by altitude: latitude, humidity, temperature and even the season of the year may also affect BP [9, 10]. This changes are normally local, consequently, short-term temporal (time scale of minutes, hours, days and weeks) variations in BP in a same location usually range around 5-15 mmHg [9].

Partial pressure of oxygen

Within the troposphere (lowest region of the atmosphere), PO_2 depends on several vari-

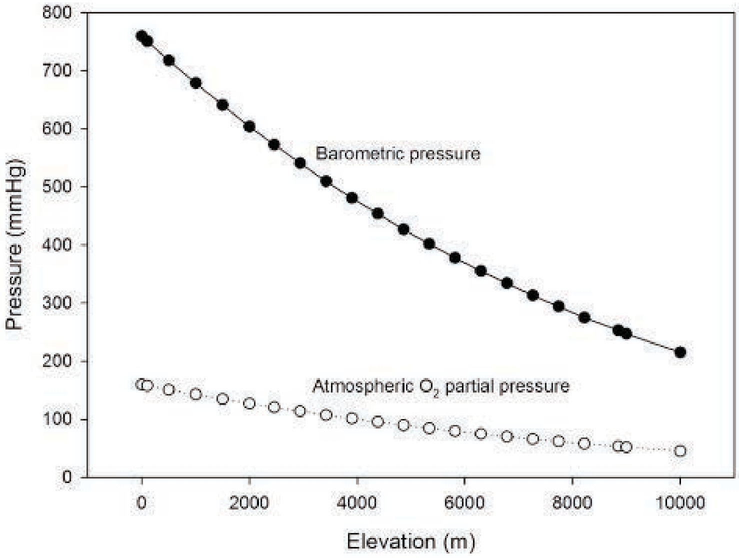

Figure 1. Relationship between elevation and Barometric Pressure (filled circles) and Atmospheric Partial Pressure of Oxygen (hollow circles). *Calculations were based on the standard atmosphere and were done by the authors.

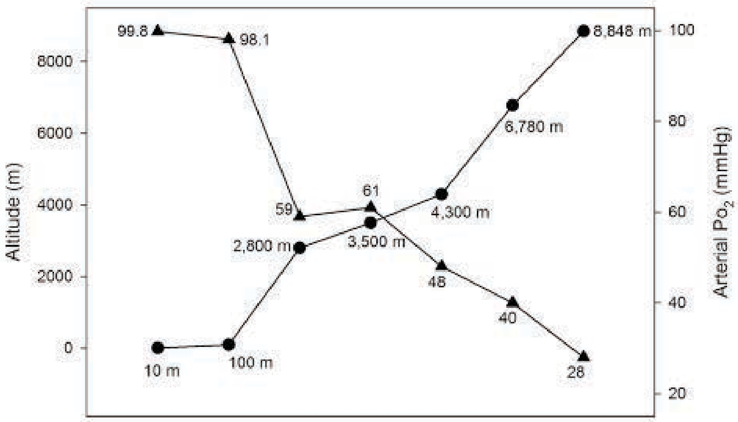

Figure 2. Arterial oxygen tension (PaO_2) at different altitudes in humans according to the values given in several reports [3, 4, 12, 17].

ables, but mainly on barometric pressure (**Figure 1**) [4]. Under physiological conditions, this relationship will be affected by any change in elevation or by modifying the fraction of inspired oxygen (FiO_2) under controlled circumstances [3, 11, 12].

Atmospheric partial pressure of oxygen ($_{Atm}PO_2$)

Humans depend on oxygen for survival, and this gas is acquired from the atmosphere where the partial pressure of oxygen ($_{Atm}PO_2$) within the troposphere depends on BP according to the Dalton's Law [13]:

$$_{Atm}PO_2 = 0.21 \cdot 760 \text{ mmHg} = 159 \text{ mmHg}$$

Humans are constantly exposed to changes in BP, either artificially or naturally, thus, pressure of inspired oxygen (as well as the other gasses) its inversely proportional reduced among those exposed to hypobaric or normobaric hypoxia [3, 14] (**Figure 1**).

Alveolar partial pressure of oxygen (PAO_2)

Once air is warmed and humidified in the nose and upper respiratory tract, the pressure of oxygen decreases while concentration of H_2O increases, thus altering effective PO_2 in this gas mixture. Therefore, oxygen partial pressure within the upper airway is noted inspired PO_2 (PiO_2) [15]. The reduction of pressure of oxygen is caused by the addition of water vapour (humidification) to the entire mixture of gases, thus reducing the pressure of the other gases [4]. The pressure of water vapour is constant at 47 mmHg at normal body temperature (37°C), and it is strongly temperature dependent [11]. This results in an effective reduction at the alveolar level in the partial pressure of oxygen (PAO_2) from 159 to 149 mmHg that is not likely to be physiologically relevant at sea level, because only represents about 6% of the total $_{Atm}PO_2$ [16]. However, when the BP is already low, such as at the summit of Mount Everest (altitude 8,848 m), a reduction of 47 mmHg (the water vapour pressure) represents almost 20% of the available $_{Atm}PO_2$, making this reduction life threatening [17, 18].

Moreover, once the inspired air has been humidified, there is an additional reduction in PO_2 from the trachea to the alveolus, due to the dead space and the mixing of inspired and expired gases [19]. This fall in the pressure of oxygen from the upper airways to the alveolus is almost all accounted for by the alveolar pressure of carbon dioxide ($PACO_2$) [10, 20]. Since inspired PCO_2 is zero and the $PACO_2$ is usually in the range of 40 mmHg, the partial pressure of oxygen must fall [21].

When oxygen is transported into the venous pulmonary capillary, an important gradient of pressure from the upcoming arterial blood pushes the CO_2 out to the alveoli [22].

The alveolar partial pressure of oxygen (PAO_2) in the alveoli-capillary barrier at sea level is calculated based on the fraction of inspired oxygen (FiO_2). At least in the troposphere, air contains a standard 20.95% of oxygen, thus the in order to estimate the alveolar PO_2 the following equation is used:

$$PAO_2 = FiO_2\ (PB-47) - 1/R\ (PACO_2)$$

Where R is the respiratory exchange ratio and equals 0.8 most of the time and the 47 correspond to the water vapour pressure at normal body temperature (37°) [4].

Arterial partial pressure of oxygen (PaO_2)

Once in the lungs, oxygen diffuses across the alveolar-capillary barrier from the alveoli into the arterial circulation. The initial diffusion gradient of pressures in the microcirculation arises when arterial partial pressure of oxygen (PaO_2) with a higher pressure is mixed with the pressure of oxygen within the veins (PVO_2) [23].

The rate of oxygen diffusion across the alveoli-capillary membrane in addition to a faster and easier elimination of CO_2, assures that capillary PaO_2 is almost equal to the alveolar PAO_2 and during normal conditions (at sea level) it correspond to 75 to 100 mmHg [24].

At sea level, during normal conditions, the partial pressure of oxygen in the arteries is high enough to satisfy the oxygen demands for the entire organism [10]. However, during high altitude exposure (hypobaric hypoxia), as barometric pressure descends, the pressure of oxygen in the arterial circulation is inversely proportion reduced [25, 26]. This reduction attributes to the significant reduction in $_{Atm}PO_2$ and determines the actual pressure of oxygen available for tissue and cellular requirements [27, 28] (**Figure 2**).

Tissue partial pressure of oxygen (PtO_2)

Once oxygen has reached the arteries, the difference in pressures (gradient of pressure) between the capillary to the cytosol of surrounding cells results in a steep diffusion gradient, the greatest in the body reaching more than 42% [4]. The average partial pressure in the tissue is called the tissue partial pressure of oxygen (PtO_2) [10].

The transport of oxygen from the atmosphere into the entire body is mediated by the rate diffusion as well as the rate of consumption between physiological barriers [29]. Diffusion is based on the kinetic theory that encompasses the rapid movement of molecules, causing a self-generated energy source to rapidly cross membranes [30]. Whereas convective transport refers to the heat transferred and energy-consuming combination of molecules to cause the movement of oxygen in the trachea and the bronchial tree with the surrounding alveoli-capillary circulation [31]. The diffusive transport is the passive movement of oxygen across several barriers, such as the endothelium, the alveolus and the mitochondrial membrane [32]. The amount of diffusive oxygen movement depends on the gradient of partial pressure of oxygen, the available surface area to diffusion, the permeability and thickness of diffusion barriers and the local metabolic demand [33, 34].

Tissue partial pressure of oxygen (PtO_2) is regulated by the blood flow, the availability of oxygen and the consumption rate from one region to another [3, 24, 35, 36]. The Bohr effect allows that hemoglobin releases more oxygen in response to the metabolic rate of that tissue in highly aerobic tissues [37]. For instance, neurons and cardiac myocytes are largely aerobic and depend on the presence of oxygen for their survival, although some lactate can be produced within the brain, most of them depended on the metabolic rate of oxygen consumption [36, 38]. Other cells, such as the bladder myocytes or the skeletal myocytes are more tolerant to hypoxia, and are able to obtain energy without the presence of oxygen for longer periods of time than can neurons in the brain [10].

Table 1. References values of PtO_2 measurements using different techniques

PtO_2 (mmHg)	Organ and Tissue	Reference	Methods	Species
30-48	Brain	Meixensberger [51], Hoffman [52], Ortiz-Prado [3]	Positron emission tomography (PET)	Human And rats
104-108	Alveoulus	Guyton [4]	Polarographic measurements of tissue oxygen tension using gold microelectrodes	Human
8	Skin epidermis	Wang [35], Carreau [53]	Microelectrodes	Human
24	Dermal papillae			
35.2	Sub-papillary plexus			
61.2	Small bowel	Müller [54, 55], Carreau [53]	Electron paramagnetic resonance oximetry (EPR)	Human
57.6	Large bowel	Müller [54, 55], Carreau [53]	Electron paramagnetic resonance oximetry (EPR)	Human
55.5 ± 21.3	Liver	Leary [56]	Electron paramagnetic resonance oximetry (EPR) with Indian ink.	Human
72 ± 20	Superficial cortex of the kidney	Muller [57], Carreau [53]	Phosphorescence lifetime technique	Human
28.9 ± 3.4	Muscle fibers	Beerthuizen [58], Carreau [53]	Proton NMR spectra of myoglobin	Human
29.6 ± 1.8				
51.8 ± 14.5	Bone Marrow	Carreau [53]	The technique of aspiration in a syringe	Human
34 ± 1.6	Femur Bone	Maurer [59]	Technique of radioactive microspheres in interosseous blood samples and blood flow in the bone	Human
71.4	Mandibule			
55	Suprarenal Gland	Bloom [60]	Phosphorescence lifetime technique	Calf
88	Ovaries	Fraser [61]	Clark electrode for pO_2	Human
18	Umbilical Arteries	Gluckman [62], Carreau [53]	Umbilical cord blood gas	Human
29.2	Umbilical Vein	Guyton [4], Gluckman [62], Carreau [53]	Umbilical cord blood gas	Human
90 ± 5	Arterial PO_2	Mah and Cheng [20], Guyton [4]	Gasometry	Human
40 ± 5	Venous PO_2	Mah and Cheng [20], Guyton [4]	Gasometry	Human
48.2 ± 3.1	Synovial Fluid	Richman [63]	Routine macroscopic and microscopic examination	Human
30.6 ± 3.1	Cornea	Bonanno [64]	Oxygen sensitive dye, Pd-meso-tetra (4-carboxyphenyl) porphine, bound to bovine serum albumin, was incubated with contact lenses	Human
22	The Eye	Bonanno [64]	The T1 mapping method was applied	Human

Intracellular partial pressure of oxygen

Once oxygen reaches the cells, the metabolic demand must to be satisfied. The gradient of partial pressure of oxygen, from the extracellular space into the cell determines the availability of oxygen to the mitochondria [39, 40].

In highly aerobic cells, such as the neurons, energy production depends largely on the availability of oxygen supplied to the mitochondria [41]. Inside this organelle, a series of enzyme-catalysed chemical reactions occur, converting metabolites into carbon dioxide and water to generate a form of usable energy in the form of high energy phosphates [42].

Although it has long been reported that the intracellular partial pressure of oxygen (iPO_2) drops around the oxygen-consuming organelle, the mitochondrion PO_2 must be very small [39]. Various attempts to determine the gradient of oxygen between the mitochondria and the extracellular fluids have led to some incongruous results [40, 43, 44]. Reported values range from one type of cell to another and ranges from below 1 mmHg measured by indirect methods to 1 to 10 mmHg by intracellular direct methods [45]. The classic insensitivity of mitochondrial respiration to local PO_2 has been challenged recently by in vivo [46] and in vitro [47] studies, in which mitochondrial oxygen consumption is dependent on PO_2 over the full physiological range.

Partial pressure of oxygen in different tissues

Once the arteries bring O_2 to the cells, the difference in pressure between the arterial vascular lumen and the tissue will cause that gases that are at higher pressures diffuse to those tissues with lower pressure, exchanging oxygen and carbon dioxide (CO_2) in both directions [29]. The average partial pressure in the tissue along this diffusion gradient is called the tissue partial pressure of oxygen (PtO_2) and varies according with oxygen consumption, capillary density, metabolic rate and blood flow [10, 48].

While under normal circumstances alveolar PO_2 is equal to 104 mmHg, the lungs will transfer this oxygen through the alveolar-capillary barrier, reaching the same PO_2 (104 mmHg), however, before reaching the left atria, the pulmonary shunt blood coming from the bronchial veins (40 mmHg) will mix with blood from pulmonary veins, reaching the atria with an arterial PO_2 of 95 mmHg. This is known as "pulmonary venous admixture" [10, 49].

From the aorta, the amount of oxygen that is released from the hemoglobin will depend upon the metabolic demands from that specific organ, that are usually matched to the arterial oxygen supply and vasomotor sensitivity [50].

In the following section we summarized the range of PO_2 according to the type of tissue, describing in more depth those which have more available data in humans. It is important to point out that due to the lack of studies in controlled environments, an specific range mean value is hard to be provided, therefore, we state the reference value according to the lowest-highest range described (**Table 1**).

Partial pressure of oxygen in the brain

The brain is an organ with one of the highest oxygen and glucose requirements, although it is not able to store metabolic products for further use, its blood supply is highly dependent of vasoactive substances, arterial blood gases and metabolic demand allowing the availability of these nutrients [3, 65, 66].

Changes in tissue brain Partial Pressure of Oxygen depends on the cerebral metabolic rate (CMR), the local cerebral blood flow (CBF) and the systemic exposure of hypoxia [3, 36, 67, 68]. Brain PtO_2 can change due to several factors like CMR, hypoxia, exercise, angiogenesis, stress and Anesthesia [3]. In general and considering that humans are in constant activity and many cofounders cannot be controlled, the available evidence suggest that cortical PtO_2 ranges from 20-25 mmHg in rest and low altitude and reach up to 48 mmHg in high altitudes or intense physical activity [51, 52, 69].

Partial pressure of oxygen in the liver

The liver receives more than 6% of the cardiac output per minute and more than 26% of the cardiac output when considering the portal venous system [10]. This organ seems to be highly oxygenated, however, during sympathetic vascular tone changes, anesthesia, restraining and also depending of the method of measurement, liver tissue PO_2 fluctuates [56]. The

Table 2. Adapted from Harold M. Swartz; Jeff F. Dunn * Minimum Volume Sampled

Method	Parameter measured	Mechanism of measurement	Site of measurement	*Volume sampled
Microelectrode	pO_2	Current generated by the electrolytic decomposition of dioxygen	Interstitial volume in contact with the tip	µl
Near infrared monitoring of haemoglobin and myoglobin	Physiological parameter relative or absolute changes in saturation	Amount or fraction of haemoglobin (Hb) or myoglobin (Mb) and its relative oxygen saturation	Location of the proteins. In the vascular system by non-linear weighting of Hb related to vessel diameter. Idem in muscle for Mb.	ml's
Near infrared monitoring or cytochromes	Physiological parameter relative changes in cytochrome oxidation	Redox state of cytochoromes	Intracellular cytochromes	5 ml's
Phosphorescent and fluorescent methods based on redox states of intermediates	Physiological parameter based on redox potential	Ratio of reduced and oxidized states of redox couples	Sites of the redox intermediates (usually intracellular)	µl's
Phosphorescent and fluorescent methods based on quenching by oxygen	O_2	Change in lifetimes of the excited states	Sites of the introduced probe molecules, intravascular or at a catheter tip	µl's
NMR perfluorocarbon relaxation	O_2	Effect on relaxation rates of fluonne nuclei	Sites of the introduced emulsion	µl-ml's
Substances that localize in hypoxic areas	Physiological parameter	Amount of material that localizes in the tissue, related to perfusion and O_2 at time of administration	Tissues where substances localize	<10 µ in biopsy
EPR oximetry based on soluble materials	pO_2	Effect on linewidth of EPR spectrum	Sites of the particles (usually interstitial)	100 µl
EPR oximetry based on soluble materials	O_2	Effect on linewidth of EPR spectrum or relaxation rates	Sites of the soluble molecules (usually throughout the tissues)	-1 ml
NMR spectroscopy	Physiological parameter metabolic correlates with oxygen	Concentrations of metabolites which change with oxidative status of cells	Sites of metabolites	-1 ml 25 µl-ml's
Proton NMR spectra of myoglobin	Physiological parameter relative or absolute change in oxymyoglobin	Relative concentrations of deoxy and oxymyoglobin	Muscle (myoglobin)	-1 ml µl-ml's
NMR overhauser effect	O_2	Relaxation rates of protons that couple to free radicals	Sites of the soluble free radicals (usually throughout the tissues)	Potential resolution of MRI
NMR bold effect	Physiological parameter	Amount of deoxyhemoglobin in the voxels	Vascular system with a non-uniform weighting to vascular diameters	<0.2 ml µl-ml's

*The minimum volume of tissue that was sampled for theoretical rather than practical interest.

liver can survive with less than 60% of the total liver blood supply due to sympathetic electric nerve stimulation, resulting in an important reduction of tissue PO_2, however under normal conditions the very few reports available in humans refer that PO_2 ranges from 50-55 mmHg [56, 70].

Partial pressure of oxygen in skeletal muscle

The muscle is a highly effective oxygen consuming tissue that responds to blood flow requirements and oxygen availability [71]. The local tissue oxygenation of the skeletal muscle is highly variable, being skeletal muscle one of the most tolerant tissues to hypoxia and metabolic acidosis [72]. Tissue oxygenation level depends on the rate of oxygen supply and the rate of oxygen consumption per tissue [73]. The critical level in which the muscle will suffer ischemia has not been explored, however, muscle PO_2 and its relationship with systemic factors such as sepsis and infections have been reported several times [58, 74]. Considering the reports available, skeletal muscle oxygenation ranges from 7.5 to 31 mmHg [74].

Partial pressure of oxygen in the skin

The skin is one of the most vasoactive tissue within the body, reacting strongly to sympathetic, thermic and metabolic changes [10]. At rest and in neutral thermal conditions, less than 2% of the total cardiac output goes to the skin [75], however, fluctuations in skin blood flow are always occurring due to sympathomimetic variability [76]. The oxygen availability measured locally depends on the influence of the microcirculation and the skin PtO_2 ranges according to the skin layers. The more external layer ranges from 3.2 to 8 mmHg, the papillary dermis from 6.4 to 24 mmHg and below the subcutaneous fat, the skin PtO_2 ranges from 8 to 38 mmHg [53, 75].

Methods to measure tissue partial pressure of oxygen

Several methods have been used to measure the availability of oxygen within the tissues (PtO_2). In **Table 2** we summarize the methods that are available nowadays with some technical specifications such as the mechanism of measurement, the site of data collection and minimum sample volume needed (**Table 2**).

Qualitative methods to measure tissue PtO_2

The most common qualitative methods available to measure brain PtO_2 include, but are not limited, to positron emission tomography (PET), near-infrared spectroscopy (NIR) and magnetic resonance imaging (MRI) or nuclear magnetic resonance (NMR) [77, 78].

Positron emission tomography (PET)

Positron emission tomography (PET) is an imaging technique that uses positron emitting isotopes which are injected into the tissue to provide a three-dimensional image or picture of functional processes in the body [79]. The parameters used to measure brain oxygenation are based on the oxygen extraction fraction (OEF) or the cerebral metabolic rate for oxygen ($CMRO_2$). The use of PET in brain oxygenation studies has been reported several times, although its use is reduced in the clinical setting due to its high cost and technical complexity [77, 80].

Near infrared spectroscopy (NIR)

Near infrared spectroscopy (NIR) is a technology based on light absorption in the near infrared spectrum (700-1000 nm) [81]. It is characterized for its ability to scatter through skin, bone and other tissues, thus detecting low resolution but real time changes in regional hemoglobin content and rarely with brain cerebral perfusion [82, 83].

Blood oxygenation level dependent MRI (BOLD MRI)

Oxyhemoglobin has diamagnetic properties whereas deoxyhemoglobin is a paramagnetic molecule [84]. These magnetic properties can be used as an endogenous source of contrast to visualize tissue oxygenation [85-87]. This technology can be used to measure brain oxygenation based on the concept that changes in deoxyhemoglobin modulate the MRI signal intensity. For example, an increase in regional cerebral blood flow caused by neural activity is accompanied by a local reduction in deoxyhemoglobin content [88].

Quantitative methods to measure brain PtO_2

The physical and chemical characteristics of oxygen can be measured according to its specific interaction with determined oxygen-reactive molecules [89]. The measurement of tissue partial pressure of oxygen (PtO_2) is expressed in mmHg, kPa or Torr and is one of the main "direct" measurements of oxygenation in the tissue [77].

Polarographic microelectrodes

Molecules of oxygen are electron acceptors and this oxidative reaction can be measured using microelectrodes [90]. This oxygen reduction reaction allows a signal that creates a potential difference which is recorded by the electrode [91]. The use of this type of electrodes has allowed the measurement of brain PtO_2 during various conditions, including head trauma, brain surgery, hypothermia and hibernation [92-96].

Electron paramagnetic resonance oximetry

Electron paramagnetic resonance oximetry (EPR) is a spectroscopic technique that detects chemical species that have unpaired electrons [97]. EPR oximetry is a relatively non-invasive method for monitoring tissue partial pressure of oxygen (PtO_2) using paramagnetic oxygen sensitive materials including perchlorotriphenylmethyl molecules or lithium phthalocyanine (LiPc) crystals [85, 97-100].

The fundamental mechanism of this technique is the detection of unpaired electron species which react with the implanted materials (i.e. LiPc crystals) [101]. The identification of these chemical species co-existing in the determined paramagnetic spectrum can be observed and interpreted as oxygen tensions [100, 102-104].

The use of EPR oximetry for the study of tissue oxygenation allows multiple measurements to be performed through the use of crystals that are highly sensitive to low PtO_2 [98]. The advantages of this method are stable calibration and relative unresponsiveness to changes in pH or redox reactions [104, 105].

Mass spectrometry and brain PtO_2 measurements

Mass spectrometry (MS) is a technique that make it possible to obtain analytical information of the molecular mass and its elemental composition of a sample or molecule [106]. For this it is necessary to ionize molecules using different techniques such as chromatographic separation in order to measure the mass to charge ratio caused by external electric and magnetic fields [83, 106].

Mass spectrometry is a complicated technology to use, Atoms are very reactive and they have a short live, thus, manipulation must be performed in a vacuum environment, with very low barometric pressures that ranges from ~10^{-5} to 10^{-8} Torr [106]. These factors, plus the greater degree of invasively, and the response time and delay of mass spectrometers, make mass spectrometry less favourable as a method [83].

Fluorescence and phosphorescence-based probes

The optical methods of oxygen detection are based on the recognition of an atom or molecule which has been electronically excited by the absorption of a photon [3]. This excitation facilitates the transitions of a species from high excitation state or activation, to a ground or low excitation state, this molecular reaction involves the emission of a photon of light [3].

Fiber optic optodes can be used to measure brain PtO_2 in awake and unanesthetized subjects, however its availability in human studies is limited. This technology is based on short pulses of light that are transmitted along a fiber optic sensor, exciting the platinum (new version) or ruthenium (older version) based tip, producing a photon-molecular reaction that is quenched by the presence of oxygen [3, 45, 107, 108].

One of the most important physiological advantages of this optical technique is that it is very sensitive during hypoxia [3]. This feature is clinically relevant when studying tumour growth which depends on oxygenation as well as when studying ischemia or brain injuries [109]. Another important feature of this technology is its insensitivity to magnetic fields. This technology allows us to measure brain PtO_2 while applying simultaneously other exploration or imaging techniques, such as MRI or EPR. This feature can be used to validate two or more methods [110].

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5. Artículos científicos sometidos a revisión por pares

5.1 A comparative analysis of lung function and spirometry parameters in genotype-controlled natives living at low and high altitude.

A comparative analysis of lung function and spirometry parameters in genotype-controlled natives living at low and high altitude

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Research Article

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Abstract

Background

The reference values for lung function are associated to anatomical and lung morphology parameters, but anthropometry it is not the only influencing factor: altitude and genetics are two important agents affecting respiratory physiology. Altitude and its influence on respiratory function has been studied independently of genetics, considering early and long-term acclimatization.

Objective

The objective of this study is to evaluate lung function through a spirometry study in autochthonous Kichwas permanently living at low and high-altitude.

Methodology

A cross-sectional study of spirometry differences between genetically matched lowland Kichwas from Limoncocha (230 m) at Amazonian basin and high-altitude Kichwas from Oyacachi (3,180 m) in Andean highlands. Chi-square method was used to analyze association or independence of categorical variables, while Student's t test was applied to comparison of means within quantitative variables. ANOVA, or in the case that the variables didn't meet the criteria of normality, Kruskal Wallis test were used to compare more than two groups.

Results

People from Oyacachi (high altitude) showed a higher predicted values than those from Limonocha (low altitude). The FVC and the FEV_1 were significantly greater among highlanders than lowlanders (p value < 0.001). The FEV_1/FVC was significantly higher among lowlanders than highlanders for men and women. A restrictive pattern was found in 12.9% of the participants.

Conclusion

Residents of Oyacachi had greater lung capacity than their peers from Limoncocha, a finding physiologically plausible according to published literature. When analyzing the spirometric patterns obtained in these populations, it was evident that no person had an obstructive pattern, while on the other hand, the restrictive pattern appeared in Limoncocha and Oyacachi populations in 12.9% although it is clear that there is a predominance of this in the individuals belonging to Limoncocha.

Introduction

Worldwide, more than 140 million people reside above 2,500 meters [1]. Studying high-altitude dwellers is essential to understand the environmental, physiological and genetic factors that are linked to the incidence and prevalence of different maladies in these populations [2]. Acute and chronic exposure to high altitude has a variety of effects on human physiology and diseases occurrence [3]. Barometric pressure decreases exponentially with increasing altitude[4]. Consequently, the partial pressure of oxygen also decreases, despite the composition of gases in the atmosphere remains unaltered. The physiological consequences of this reduction in oxygen availability begin to be noticeable, even at rest, from an altitude of 2,500 m [4].

Living at high altitudes requires different genetical, molecular, physiological and anatomical adaptive mechanisms to counteract the effects of acute or chronic hypoxia[5, 6]. Those mechanisms or changes that attempt to improve the ventilatory and cardiovascular responses are likely to be the most significant[7, 8]. Anatomical changes including chest depth and chest width have been described among high altitude natives[9–12]. Improved hypoxic ventilatory responses (HVR) and differences in ventilations rates have also been described among high altitude population[13–15]. All these changes in general translate into a better ventilation and improved spirometric values when compared with individuals living at sea level[16, 17]. Among healthy people living at different altitudes, it has been shown that lung capacity is generally higher in individuals living at high altitudes than in those living at sea level[18]. Pulmonary function seems to relate to the time that elapses between exposure to hypoxia and the performance of the spirometry. For instance, in non-adapted subjects who are acutely exposed to high altitudes, lung capacity decreases temporarily. Compte-Torrero et al., reported that espiratory volume during the first second of forced expiration (FEV_1) was reduced by 12.3% (± 5.7%) and the mean Forced vital capacity (FVC) by 7.6% (± 6.7%) among 8 mountaineers who ascended to 3,000 m[19]. They also found that the FEV1/FVC ratio, also called Tiffeneau-Pinelli index remained normal[19]. Another short term exposure analysis performed by Cremona et al. at 1,200m and 4,559m of showed that the FVC did not present significant variations but the FEV_1 increased by 2% among the high altitude group [20].

In terms of long-term exposure, several studies show people who live at high altitudes have significantly higher spirometric values than those who live at sea level[17]. According to Weitz et al., people who reside above 3,200m have greater FVC and FEV_1 parameters than those low altitude dwellers [21]. Similarly, Brutsaert et al., compared the results of two Bolivian populations located at 3,600m and 420 m of elevation [10]. They found greater FVC and FEV_1 volumes when comparted to the subjects located at a lower elevations [10].

In this sense, in order to add important insights in terms of physiological differences between low and high altitude dwellers, we have performed a comparative analysis between a unique Andean genotyped-controlled indigenous population that reside at two different locations in Ecuador. The Kiwcha natives from Limoncocha that lives at 230m of elevation were invited to participate as the low altitude control group, while the Oyacachi native population that lives at 3,800m were part of the high-altitude group.

Methodology

Study design

A cross-sectional analysis of the differences in spirometric parameters was carried out in two populations of Kichwa natives from Ecuador living at two different elevations.

Setting

This study was carried out in Ecuador in two geographically different areas, the Andes and the Amazon Basin. The research work began in January 2017 and concluded in August 2019.

Ecuador with an area of more than 283,000 Km2 is the smallest country in the Andean mountainous region in South America. The country is divided into 4 geographical regions, the coast, the highlands, the Amazon region, and the Galapagos Islands. The political division encloses 24 provinces, 10 from the highlands, 7 from the coast, 6 from the Amazon region and 1 from the insular region of Galapagos. Every province has several political divisions called cantons and they are comparable to cities elsewhere. The country has 141 cantons at low altitude, 28 at moderate altitude, 41 at high altitude and 11 at very high altitude. Limoncocha is located at low altitude while Oyacachi is located at very high altitude (Figure 1).

Participants

The study was carried out with the voluntary participation of 71 members of the Oyacachi community (high-altitude group) located at 3,800 m of elevation and 76 people from Limoncocha (low-altitude control group) located at 230 m of altitude. All the participants who voluntarily agreed are members of the Kiwcha indigenous group in Ecuador

Inclusion criteria

Healthy volunteers of both sexes between the ages of 21 and 75 who were born and currently reside in Oyacachi(high-altitude group) and Limoncocha (low -altitude control group).

Exclusion criteria

Volunteers under 21 years of age, born in another community and who do not normally reside in the parishes were excluded from the study, in addition to those with a history of acute coronary syndrome, acute retinal detachment, aortic aneurysm, endocranial hypertension, and pneumothorax less than one month.

Variables and outcomes

Sociodemographic variables such as age, sex, place of residence was recorded. General anthropometric measurements including weight, height and BMI were obtained. The following spirometry parameters: FEV_1, FVC, FEF25-75% and PEF were included according to predicted values for reference population, meanwhile FEV_1 / FVC, known as Tiffeneau-Pinelli index was calculated according to observed values [22].

DNA extraction and analysis of ancestry ratios

To compare the ancestry of the two populations, a subsample of 47 unrelated individuals (30 Oyacachi vs 17 Limoncocha) was selected. We looked for a subsample among all the individuals to identify those subjects who did not have any first order degree of consanguinity, condition that is based on our laboratory protocol for ancestry analysis. DNA extraction was performed from FTA cards (GE Healthcare) by the Chelex method, then the extracts were diluted to a concentration of 5 ng / ul using the NanoDrop 2000 UV-Vis spectrophotometer (Thermo Scientific, Waltham, MA)[23]. 46-plex autosomal ancestry informative deletion-insertion markers (46-plex AIMs-InDel) were amplified. Fluorescent amplicons were sized by capillary electrophoresis in Pop-7 polymer using a genetic analyzer ABI 3130 (Applied Biosystems, Austin, TX). Alleles were named by the software Genemapper V 3.1 (Life Technologies, Carlsbad, CA) following nomenclature described by Pereira et al, 2012[24]. Taking into account tri-hybrid historic mixture in Ecuador[25–27], Inference of ancestry proportions were obtained considering the admixture model with K = 3 (based in Runs consisted of 100,000 burnin steps, followed by 100,000 Markov Chain Monte Carlo (MCMC) using STRUCTURE V2.3.4 software (Pritchard et al., 2000).

{Citation}All runs were made without any prior information on the origin of samples and only considered the genetic background for the ancestral continental populations based on reference samples: European, EUR (n = 158); African, AFR (n = 105); and Native American, NAM (n = 64). Reference genotypes were extracted from the diversity panel of the Human Genome Diversity Project-Center d'Etude du Polymorphisme Humain (HGDP-CEPH). The populations selected as comparative groups for Africa were: Angola (n = 1), Botswana (n = 4), Central African Republic (n = 23), Congo (n = 13), Kenya (n = 11), Lesotho (n = 1), Namibia (n = 6), Nigeria (n = 22), Senegal (n = 22) and, South Africa (n = 2); for South America: Brazil (n = 22), Colombia (n = 7), and Mexico (n = 35); and for Europe were: France (n = 52), Italy (n = 49), Orkney Islands (n = 15) and Russia (n = 42).

Exposure

The chronic exposure to high altitude among indigenous people living in Oyacachi located at 3,800 m.

Outcome

Lung function and spirometry parameters among exposed and not exposed subjects when compared to the spirometric predicted value.

Data sources

Individual-level socio-demographic information, place of residence and past medical history was obtained in-situ in both communities. A physical examination including body weight, height and weight was performed. Pulmonary function variables were obtained by performing spirometry in all participants FEV_1, FVC, FEV1 / FVC, FEF25-75% and PEF were recorded.

Study size and sample size calculation:

In terms of the number of patients required to achieve significance the sample size (*n*) and margin of error (*E*) were given by the following formula:

$$x = Z(^{c}/_{100})^2 r(100-r)$$

$$n = {}^{N\,x}/_{((N-1)E^2 + x)}$$

$$E = \text{Sqrt}[^{(N-n)x}/_{n(N-1)}]$$

Where *N* is the population size (n=570 in Oyacachi and n=890 in Limoncocha), (*r*) is the fraction of predicted responses (50%), and *Z*(*c*/100) is the critical value for the confidence level (*c*). The total number of medical and physical evaluation required to achieve significance was 82 for the high altitude group and 96 for the low-altitude control group. The total number of medical and physical evaluations required to achieve statistical significance was 82 for the high-altitude group and 96 for the low-altitude group. Through a non-probability convenience-based sampling technique 118 patients (40 men and 78 women) were included in Limoncocha and 95 (39 men and 56 women) for Oyacachi. A sub-group analysis of only those who met the inclusion criteria for spirometry were included within our study.

Data analysis

Descriptive statistics were used to analyze and visualize differences between the two populations. T-tests were used to analyze differences between continue variables and Chi square test were the association or independence of categorical variables. When the predicted values were less than 5 in any of the categories, Fisher's exact test or Spearman's test were used when the variable had evident asymmetries with histograms prior to the selection of the test. The strength of association between categorical variables was performed using the V-Cramer test.

All statistical analysis accepted significance with a p-value <0.05. Calculations were completed using the IBM Corp. Released 2014. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: and R Core Team software 2018 version 3.5.1. Cartography was generated using QGIS Development Team 2.8 and all the references were managed using the open source software Zotero 5.0.85

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Ethical consideration

A full ethical approval was obtained (#MED.EOP.17.01) thought out the Universidad de las Americas bioethics committee (CEISH). All patients voluntarily signed an informed consent. For people who could not read or write, an official community translator and a family member capable of understanding what was described in the document were used to explain the entire context of the project and ensure that there were no doubts about it. To protect the identity and autonomy of patients, all personal information was coded to ensure anonymity

Results

We included 213 patients from both communities, 69 % (n = 118) were from Limoncocha and 31% (n = 95) from Oyacachi. The spirometry subgroup included 147 patients, 52 % (n = 76) from the low altitude group and 48 % (n = 71) from the high altitude group.

Age and sex differences

Within our cohort, women were one year younger (36.5 y/o) than men (37.5 y/o), while within sex, those living at low altitude were on average of 38 y/o, and those from the high altitude group were 35 y/o, none of these differences were statistically significant (Table 1).

Men living at low altitude where on average 7 years older than men living at high altitude nevertheless, this difference was not significant.

Weight, height, and BMI

In relation to weight, women from the low altitude location were on average 5% heavier than those women living at high altitude (p: 0.035), while low altitude men were 8.5% heavier than their high altitude counterpart ($p < 0.001$) In terms of height, both men and women had an average height of 151 cm and 161 cm respectively, having no differences within groups (Table 1).

[insert Table 1 here]

Table 1
Sociodemographic, anthropometric and risk factors analysis from the low and high cohorts.

		Female				Male			
		Low altitude	High altitude	(%) Diff	Sig.	Low altitude	High altitude	(%) Diff	Sig.
Age (mean)		38.0 (28.0–48.0)	35.0 (30.0–41.0)	3.00%	0.596	41.0 (29.0–50.0)	34.0 (27.0–52.0)	4.33%	0.319
Age categories	Young Adult	28 (71.8)	33 (80.5)	16.40%	0.641	23 (62.2)	22 (73.3)	4.44%	0.348
	Adult	10 (25.6)	7 (17.1)	35.29%	0.641	12 (32.4)	8 (26.7)	40.00%	0.348
	Elderly	1 (2.6)	1 (2.4)	0.00%	0.641	2 (5.4)	0 (0.0)		0.348
Weight (Kg) - median (IQR)		64.0 (57.0–75.0)	59.0 (55.0–66.0)	5.00%	**0.035**	73.0 (66.0–80.0)	64.5 (60.0-67.5)	8.50%	**0.001**
Height (cm) (m ± SD)		1.51 (0.05)	1.51 (0.06)	0.00%	0.676	1.61 (0.06)	1.61 (0.05)	0.00%	0.859
BMI - median (IQR)		28.2 (25.0-31.4)	26.5 (24.0-27.6)	1.70%	**0.015**	27.6 (25.8–30.0)	24.8 (23.2–26.0)	2.80%	**0.041**
BMI categories	Under Weight	0 (0.0)	0 (0.0)		**0.048**	0 (0.0)	0 (0.0)		**0**
	Normal	9 (23.1)	13 (31.7)	36.36%	**0.048**	4 (10.8)	16 (57.1)	120.00%	**0.001**
	Over Weight	17 (43.6)	23 (56.1)	30.00%	**0.048**	23 (62.2)	11 (39.3)	70.59%	**0.001**
	Obesity	7 (17.9)	5 (12.2)	33.33%	**0.048**	7 (18.9)	1 (3.6)	150.00%	**0.001**
	Extreme Obesity	6 (15.4)	0 (0.0)		**0.048**	3 (8.1)	0 (0.0)		**0.001**
	Total	39 (100.0)	41 (100.0)	5.00%	**0.048**	37 (100.0)	28 (100.0)	27.69%	**0.034**
Smoking	Yes	0 (0.0)	2 (4.9)		0.162	0 (0.0)	4 (13.3)		**0.036**
	No	39 (100.0)	39 (95.1)	0.00%	0.162	37 (100.0)	26 (86.7)	34.92%	**0.036**
	Total	39 (100.0)	41 (100.0)	5.00%	0.162	37 (100.0)	30 (100.0)	20.90%	**0.036**
Lung Disease	Yes	0 (0.0)	3 (7.3)		0.085	0 (0.0)	4 (13.3)		**0.036**

		Female				Male			
	No	39 (100.0)	38 (92.7)	2.60%	0.085	37 (100.0)	26 (86.7)	34.92%	**0.036**
	Total	39 (100.0)	41 (100.0)	5.00%	0.085	37 (100.0)	30 (100.0)	20.90%	0.036

Measured Spirometric results

The high altitude group have a greater FVC and the FEV_1, nevertheless, these differences are not significant. The FEV_1/FVC ratio was inferior at the high altitude group as well as the forced expiratory flow measurements (Table 2).

Table 2
Measured spirometric values between low and high altitude locations

Indicator	Sex	Low Altitude	High Altitude	Mean Differences	Sig.
FVC (L)	Women	2.6187	2.939	-0.3203	0.789
	Men	3.5362	3.957	-0.4208	0.720
FEV_1 (L)	Women	2.5541	2.7251	-0.171	0.794
	Men	3.3505	3.602	-0.2515	0.396
FEV_1/FVC ratio	Women	95.4385	92.761	2.6775	0.354
	Men	94.927	91.3533	3.5737	0.391
FEF25-75%	Women	3.9028	3.9478	-0.045	0.781
	Men	4.7384	4.5457	0.1927	**0.017**
FEF25-75% – 85%	Women	1.8954	1.7346	0.1608	0.536
	Men	2.4084	1.862	0.5464	**0.008**
PEF L/s	Women	5.6669	5.8726	-0.2057	0.655
	Men	7.8292	7.8143	0.0149	0.906

FVC (forced vital capacity), Forced expiratory volume in 1 second (FEV1) ml, Forced vital capacity (Liters), Forced expiratory volume in 1 second (FEV1) Liters, The FEV1/FVC ratio, also called Tiffeneau-Pinelli index) %, Forced expiratory flow at 25–75% of forced vital capacity (FVC) (FEF25-75%) (Liters/sec), Forced expiratory flow at 25–75% of forced vital capacity (FVC) (FEF25-75% – 85%) Liters/ sec, Peak Expiratory Flow (L/s), Body mass index (BMI)(kg/m2)

Predicted Spirometric results

The predicted values demonstrate that high altitude dwellers have greater FVC for both men and women. Also, when compared to the predicted values, the FEV1 was greater for both sexes although only significant among women (Table 3).

Table 3
Predicted Spirometry values according to sex by altitude

	Female				Male			
Variables	Low altitude	High altitude	(%) Diff	Sig.	Low altitude	High altitude	(%) Diff	Sig.
FVC (L)	93.51 (15.40)	108.93 (19.70)	15.23%	**0.001**	92.24 (15.16)	100.43 (15.56)	8.50%	**0.033**
FEV1 (L)	101.36 (23.03)	115.15 (14.92)	12.74%	**0.002**	104.32 (16.48)	105.00 (24.02)	0.65%	0.892
FEV1/FVC - (IQR)	1.18 (1.11–1.23)	1.14 (1.10–1.18)	4.0	**0.029**	1.20 (1.15–1.24)	1.14 (1.10–1.18)	6.0	**0.003**
FEF 25–75% (L/s)	110.32 (26.75)	112.54 (24.88)	1.99%	0.703	114.25 (23.45)	109.07 (21.65)	4.64%	0.358
PEFR (L/s)	94.00 (17.46)	97.17 (18.32)	3.31%	0.431	95.46 (16.60)	96.03 (26.26)	0.60%	0.914

The maximum flow rate generated during a forceful exhalation (PEFR) was also greater among highlanders when compared to the predicted values, nevertheless, the differences where not significant (Fig. 2).

Discussion

In our study we found that high altitude dwellers have greater pulmonary capacities, similar to those results published by other authors[10, 16–18]. We found that people living at high altitudes have a higher forced vital capacity than those living at low altitudes, and this difference is statistically significant for both men and women (Fig. 2).

Having greater FVC is probably linked to anatomical changes that have evolve from centuries of adaptation[6, 29–31]. Some of these evolutionary anatomical adaptations (wider and deeper chest) confer these populations with larger lungs, which result in a greater capacity to accommodate more air. Wider chest and improved pulmonary performance go along with stronger expiration rates. The FEV_1, was also higher in those living at high altitudes, nevertheless, greater lung capacity was also related with slightly lower FEV_1/FVC ratio.

These findings have even correlated with similar findings reported in people who rapidly ascend to significant elevations. Sharma et al., in 2007 found that at 3,450m FVC had an initial increase of 9% within the first 24 hours followed by a significant decrease in the FVC as well as in FEF_1 and within the maximal voluntary ventilation. At 5,350 m there was a 21% increase in FVC within the first 48 hours, with a subsequent decrease as with the other measured values[32]. In relation to age, it appears that the findings on lung capacity are maintained throughout life. Cid-Juarez et al. in 2019 found that inspiratory capacity and forced vital capacity among healthy individuals between 9 and 81 years of age residing above 2,240 m elevation presented an enviable increase in these parameters, with the highest peak from 9 to 20 years of age[33]. Another interesting study this time investigating the effects of acute hypoxia on respiratory parameters among young subjects demonstrated that[34]. The "Young Everest study" concluded that at 3,500 m above sea level, lung function remained within 7% of baseline among children. They also observed that rapid exposure to high altitude was associated with a significant reduction (up to 23%) in the overall FVC and 16% in FEV_1 in children[34].

Comparing the spirometric values against predictive values is a more fair comparison. The results of these analysis is to observe how their lungs are performing against of what we would predicted for the same sex, age, weight and height[35, 36]. In Ecuador we do not have defined equations to obtain predetermined pulmonary function values. According to the Third National Health and Nutrition Examination Survey of the American Union (NHANES III), in these cases where data is not locally available, the equations to be used are those coming from their closest peers[37]. In Latin America, spirometric studies are relatively scarce. One of the most important projects related to the subject is the Latin American Project for Research in Pulmonary Obstruction (PLATINO). This group found that the predicted values at the pulmonary function level in the Latin American population are like the American population of Mexican origin within the NHANES III study[38]. A study has recently been published in which predictive equations have been performed for each spirometric variable among children living at moderate and high altitude in Colombia, which could be useful for further analysis among children[39].

In this sense, scarce literature is available within the Andean region, nevertheless, Lopez et al., have published an interesting study about the references values among highlanders from south America[17]. They observed higher predictive values in populations living at high altitudes when compared to those predicted values from people located at sea level[17]. Similar results were published by Firoi et al., conducted a study in Central Asia where he compared the Kirghiz population with their medium and low altitude counterparts and observed that FEV_1 and FVC were lower in the high altitude populations [40].

The objectives of our study were not to identify etiologic factors of chronic obstructive pulmonary disease (COPD), nonetheless with the few patients who had a previous pathologic history we were able to find that both populations had a restrictive pattern in 12.9% with a predominance in the low altitude group. In other high altitude regions, COPD seems to be a significant health problem. In Yanfei Guo et al., publication, COPD in residents living at 2,100-4,700 m above sea level, at least 8.2% reported pulmonary patterns compatible with COPD and concluded that the prevalence of COPD was inversely related to altitude, a similar conclusion that the one reported by Laniado et al., in 2012 [41, 42].

In relation to the presence of smoking or any history of pulmonary disease, we found that women and men at high altitude smoke more than those living at lower altitude (Table 1). One study tried to address the implications of smoking in subjects who reside but were not necessarily born at high altitude. This 5-year prospective cohort study sought to monitor lung function among individuals exposed to chronic intermittent hypoxia (CIH) working in high altitude mines[43]. They found an annual small but significant decrease in FVC and FEV_1 among those intermittently exposed to hypobaric hypoxia. They reported that the group of smokers have an earlier deterioration of the pulmonary function than then non-smokers [43].

Our results are the first one in using two genotype-controlled natives living at low and high altitude locations. To our knowledge, this is the first study of this kind and the results of this study can be primarily used for further explore the relationship between chronic hypoxia exposure and pulmonary function among adapted and non-adapted subjects living in the Andes.

Conclusion

Residents of Oyacachi had greater lung capacity than their peers from the Limoncocha, indicating a greater pulmonary capacity, physiologically plausible according to published literature. When analyzing the spirometric patterns obtained in these populations, it was evident that no person had an obstructive pattern, while on the other hand, the restrictive pattern appeared in Limoncocha and Oyacachi populations in 12.9% although it is clear that there is a predominance of this in the individuals belonging to Limoncocha.

Limitations

The main limitation is that, despite obtaining a significant sample size to carry out this study, not all the population belonging to these indigenous communities that met the inclusion criteria were willing to participate. So, even if it is a small probability, it cannot rule out that the inclusion of the data corresponding to those people who did not participate could produce variations in our results or even alters our interpretation. Another potential weakness is the gender asymmetry in the sample because men were a lower number of participants than women. Another limitation is the fact that we do not have local spirometry equations for the correct analysis of the predictive values among highlanders in Ecuador.

Declarations

Ethics approval and consent to participate

All data were collected from the patient's medical records after obtaining written informed consent. The study was approved by the Hospital Eugenio Espejo review board. All data was anonymized, and all identifiable information and biological samples were stored according to the local guidelines.

Data availability

The datasets generated and analysed during the current study are available in the following link https://github.com/covid19ec/Spirometry

Consent to publish

Written informed consent was obtained from every patient in the study.

Author Disclosure Statement

The authors declare no conflicts of interest

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Ecuador.

Authors' Contributions

EOP was fully responsible for the conceptualization, data collection and elaboration of the study. EOP, SE, LGB and JM participated in drafting the manuscript equally and are fully responsible for it. SE, JM, DD and IO visited indigenous communities and apply the spirometry tests. KSR, JSIC and EOP contributed with the data collection and the construction of figures and tables. EOP, MC, EV, and GV contributed with the descriptive statistical analysis and the discussion section of the manuscript. GB was fully responsible for the ancestry analysis and EOP, GV and MC critically reviewed the entire manuscript and produced several comments prior to the submission.

All authors have read and approved the manuscript.

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Topographic map of Ecuador highlighting Limoncocha (230m) and Oyacachi (3,800m).

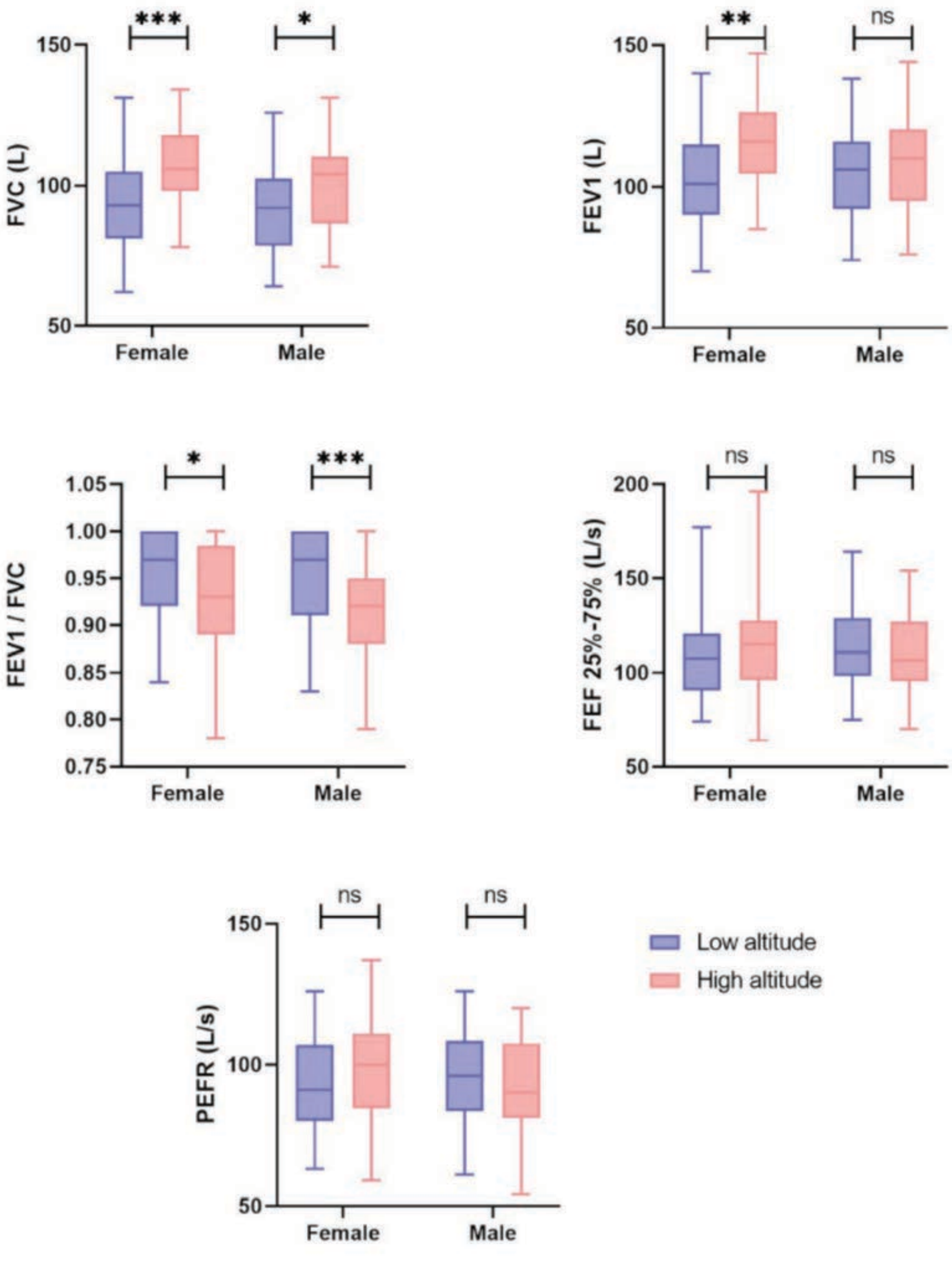

Figure 2

Spirometric values compared to predicted values among low and high altitude dwellers.

5.2 Anthropometric and body composition differences among genotype controlled indigenous adult Kichwa natives living at low (230 m) and high altitude (3,800 m) in Ecuador.

Anthropometric and Body Composition Differences Among Genotype Controlled Indigenous Adult Kiwcha Natives Living at Low (230 M) and High Altitude (3,800 M) in Ecuador

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Research

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Abstract

Background: Anthropometric measures have been classically used to understand the impact of environmental factors on the living conditions of individuals and populations. Most reference studies on development and growth in which anthropometric measures were used were carried out in populations that are located at sea level but there are few studies carried out in high altitude populations

Objective: The objective of this study is to evaluate anthropometric and body composition in autochthonous Kiwchas permanently living at low and high-altitude.

Methodology: A cross-sectional study of anthropometric and body composition between genetically matched lowland Kiwchas from Limoncocha (230 m) at Amazonian basin and high-altitude Kiwchas from Oyacachi (3,180 m) in Andean highlands. Student's t-test was used to analyze differences between continue variables and Chi square test was performed to check the association or independence of categorical variables. Fisher ´s exact test or Spearman test were used when the variable had evident asymmetries with histograms prior to the selection of the test.

Results: Our study shows that low altitude women are shorter and heavier, but these differences are not statistically significant (p value 0.333) on the other hand high altitude men are shorter than their counterparts who live at low altitude with a p value 0.019. In relation to body muscle %, women at high altitudes have less body muscle % (-24.8%) while men at high altitudes have significantly more muscle body mass % (+ 13.5%) than their lowland counterpart. Body fat % is lower among low altitude women (-15.5%) and no differences were found among men.

Conclusions: This is the first study to be performed in two genotyped controlled matching populations located at different altitudes. The anthropometric differences vary according to sex, demonstrating that high altitude population are in general lighter and shorter than their low altitude controls. Men at high altitude have more muscled bodies than their lowland counterpart but their body age was older than their real age.

Introduction

Body composition and size, weight, and height as well as body mass index (BMI) are shaped by genetic, environmental, and sociodemographic circumstances. These features can be subtle or marked, and depending on time; they can be temporal or perennial(1, 2). These changes depend on genetic traits that have been passing from generation to generation and can modify how humans evolve, resulting in different phenotypes for different populations (3–8).

One of the factors associated with evolutionary changes has been the elevation at which a population resides(9). High altitude exposure is associated with a reduced oxygen availability, utilization or consumption that has several physiological and pathological implications among acclimatized and adapted humans(10).

These adaptations often vary from place to place and more importantly in how much time the exposure has had to push genetic, anatomical, morphological, or physiological changes(9, 11). In this sense, long-term high altitude exposure has triggered several adaptation mechanisms and anthropometric differences that vary from region to region(9, 12–14).

Most reports on the adaptive mechanisms that humans have undergone in relation to the environmental conditions at which their ancestors were exposed have been studied in populations located at sea level, nevertheless, high-altitude triggered changes are significant(15, 16).

Some adaptive changes described among high altitude populations rely on how much time has passed(17). For instance, inhabitants from the Himalayas mountainous regions have adapted differently than Andean high altitude dwellers(18, 19). Greater and wider chest as well as smaller bodies are some of the features of the Andean high altitude natives, while thinner and taller bodies have been described among Himalayan Sherpas(9, 17–19).

Some of these morphological and adaptative differences are evident at birth, while others can be observed al older ages (20, 21). A study carried out by Bolaños et al. in Peru within populations located at 3,000 meters above sea level and 2,320 meters above sea level reported that physical growth at high altitudes, it is affected by a small (1–4 cm) delay in linear growth and skeletal maturation (22). It was also observed that the chest circumference among high altitude children (4,150 m) is 12–15% greater compared to American and Peruvian children that were born at sea level (22).

Most of those anthropometric and physiological differences between the populations living at high altitudes in different parts of the world are based in the wide differences in the time and generations passed from the initial colonization of these high altitude ecological niches(23, 24). So, genetical architecture of altitude adapted human populations could play an important role in their anatomical and morphological development as a mean to better survive at high altitude. As noted, evolutionary differences between various populations have been compared on some occasions, however, the comparisons are usually between distinct populations residing in different locations.

The main goal of this study was to compare some anthropometrical variables and body composition parameters in two genetically homogeneous populations of Kiwcha ascent living at low and high altitudes from several generations.

Methodology

Study design

A cross-sectional analysis of the differences in anthropometry parameters and body composition was carried out in two populations of kiwchas, natives from Ecuador.

Setting

This study was carried out in Ecuador in two geographically different areas, the Andes and the Amazon Basin. The research work began in January 2017 and concluded in August 2019.

Ecuador with an area of more than 283,000 Km2 is the smallest country in the Andean mountainous region in South America. The country is divided into 4 geographical regions, the coast, the highlands, the Amazon region, and the Galapagos Islands. The political division encloses 24 provinces, 10 from the highlands, 7 from the coast, 6 from the Amazon region and 1 from the insular region of Galapagos. Every province has several political divisions called cantons and they are comparable to cities elsewhere. The country has 141 cantons at low altitude, 28 at moderate altitude, 41 at high altitude and 11 at very high altitude. Limoncocha is located at low altitude while Oyacachi is located at very high altitude (Figure 1).

Participants

All the participants who voluntarily agreed are members of the Kiwcha indigenous group from Ecuador. The high-altitude group came from Oyacachi, a small Kiwcha community located at 3,800 m of elevation while the low-altitude group came from Limoncocha, located at 230 m of elevation.

Inclusion criteria

The study will be carried out in healthy volunteers of both sexes without any type of comorbidity or chronic disease, between the ages of 18 and 85 who were born and currently residing in Oyacachi (high-altitude group) and in Limoncocha (low altitude group).

Exclusion criteria

Volunteers who are under 18 years of age, who were born in another community and those who does not habitually reside in the parishes were excluded from the study. Those volunteers who did not complete the anthropometric measurements were excluded from the analysis.

Variables and outcomes

Sociodemographic variables, such as age, sex, marital status, and place of residence were recorded. We included the following anthropometric measurements Weight (Kg), Height (cm), Body Mass Index (BMI), Shoulder height (cm), Hip height (cm), Buttock height (cm), Lateral arm length (cm), Shoulder height (cm)-median (IQR), Biacromial Shoulder Width (cm), Biiliac width (cm), Arm length (cm), Chest circumference (cm), Waist circumference (cm), Head circumference (cm) ,Body composition grease (%), Body composition Muscle (%),Corporal Age (years), Real Age (years).

The main outcome is to determine the possible anthropometric differences between genotype-matched Kiwcha indigenous people who live at high altitudes versus their counterparts who live at low altitudes

Data sources

Individual-level socio-demographic information, place of residence and past medical history was obtained in-situ in both communities. A complete physical examination including body weight, height, and t anthropometric variables recording was performed.

Study size and sample size calculation:

In terms of the number of patients required to achieve significance the sample size (*n*) and margin of error (*E*) were given by the following formula:

$$x = Z(^{c}/_{100})^2 r(100\text{-}r)$$

$$n = {}^{N x}/_{((N\text{-}1)E^2 + x)}$$

$$E = \text{Sqrt}[^{(N - n)x}/_{n(N\text{-}1)}]$$

Where *N* is the population size (n=570 in Oyacachi and n=890 in Limoncocha), (*r*) is the fraction of expected responses (50%), and *Z*(*c*/100) is the critical value for the confidence level (*c*). The total number of medical and physical evaluations required to achieve statistical significance was 82 for the high-altitude group and 96 for the low-altitude control group. Through a non-probability convenience-based sampling technique 117 patients were included in Limoncocha and 95 for Oyacachi.

DNA extraction and analysis of ancestry ratios

To compare the ancestry of the two populations, a subsample of 47 unrelated individuals (30 Oyacachi vs 17 Limoncocha) was selected. We looked for a subsample among all the individuals to identify those subjects who did not have any first order degree of consanguinity, condition that is based on our laboratory protocol for ancestry analysis. DNA extraction was performed from FTA cards (GE Healthcare) by the Chelex method, then the extracts were diluted to a concentration of 5 ng / ul using the NanoDrop 2000 UV-Vis spectrophotometer (Thermo Scientific, Waltham, MA)(25). 46-plex autosomal ancestry informative deletion-insertion markers (46-plex AIMs-InDel) were amplified. Fluorescent amplicons were sized by capillary electrophoresis in Pop-7 polymer using a genetic analyzer ABI 3130 (Applied Biosystems, Austin, TX). Alleles were named by the software Genemapper V 3.1 (Life Technologies, Carlsbad, CA) following nomenclature described by Pereira et al, 2012(26). Taking into account tri-hybrid historic mixture in Ecuador(27–29), Inference of ancestry proportions were obtained considering the admixture model with K = 3 (based in Runs consisted of 100,000 burnin steps, followed by 100,000 Markov Chain Monte Carlo (MCMC) using STRUCTURE V2.3.4 software(30).

All runs were made without any prior information on the origin of samples and only considered the genetic background for the ancestral continental populations based on reference samples: European, EUR (n = 158), African, AFR (n = 105), and Native American, NAM (n = 64). Reference genotypes were extracted from the diversity panel of the Human Genome Diversity Project-Center d'Etude du Polymorphisme Humain (HGDP-CEPH). The populations selected as comparative groups for Africa were: Angola (n = 1), Botswana (n = 4), Central African Republic (n = 23), Congo (n = 13), Kenya (n = 11), Lesotho (n = 1), Namibia (n = 6), Nigeria (n = 22), Senegal (n = 22) and, South Africa (n = 2), for South America: Brazil (n = 22), Colombia (n = 7), and Mexico (n = 35), and for Europe were: France (n = 52), Italy (n = 49), Orkney Islands (n = 15) and Russia (n = 42).

Data analysis

Descriptive statistics were used to analyze and visualize differences between the two populations. Student's t-test was used to analyze differences between continue variables and Chi square test was performed to check the association or independence of categorical variables. When the expected values were less than 5 in any of the categories, Fisher's exact test or Spearman's test were used when the variable had evident asymmetries with histograms prior to the selection of the test. The strength of association between categorical variables was performed using the V-Cramer test.

All statistical analysis accepted significance for a p-value <0.05. Calculations were completed using the IBM Corp. Released 2014. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: and R Core Team software 2018 version 3.5.1. Cartography was generated using QGIS Development Team 2.8 and all the references were managed using the open source software Zotero 5.0.85

Ethical consideration

A full ethical approval was obtained (#MED.EOP.17.01) thought out the Universidad de las Americas bioethics committee (CEISH). All patients voluntarily signed an informed consent. For people who could not read or write, an official community translator and a family member capable of understanding what was described in the document were used to explain the entire context of the project and ensure that there were no doubts about it. To protect the identity and autonomy of patients, all personal information was coded to ensure anonymity

Results

A total of 212 subjects were recruited successfully in both communities. 55% (n = 117) were included from the Limoncocha low altitude group and 45% (n = 95) from the Oyacachi high altitude group. In general, women represented 63% (n = 134) from the entire cohort and men 37% (n = 78).

Age and sex differences

Within our cohort, women from the low altitude group were on average 4 years older (41.0 [30.0–59.0]) than women from the high altitude group (36.0 [29.0–48.0]), nevertheless, this difference was not statistically significant (p: 0.121) (Table 1) Low altitude men were on average 5 years older (42.0 [30.0–52.0]) than men living at high altitudes (36.0 [25.0–57.0]), similarity to women, this difference was not significant (p value 0.420).

Weight (Kg) and BMI

In relation to weight, we found that women at high altitudes (60.84 Kg ± 8.333 Kg) are on average 1.9 kilos lighter than women at low altitudes (62.75 ± 14.44Kg) but this difference was not statistically significant (p value 0.374). Men living at high altitudes are 20.7% lighter than their counterpart at low altitudes (p-value < 0.0001) (Table 1).

In terms of overweight, women living at high altitudes have a higher proportion (51.8%) of overweight subjects than those living at low altitudes (39.7%); however, for men, this relationship is reversed, with those living at low altitudes having a higher proportion (55%) of overweight subjects than those living at high altitude (41%).

In terms of obesity, the low altitude group in both men and women has a higher proportion of obese subjects (16.4%) than those subjects living at high altitudes (8.8%), being these differences statistically significant (Table 1). In terms of extreme obesity, we only found 10 women and 6 men having extreme obesity (BMI > 40), belonging all of these to the low altitude group (Table 1).

Table 1
Sociodemographic, anthropometric and risk factors analysis from the low and high cohorts.

		Female				Male			
		Low altitude	High altitude	(%) Diff	Sig.	Low altitude	High altitude	(%) Diff	Sig.
Age (Years) - median (IQR)		41.0 (30.0–59.0)	36.0 (29.0–48.0)	13.0	0.121	42.0 (30.0–52.0)	36.0 (25.0–57.0)	15.4	0.420
Age categories	Young Adult	45 (57.0)	41 (73.2)	9.3	0.086	24 (54.5)	27 (67.5)	11.7	0.475
	Adult	19 (24.1)	11 (19.6)	53.3	0.086	15 (34.1)	10 (25.0)	40.0	0.475
	Elderly	15 (19.0)	4 (7.1)	115.8	0.086	5 (11.4)	3 (7.5)	50.0	0.475
Weight (Kg) - mean ± SD		62.75 ± 14.44	60.84 ± 8.33	3.1	0.374	74.26 ± 10.83	60.34 ± 8.71	20.7	**0.000**
Height (cm) - mean ± SD		149.22 ± 7.01	152.61 ± 8.62	2.3	0.333	159.90 ± 6.39	155.51 ± 9.93	2.8	**0.019**
BMI - mean ± SD		27.90 ± 5.10	26.10 ± 3.10	6.7	**0.022**	29.00 ± 4.20	24.90 ± 2.90	15.2	**0.000**
BMI categories	Under Weight	0 (0.0)	0 (0.0)	0.0	**0.036**	0 (0.0)	0 (0.0)	0.0	**0.000**
	Normal	25 (32.1)	20 (35.7)	22.2	**0.036**	5 (12.5)	21 (53.8)	123.1	**0.001**
	Overweight	31 (39.7)	29 (51.8)	6.7	**0.036**	22 (55.0)	16 (41.0)	31.6	**0.002**
	Obesity	12 (15.4)	7 (12.5)	52.6	**0.036**	7 (17.5)	2 (5.1)	111.1	**0.003**
	Extreme Obesity	10 (12.8)	0 (0.0)		**0.036**	6 (15.0)	0 (0.0)		**0.004**

Stature (cm)

In terms of stature, women from the high altitude group are 3.3 cm taller (152.6 cm ± 8.62 cm) than women from the low altitude group (149.2 cm ± 7.01 cm), however this difference was not statistically significant (p value 0.333). Among men, however, high altitude dwellers are 4.3 cm shorter (155.5 cm ± 9.93 cm) than lowlanders (159.9 cm ± 6.39 cm), being this difference statistically significant (p value 0.019) (Fig. 2).

Anthropometric characteristics

Low altitude women are shorter (− 2.3%) and heavier (+ 3.1%) than women living at high altitude (Table 1). Shoulder height (-0.3%), chest circumference (-0.7%) and waist circumferences (-9.1%) were also smaller in the low altitude group (Fig. 3).

Head circumferences

We found that head circumference is significantly smaller among low altitude women (− 3.6%) and those women living at high altitude. Head Circumference was also smaller for low altitude men (-2.7%) (Table 2 and Fig. 3).

Table 2
Anthropometric measurements among low and high altitude dwellers

	Female				Male			
	Low altitude	High altitude	(%) Diff	Sig.	Low altitude	High altitude	(%) Diff	Sig.
Shoulder height (cm)	126.7 ± 6.8	127.1 ± 7.6	0.3	0.729	136.5 ± 6.8	128.90 ± 8.2	5.7	**0.000**
Hip height (cm)	85.0 ± 4.5	84.1 ± 5.6	1.1	0.323	89.0 ± 4.0	83.2 ± 6.1	6.7	**0.000**
Buttock height (cm)	66.6 ± 3.7	65.4 ± 4.7	1.8	0.095	69.5 ± 3.0	66.7 ± 5.5	4.1	**0.011**
Lateral arm length (cm)	153.0 (148.0-156.0)	152.0 (149.0-160.0)	0.7	0.520	165.0 (158.0-175.0)	161.0 (151.0-167.0)	2.5	**0.048**
Shoulder height (cm)*	40.0 (37.0–41.0)	41.0 (39.0–45.0)	2.5	**0.002**	44.0 (43.0–46.0)	42.0 (40.0–44.0)	4.7	**0.004**
Biacromial Shoulder Width (cm)	52.0 (49.0–57.0)	50.0 (43.0-53.5)	3.9	**0.001**	52.0 (47.0–55.0)	49.0 (39.0–52.0)	5.9	**0.045**
bi-iliac width (cm)	50.0 ± 8.0	49.00 ± 5.0	2.0	0.641	49.0 ± 5.0	48.0 ± 5.0	2.1	0.477
Arm length (cm)	66.1 ± 3.7	66.9 ± 6.5	1.2	0.417	70.8 ± 5.4	69.5 ± 5.1	1.9	0.268
Chest Circum. (cm)	95.2 ± 10.1	95.9 ± 11.1	0.7	0.707	96.2 ± 10.1	94.2 ± 10.9	2.1	0.391
Waist Circum. (cm)	84.1 ± 11.1	92.1 ± 8.70	9.1	**0.000**	89.4 ± 10.4	88.8 ± 9.1	0.7	0.782
Head Circum. (cm)*	54.0 (53.0–55.0)	56.0 (55.0–57.0)	3.6	**0.000**	55.0 (55.0–57.0)	56.5 (55.0–57.0)	2.7	**0.012**
Body fat (%)	28.5 ± 6.6	33.3 ± 9.1	15.5	**0.002**	28.7 ± 6.7	28.7 ± 11.3	0.0	0.985
Body muscle (%)	36.3 ± 7.5	28.3 ± 6.7	24.8	**0.000**	29.0 ± 6.1	33.2 ± 8.3	13.5	**0.038**
Corporal age (years)	29.0 ± 11.0	46.0 ± 14.0	45.3	**0.000**	36.0 ± 9.0	39.0 ± 17.0	8.0	0.523
**Median (IQR)*								

High altitude men have shorter shoulder height (– 4.7%), smaller chest circumference (-2.1%) and waist circumference (-0.7%) and shorter buttock height (-4.1%) (Fig. 4).

Body composition

In relation to body muscle %, women at high altitudes have less muscle (-24.8%) mass than their counterparts at low altitudes, while men at high altitudes have significantly more muscle mass (+ 13.5%) than their lowland counterpart. Body fat % is lower among low altitude women (-15.5%) and no differences were found among men.

Body age was automatically calculated, and we found that high altitude women and men are 10 and 3 years older respectively than their real age, while low altitude men and women are 3 and 12 years younger than their real age (Table 2).

Discussion

The results of our study are the first to compare anthropometric differences in a genotype controlled indigenous adult population living at low (230 m) and high altitude (3,800 m). When analyzing the data, we observe that in general, women at high altitude are slightly lighter and slightly taller than women from the lowlands, nevertheless, high altitude men are significantly shorter and lighter than low altitude men (Fig. 4). Our findings are similar to those reported in Bolivia by Leatherman et al. in 1984. This study conducted an anthropometric survey among 138 men from rural mountainous areas of Bolivia (3,700 m) and concluded that high altitude men are shorter and lighter than their low altitude counterparts(31). Among Quechuas, a similar native group from Peru, Toselli et al., in 2001 found shorter individuals at high altitude in relationship to their corporal mass(32). In contrast to earlier findings, however, no evidence of these results was detected by Khalid et al., in 1995 when he showed that high altitude residents from Saudi Arabia were significantly heavier and taller than the low altitude control group(33). These differences between two populations (the Andean and the Saudis) could demonstrate differences in terms of adaptation, something that has been described extensively before(6, 19, 20, 34, 35).

It has been hypothesized that at least 5% of high altitude natives from Peru possess a newly discovered gene named *FBN1*. This gene seems to be associated with favoring high altitude Andean natives with low stature and possibly thicker skin(36). It is well known that high altitude dwellers and animals living at such altitudes are often smaller, an evolutionary response to the shortage of food or oxygen as well as thicker skin, which may help shield the body from intense UV radiation in such a places (36, 37)

It is well known that weight among newborns is significantly lower among high-altitude neonates than the sea level counterpart (38, 39), a situation that might continue not only during pregnancy but during the first years of childhood and adolescence (20, 21, 40).

The fact that newborns are smaller has to do with an adaptive process that aims to reduce oxygen consumption by the fetus, being more efficient to deliver oxygen to a smaller organism throughout a smaller placenta(41–43).

Humans chronically exposed to high altitudes have compensate the reduced partial pressure of oxygen (APO_2) with anatomical and morpho-functional changes(44). For instance, larger, wider and deeper thoraxes and chest have been described among highlanders when they have been compared to low altitude dwellers(6, 45, 46). This is probably due to the greater lung capacity of high altitude humans, especially those residing in the new world (47, 48). Although this assertion has been demonstrated previously, in our study we found no statistically significant differences in chest diameters, although women seem to have a slightly greater chest, than their lowlands counterparts.

In terms of anthropological differences, several authors have reported morphological findings that demonstrate adaptive differences among the inhabitants of the high altitudes. For instance, and beside chest diameters, weight and stature, arm and legs lengths have been analyzed. Eichstaedt et al., in 2015, reported that arm length was shorter among high altitude natives, similar results that the one we found (49).

In one report published on anthropometric differences among young natives, Pandey et al., 1990 reported that high altitude living is associated with higher proportion of ectomorphism and mesomorphism than the low altitude group(50). In our results, the group located at a higher altitude is more prone to be overweight, especially among women but in terms of obesity and extreme obesity, lowlanders reported higher proportion of BMI > 30 (Table 1).

There are several reports showing that after acute exposure to high altitude, weight loss and loss of body fat % are evident(51). In a study conducted by Zaccagni et al. in 2014, certain adaptive changes were evidenced after acute exposure to different altitudes (550 m to 5,300 m). The authors reported that both sexes lost up to 4.0% of initial body mass, corresponding to 7.6% fat mass and 3.5% lean mass in men and 5.0% fat mass in women as well as 3 to 6% lean mass in women(52). They concluded that there is a significant acclimatization in terms of reduction of body mass measurements, regardless of the amount of physical activity performed. Despite these findings, in populations chronically residing at high altitude, the incidence of obesity appears to be lower with a significant increase in the percentage of muscle mass as we also found in this report. Long-term high-altitude exposure produces adaptive changes in numerous blood biochemical indicators, as well as a significant loss in body mass, including both lean and fat components(53). In our report there was a clear difference in trends between men and women in terms of body composition; whereas no difference was detected in fat body percentage in men, a significant higher fat accumulation is found in women at high altitude(54). The presence of low adiposity % among Quechua natives from Peru is like our findings, especially for men. This lower body fat % could be associated with the stress of living at higher altitudes, as reported by Toselli et al., in 2001, findings that correlates those previously reported by Bharadwaj et al., in 1981(32, 55).

Very few studies in terms of bony structure's differences have been conducted, nevertheless, seem like the very few that have measured head circumferences offer dissimilar results. In a study of Aymara children in Peru, it was found that the head circumference of high-altitude children was smaller than that of their low-altitude counterparts, but we found the opposite among high-altitude dwellers, having these significantly larger circumferences than the low altitude control(56).

Using bioelectrical impedance body meters, we have calculated a series of parameters that allowed us to calculate body composition (body fat % and body muscle %) as well as corporal age (57–59). Our findings are noticeable, and we believe they are one of the very first reports to highlight this among high altitude populations. We have found a significant difference between real age and body also called corporal age among volunteers. We have found that low altitude dwellers in general have a body age that is on average 9 years younger than their real average year; while body age among high altitude dwellers is significantly higher than their real age in at least 6 years. These differences could be due to the hardness and the type of work performed at higher elevations and geographically remote areas. Steeper terrain, constant rainfall and cold weather could have some association with these findings(60). on the other hand, another reason supporting the differences between men and women could be the role played by men versus women in both populations. for example, we have seen that women at high altitudes are generally heavier than those at low altitudes, but men are much more muscular and less overweight and obese than their counterparts at low altitudes. This could be explained by the arduous and laborious work that men do at high altitudes while women take care of children and domestic chores. For example, work at high altitudes is related to agriculture, in some cases mining and in other cases tourism. The vast majority of these activities are carried out by men who have to carry heavy loads, which has been observed since 1950(37). Pugh's observations on the Everest trek in 1952 and 1953 show that porters frequently carry weights of 40–50 kg, plus a 10 kilogram personal bag alone, for 10–12 hours over 10–12 kilometers per day. Ascents and descents of 1,000–1,200 m are common, with loads of tea or paper weighing more than 60 kg being carried on occasions(61). On the other hand, At the amazon basin, women must travel long distances to look for food and often contribute to activities related to fishing, gathering and hunting(62, 63).

Another factor that has biological plausibility and that could influence this "body aging" that we have seen among those living in Oyacachi at 3,800 m, could be the effect of solar radiation that is greater at high altitudes, the chronic hypobaric hypoxia and the possible effect that free radicals have on the muscles(64–66). At the same time, the great diversity of foods at low altitudes could contribute to a better absorption of antioxidants in the diet of those living at low altitudes. Although these assertions have little bibliographical support, they are findings that could lead to future research.

Limitations

The main limitation of this study was the absence of a dietary and exercise assessment, as diet massively alter body composition and anthropometry. Also, despite obtaining a significant sample size to carry out this study, not all the population belonging to these indigenous communities that met the inclusion criteria were willing to participate. So, even if it is a small probability, it cannot rule out that the inclusion of the data corresponding to those people who did not participate could produce variations in our results or even alters our interpretation. Another potential weakness is the gender asymmetry in the sample because men were a lower number of participants than women.

Conclusion

This is the first study to be performed in two genotyped controlled matching populations located at different altitudes. The anthropometric differences vary according to sex, demonstrating that high altitude population are in general lighter and shorter than their low altitude controls. Men at high altitude probably due to extenuating workloads are lighter and have more muscled bodies than their lowland counterpart. Chest diameter and bi-acromial length was not greater among high-altitude dweller as we expected. Finally, we found that body age is significantly higher than their real age among high-altitude populations, while low altitude populations have younger body age than their real age, possibly linked to the climatic and socio-demographic conditions found in these locations.

Declarations

Ethics approval and consent to participate

All data were collected from the patient's medical records after obtaining written informed consent. The study was approved by the Hospital Eugenio Espejo Review Board. All data were anonymized, and all identifiable information and biological samples were stored according to the local guidelines.

Consent to publish

Written informed consent was obtained from every patient in the study.

Author Disclosure Statement

The authors declare no conflicts of interest

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Authors' Contributions

EOP was fully responsible for the conceptualization, data collection and elaboration of the study. EOP was responsible for the data collection and analysis of all the data from this project. KSR and LGB contributed with part of the descriptive statistical analysis and the graphical display of the charts. EV and SL were responsible for the operationalization of the bibliographic references and for part of the preparation of the introduction section within the manuscript. GV and MC contributed with part of the descriptive statistical analysis, the scientific approach employed within this project and critically reviewing the entire manuscript, highlighting observations that enhanced the quality of the present version of the document. Finally, all authors have read and approved the final version of this manuscript.

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Figures

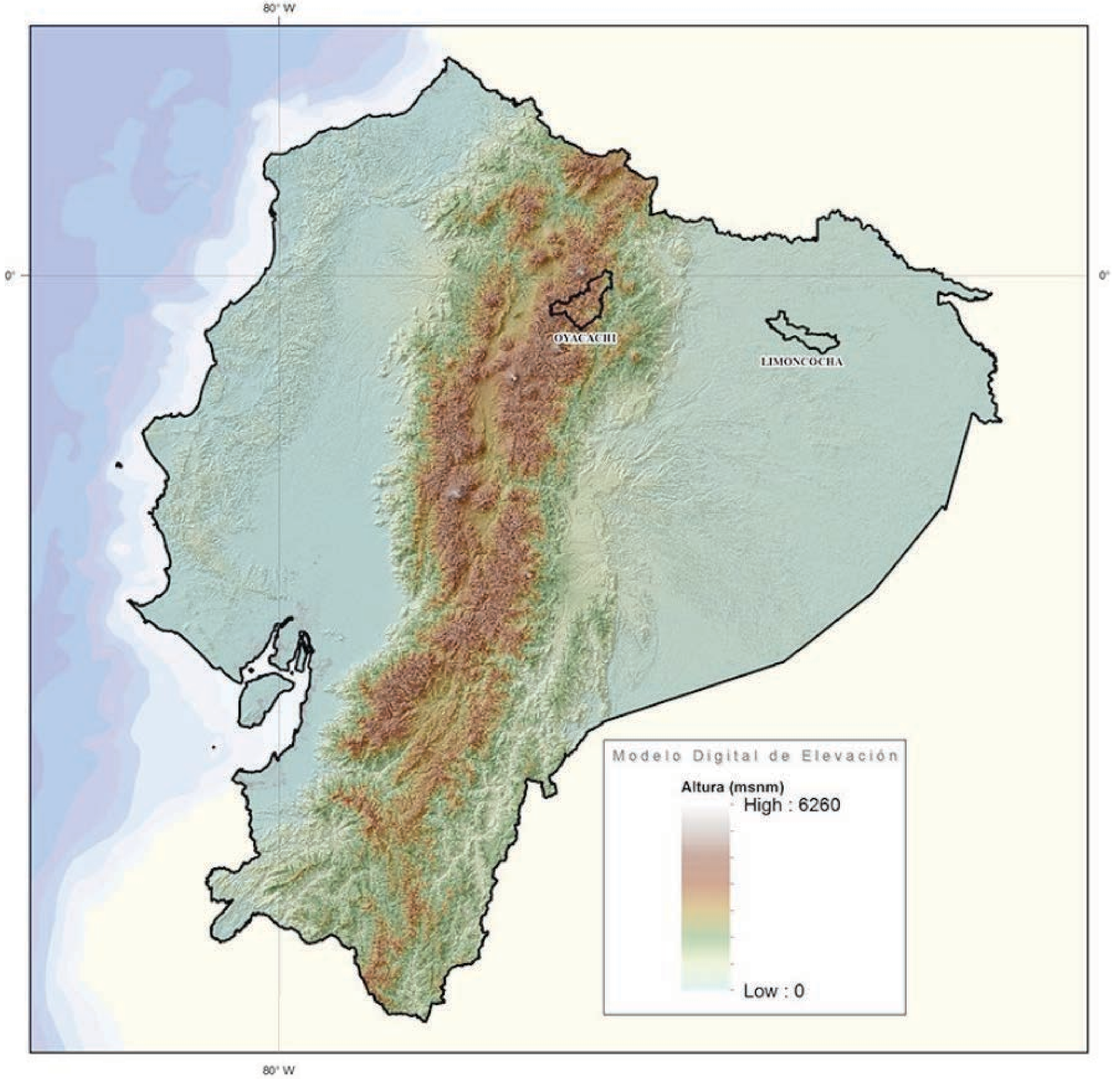

Figure 1

Topographic map of Ecuador highlighting Limoncocha (230m) and Oyacachi (3,800m).

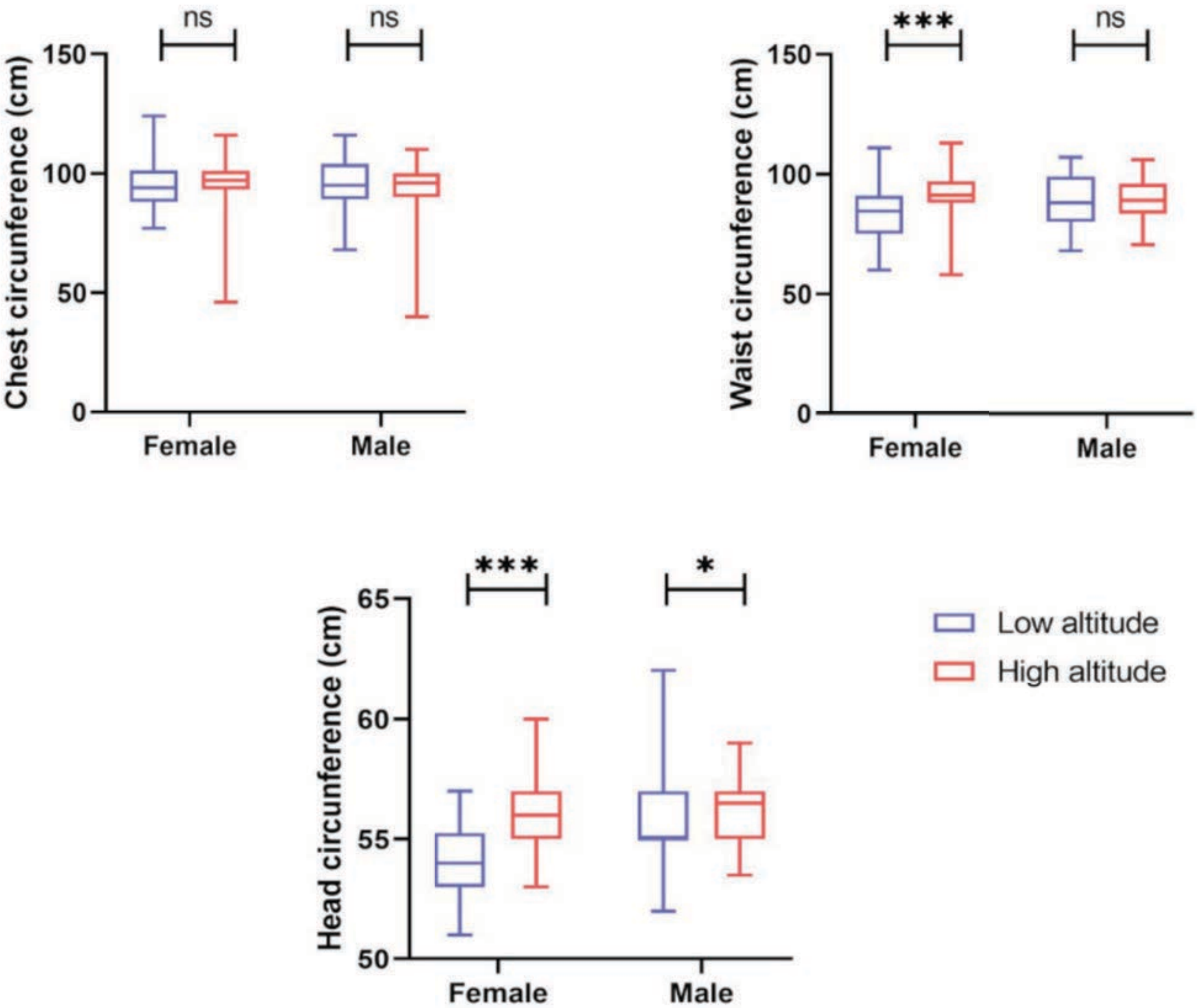

Figure 3

Chest, Waist and Head circumference among low and high altitude men and women

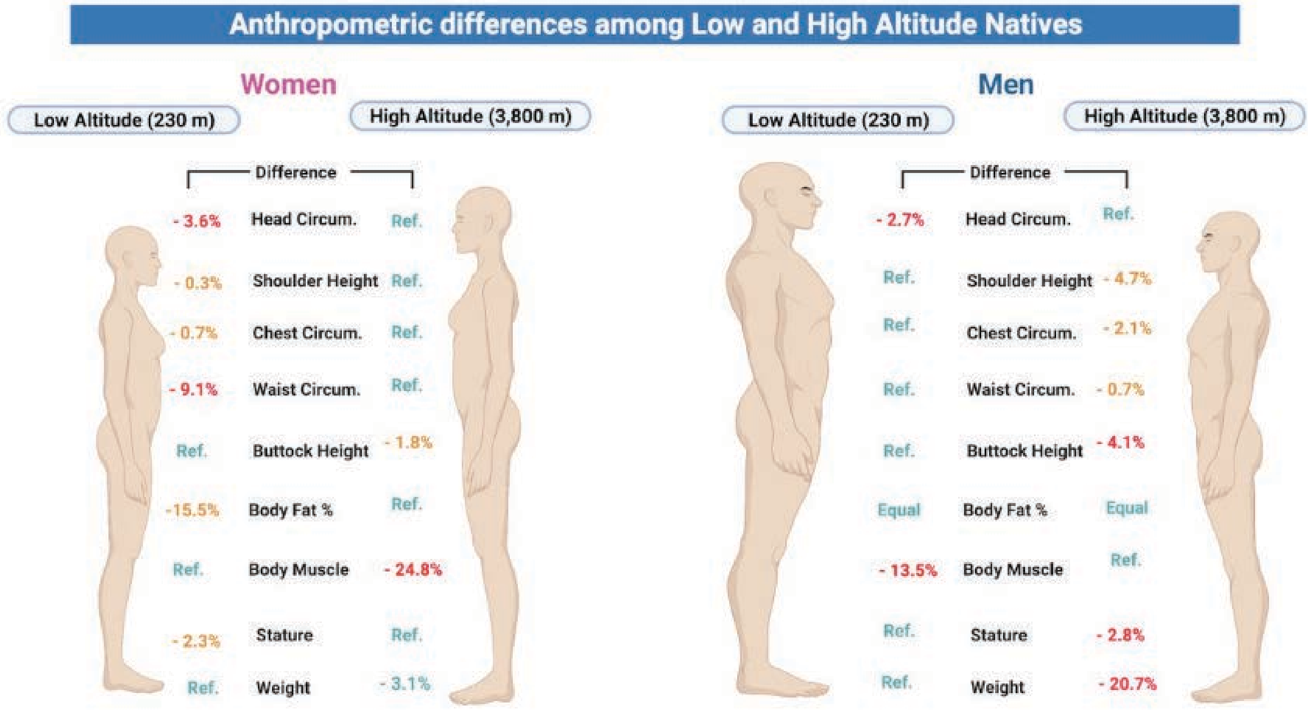

Figure 4

Anthropometric differences between Kiwcha men and women living at low and high altitude

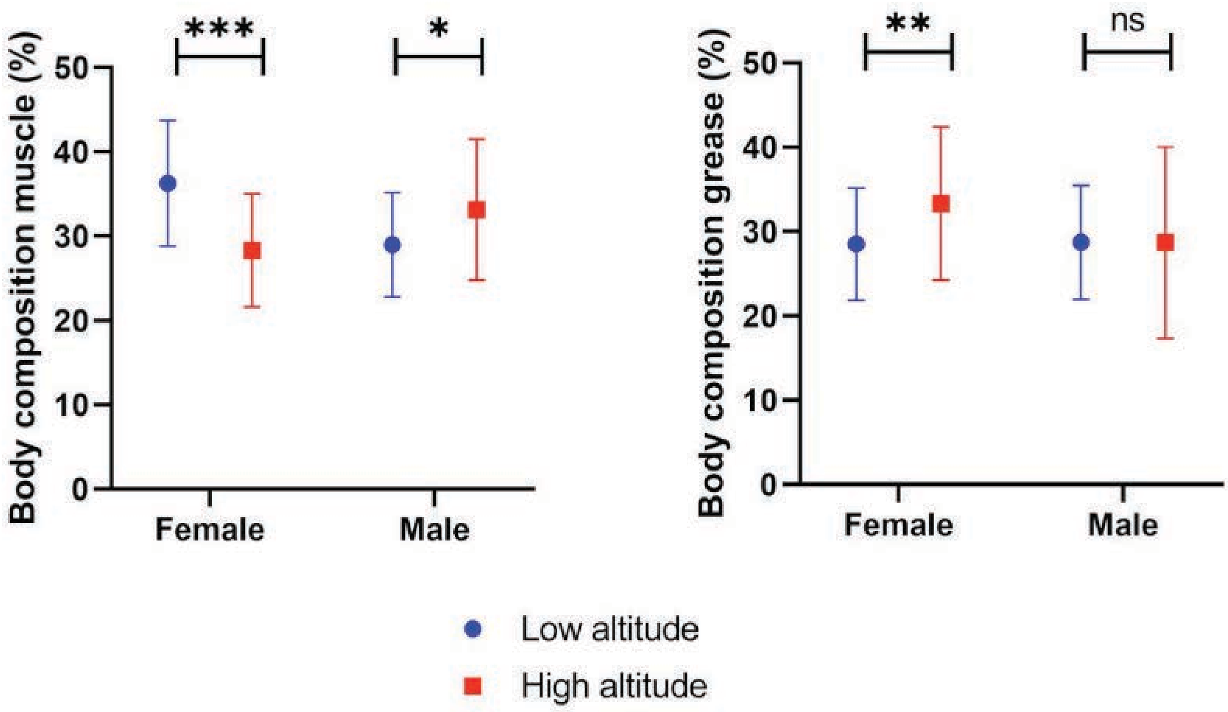

Figure 5

5.3 High altitude exposure and the epidemiology of ischemic stroke, A Systematic literature review.

BMJ Open

High altitude exposure and the epidemiology of ischemic stroke, A literature review

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Keywords:	Stroke < NEUROLOGY, ALTITUDE MEDICINE, EPIDEMIOLOGY

High altitude exposure and the epidemiology of ischemic stroke, A literature review

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Abstract

Introduction

About 5.7% of the world population resides above 1,500 m. It has been hypothesized that acute exposure to high-altitude locations can increase stroke risk, while chronic hypoxia can reduce stroke-related mortality.

Objective

This review aims to provide an overview of the available evidence on risk prevalence, risk of stroke incidence, and or mortality when exposed to acute or chronic hypoxia.

Design

A Systematic literature review of the available information was performed to answer the link between hypobaric hypoxia due to high altitude exposure and stroke. The following libraries, repositories, and databases were accessed using the University of Southampton library tool Delphis: AMED, EMBASE, Cochrane Library, PubMed, MEDLINE, and Europe PMC. The Latin-American bibliographic database Scielo was also included in a separate search from its website repository.

Results

We reviewed a total of 1,518 abstracts retrieved during the first step of the literature review process. The authors included 191 manuscripts, while the rest of the abstracts were removed from the process for not meeting the inclusion criteria. Only 11 documents were included in the literature review, analysed in-depth, and discussed in the present document.

Conclusions

The risk of developing stroke seems to be higher in those living at low altitudes (< 2,000 meters), and the protective hypothesized effect seems to occur between 2,000 up to 3,500 meters of elevation. Increased irrigation due to angiogenesis and increased vascular perfusion might be the reason behind improved survival profiles among those living within this range. In contrast, above 3,500 meters, the presence of polycythaemia and other factors such as increased blood viscosity and the presence of a proposed hypercoagulable state might increase the risk of developing stroke among those acutely exposed to very high altitudes.

Keywords: Stroke; High altitude; Hypoxia; Thrombosis; angiogenesis; Review

Strengths and limitations of this study

- This systematic review represents, to our knowledge, the first and only comprehensive examination of the intricated relationship between high altitude exposure and stroke available worldwide.
- The information provided within this review invites further researchers to explore the relationship between high-altitude related hypoxia, time of exposure, acclimatization and adaptation and the risk of developing stroke among highlanders.
- Future research is needed to obtain a definitive answer; nevertheless, the information provided in this document can be used as an updated guide of the possible role of high-altitude exposure as a risk factor for developing a stroke.
- The lack of follow-up data and the scarcity of information around stroke size, stroke severity or stroke sequela are important limitations when concluding the role of high altitude living and the risk of developing cerebrovascular events.
- This review only found observational studies, therefore causality cannot be inferred from this analysis before completing further research.

Introduction

Stroke, also known as a cerebrovascular event, is a severe and often life-threatening medical condition that appears when the blood supply to part of the brain is interrupted [1]. It causes a rapid, acute, and potentially progressive brain function loss due to a disturbance in blood supply, oxygen, and nutrients that lasts at least 24 hours [2].

Cerebrovascular events or stroke is the second leading cause of death worldwide, affecting more than 16 million people each year[1]. Around 1 in 6 men and 1 in 5 women will have a stroke in their lifetime, and it is the third leading cause of disability worldwide [3,4]. Stroke affects people of all ages, though the causes of a stroke at a younger age are often different from those at older ages, especially in terms of risk factors and severity [5,6].

Clinical manifestations usually depend on the severity of the anoxia, the brain's location, the type and subtype of stroke, and the presence of other individual risk factors. The most common clinical manifestations are sudden unilateral weakness or numbness, diplopia, ataxia, and aphasia [1].

Stroke risk factors are often classified as traditional and non-traditional, and from this, they can be modifiable or non-modifiable [7]. In general terms, these risk factors have been classified as those which cause an ischemic stroke or haemorrhagic, being the most common and recognized as displayed in table 1.

Table 1 Traditional modifiable and non-modifiable risk factors of stroke

		Traditional risk factors	
		Non-modifiable	**Modifiable**
		Age	
		Sex	
		Ethnicity	
		Socio-economic status	
		Family History	
			Waist circumference
	Thrombotic	Arterial dissection	Alcohol misuse
			Obesity (BMI, WC, WHR)
			Diabetes
			Cigarette Smoking
		Atrial fibrillation	
Ischemic Stroke		Intracardiac thrombus	
	Embolic	Heart valve disease	Physical inactivity
		Trauma and fractures	Apolipoprotein B to A1
		Some types of Surgeries	Hyperlipidaemia***
	Systemic	Post-traumatic hypovolemia	
		acute systemic hypoxia	
		Vascular Malformations	Hypertension
	***ICH**	bleeding diatheses	Cigarette smoking
		Trauma	Obesity
			Waist -to-hip ratio
Haemorrhagic stroke		Cocaine Abuse	Diet
	****SAH**	Amphetamines	

*Intracerebral haemorrhage ** Subarachnoid haemorrhage *** High LDL serum levels

The risk of developing stroke increases with the presence of causal factors, which include arterial hypertension, atrial fibrillation, cigarette smoking, hyperlipidaemia, and diabetes mellitus [1]. Other modifiable factors are obesity, chronic kidney disease, excessive alcohol and cocaine consumption, sedentarism, psychological stress or depression [8–10]. Other factors such as Vitamin D or high-altitude may play a role but have been less studied than the traditional vascular risk factors [11–15].

Rationale for high altitude exposure and stroke

Globally, at least 5.7% of the population lives above 1,500 meters, nevertheless, the association between high-altitude exposure and stroke has been poorly studied [12,13,16]. The available literature is based mainly on case reports due to acute exposure to extreme altitudes, rather than longer-term living among high-altitude dwellers [12,17–19]. The few reports available suggest that living in high-altitude regions (>2,500 m) increases the risk of developing thrombosis through hypoxia driven polycythaemia which leads to a hypercoagulation unbalance, that have been associated with increased risk for the development of atherothrombotic stroke [20–22].

Although most of the information comes from a case or case-series reports, no cohorts' studies have been published in this area. The only available information came from very few cross-sectional analysis that has found a significant association between living in high-altitude regions and having a greater risk of developing stroke, especially among younger populations [12,13,18,19].

Objective

To further explore this relationship, we have conducted a literature review of the available information in terms of the link between high-altitude chronic exposure and the risk of developing ischemic stroke.

Methods

Research Question

Does living at high-altitude increases the risk of developing ischemic stroke?

Study Design

To answer the link between hypobaric hypoxia due to high altitude exposure and stroke; a literature review of the available information was performed. The first step prior the analysis was conducting a review of the existing published evidence. To conduct a comprehensive study of the available literature we performed a systematic search within the main bibliographic databases (see below). The review search was conducted in accordance with preferred reporting for systematic reviews and meta-analyses (PRISMA) guidelines. No protocol was registered in PROSPERO for this review because of its small size.

Information sources

The literature review process was performed in English to cover the largest number of scientific databases and repositories containing academic literature from all over the world that are accessible for most researchers. The following libraries, repositories, and databases were accessed using the University of Southampton library tool Delphis: AMED, EMBASE, Cochrane Library, PubMed, MEDLINE, and Europe PMC. The Latin-American bibliographic database Scielo was also included in a separate search from its website repository.

Search strategies

We identified the specific population using the PICO question (population, intervention, comparator, outcome) In this review, we stipulated the question as every study available from 1960 to 2019 that include stroke and chronic high altitude exposure excluding case reports. The following terms were used during the search strategy within the tittle (TI) or the abstract (AB): High altitude OR High altitude Exposure OR High Altitude living OR High altitude dwellers AND combined with the complete or trunked MESH terms stroke OR Cerebrovascular accident OR CVA OR Ischemia OR Thrombosis OR Hemorrhag* OR Haemorrhag* OR subarachnoid haemorrhage OR subarachnoid hemorrhage OR haemorrhagic stroke OR hemorrhagic stroke OR Ischemic stroke.

Inclusion and Exclusion criteria

This literature review excluded all in vivo and in vitro studies, and all the data analysed that did not concern human studies. If the search term "stroke" referred to cardiac output or stroke volume, the results were also excluded. Case reports were excluded from the study. The data extraction length was set from 1960 to 2019, and any study that matched the search strategy and did not counterpose the exclusion criteria was revised. We set the cut-off point of short or long-term exposure in 28 days based on previously published data.

Bias assessment

In order to reduce risk of any type of bias, the data extraction process was performed by EO and SC independently and in different times. in order to minimize errors while gathering information from any primary study, any disagreements was resolved after reaching consensus. In addition, while assessing the quality of primary studies, the CASP critical appraisal tool was used to reduce confirmation bias.

Ethical consideration

This secondary data analysis of publicly available anonymized data received ethical approval from the University of Southampton with the Faculty of Medicine Ethics Committee ERGO 51422.R3 number.

Patient and Public Involvement

No patient involved

Results

Literature review

Several anecdotal case reports and case series of people suffering from stroke-related disorders at high-altitude have been published since the late 1800s [23]. Despite this apparent relationship, very few well-conducted epidemiological studies have been conducted worldwide, and we have only included those studies that fulfilled our inclusion and exclusion criteria [12,13,18,19,24,25].

We included 1,518 manuscripts during the first step of the literature review process, and only those that fulfil the inclusion criteria were revised. After this process, the authors evaluated 191 abstracts. In the end, we included 11 manuscripts within this literature review.

Figure 1 Prisma chart diagram for reporting literature review search and metanalysis

Specific studies

Study 1: The first study published by Razdan et al. in 1988 looked into the prevalence of stroke in elevations above 1,500 m [26]. They found that the crude prevalence of stroke was higher than the populations residing below this elevation (Table 2) [26].

Study 2: In 1990, Annoml et al. published an article about the incidence of cerebrovascular accidents in children with sickle cell disease residing at high and low altitudes in Saudi Arabia. They found that 4% and 5% of the 400 children included in the study who were living at low and high altitudes developed stroke.

The authors did not explore any causal relationship or controlled for confounders. The results presented in that study are not significant, considering the total number (n=8) of children with sickle cell diseases and stroke [27].

Study 3: In 1994, Garcia-J reported the prevalence of risk factors of developing stroke at 2,500 m in a community in Peru; nevertheless, the study focused on the association between risk factors and stroke and not in the relationship with elevation[28].

Study 4: In 1995, Jaillard et al. published one of the most cited stroke documents at high-altitude. A document from Perú described the results from a "door to door" survey in Cuzco, a city located at 3,380 meters above sea level. They reported a crude prevalence rate of 6.47 per 1,000 population; nevertheless, comparisons were performed using standard populations from other locations, while not giving enough information about the association of high-altitude and stroke per se. This study's evidence is limited since the comparison was performed with other reports at lower elevations; therefore, the conclusions should be taken cautiously [18].

Study 5: A Population-based analysis published by Jha et al. in 2002 reported a significantly higher incidence of stroke among patients admitted to a single tertiary hospital in India. They classified those patients that came from lower altitudes (<3,000 m) and higher altitudes (>3,000 m). They reported that the majority of stroke cases at high-altitude were presented in otherwise-healthy young men (<45 years old) exposed to high-altitude for months (nine months on average). The hospital admission rate at high-altitude was reported to be 12 times greater (12.8/1,000) than at lower altitudes (1.0/1,000), being this results statistically significant [12].

Study 6 In 2003, Niaz et al. conducted a case-control study to describe the prevalence of stroke above 4,571 m. They included 4,000 soldiers (20-40 y/o) from a military hospital to observe stroke occurrence. They reported 10 cases of stroke among young men patients from the high-altitude group versus only one case from the lower land cohort. Although no further information about size effect or standardization of the sample was provided, the researchers concluded that living at elevations above 4,500 m was associated with ten times more risk of developing stroke. The authors concluded that chronic (> 28 days) hypobaric hypoxia exposure it is associated with a higher risk of developing stroke, being massive ischemic stroke the most frequent presentation [13].

Study 7 In 2004, Mahajan et al. conducted a cross-sectional study in Himachal, Pradesh, India, among 100 patients hospitalized in a tertiary level hospital located at an altitude of 2200 meters. They reported that the incidence of stroke was lower when compared with previously published studies from India. Although information from the type of stroke and clinical features are available, the role of elevation was not discussed in depth. The authors compared the results with other studies, but no confounding analysis was made for the current report [29].

Study 8: An ecological study published by Faeh et al. in 2009 reported that stroke mortality is lower in higher locations in Switzerland (Faeh D et al., 2009). They reported that mortality from stroke decrease 12% per every 1000 m gained in elevation. The effect of altitude on the cardiovascular and cerebrovascular disease was assessed using sociodemographic information, places of birth and residence among men and women between 40 and 84 years of age living at altitudes of 259 to 1960 m. The protective effect of living at higher altitudes on coronary heart disease and stroke mortality was consistent and became stronger after adjustment for potential confounders [19].

Study 9: A study presented by Ezzati et al. in 2011, used from the National Elevation Dataset, National Centre for Health Statistics, and US Census. The authors analyzed the crude association of mean county altitude with life expectancy and mortality from ischaemic heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), and cancers. Living at higher altitudes showed a beneficial association with ischemic heart disease mortality, but the results were not statistically significant for stroke [30].

Study 10: A study published by Dhiman et al. 2018 reported the evolving Pattern and Outcome of Stroke at Moderate Altitude. This prospective, observational study was carried at 2,000 meters above sea level and included the clinical features and risk factors profile of 235 patients diagnosed with a stroke. The results only compared how the data compared with a report published 15 years ago, and the authors concluded that the occurrence of stroke decreased among hospitalized patients compared to the 2004 report [29,31].

Study 11: An Ecological study design published by Khattar et al. in 2019 demonstrated that ischemic stroke is most likely to occur at elevations above 3,000 m and although this diagnosis is not technically considered stroke, the physiopathology of it might indicate some relationship with the development of ischemic cerebrovascular events. Despite some of these findings that targeted high-altitude as a possible risk factor for developing stroke, in 2009 [32] (Table 2)

Table 2 Critical appraisal and summary of the literature.

Author and year	Tittle	Sample, setting and elevation	Aim	Design, type and length of Exposure	Main findings	Strengths	Limitations and confounding. Bias Analysis

Razdan et al. 1988	Cerebro-vascular Disease in Rural Kashmir, India	-Kuthar Valley, India -Age (5 and 65) years. -80% of pop. Are shepherds and cultivators while others are immigrants. -Elevation 1,530 m.	To find the prevalence and trends related to stroke in this region	-A cross sectional survey to find if population has suffered from stroke. -First part of the survey was delivered by trained med student. -Second part included two neurologist who visited the houses of those who were likely to have suffered from stroke. - An ex post-facto relationship was performed using the Garraway diagnosis criteria -Long term hypoxia exposure was identified. The final outcome was stroke prevalence. No confounder factors were controlled, and the presence of multi-ethnic immigrants might have played a role in the interpretation.	- 91 cases of stroke were detected - Crude prevalence rate 143/100,000 - Proportion in men (69,23%) and women (30,77%) - >40 y/o 630/100,000 ->15 y/o 244/100,000 - the most common risk factor among the elderly was hypertension - In young stroke patients valvular heart disease and postpartum cerebral venous thrombosis.	-First of its kind in India and probably the world. In exploring the role of high-altitude. -A team of neurologists interviewed and examined all suspected cases of strokes including 500 home visits. -A good sense of case control matches was reported	-Elevation not greater than 2,000 meters, hypobaric hypoxia not enough to cause a physiological long term-response -They did not differentiate between cerebral infarction or haemorrhage -They did not consider smoking habits
Annoml et.al 1990	Cerebrovascular accidents in children with sickle cell disease residing at high and low altitudes of Saudi Arabia	-Patients with sickle cell disease residing at high and low altitudes -3,000 m	- To compare the clinical and radiological indications of stroke in sickle cell patients constantly residing at low and high-altitudes.	-Analyses of 8 cases of stroke among children with sickle cell disease -extracted from 400 cases detected in Saudi Arabia. -Sample size was not representative and the differences between low and high altitude was only one patient. -The risk of interpretation bias is present, and we recognized this limitation.	-The incidence of stroke in children with sickle cell disease similar regardless elevation. -Clinical manifestations were more severe in those residing al low altitude.	Complete studies were performed on children such as physical exams, blood tests and imaging studies, thus, diagnosis was accurate.	-The number of subjects is too small to extrapolate results with confidence. -No confounders were controlled, and the difference found in both elevations was not significant neither clinically relevant.

Garcia, J 1994	Cerebrovascular Disease: Risk Factors analysis of Natives living at high-altitude.	-50 patients with a confirmed diagnosis of stroke and 52 healthy patients -2,500 m	To understand the role of different risk factors in patients located at high altitudes	Retrospective case-control study - Population selection based on criteria (cases), random population (controls) - Survey method and information on risk factors was obtained through investigation sheets - The factors were divided into 2 groups: causal and aggravating - Diagnosis of stroke was corroborated by neurologists in all cases.	- Atherosclerosis was the most important risk factor for CVD in the highland natives. - Hypertension and nonrheumatic atrial fibrillation came afterward. - Old age, frequent alcohol consumption and prior CVD were contributor factors. - Cerebral infarction was the most frequent type of CVD, it was present in 90% of cases. -The main clinical category of cerebral infarction was atherothrombotic in 56% of cases, with a notable predominance in the male sex.	- The study analyses the relationship between hypertension with developing of stroke, in addition to other triggers of this disease. - Diagnosis of stroke was corroborated by neurologists in all cases which decrease bias - This study determines that the prevention of risk factors is the key for the prevention of this disease	The sample used in the study is small -The important risk factors that were not included in this study, are ischemic heart disease and diabetes, are clinically proven that these factors are also causes of developing stroke
Jaillard, 1995	Prevalence of Stroke at High-altitude (3380 m) in Cuzco, a Town of Peru A Population-Based Study	-3,246 subjects interviewed -men and women older than 15 years old were included -97% Mestizos, 1.3% white, 1.1% Quechua, 0.1% Aymara, and 0.2% were of other racial groups -3,800 m	to study the prevalence of stroke and its association with stroke risk factors in a high-altitude location.	A door to door population-based analysis using a survey as a tool for collecting data.	-Age, polycythemia, high consumption of alcohol, and area of residence were associated with higher stroke prevalence. -Sedentarism and high income was associated with higher OR of stroke in El Cuzco - 21 strokes cases were identified	Clinical evaluation of the patients with stroke was performed by two neurologists, offering an accurate diagnosis *ex post facto.*	-No control group at lower altitudes. -No method of randomization was mention. the diagnosis was established on clinical criteria, and no attempt was made to distinguish haemorrhagic from ischemic strokes.

Jha et. al 2002	Stroke at High-altitude: Indian Experience	-Clinical evaluation of 2,184 patients transferred from different medical units situated at different elevations and managed at the main Hospital in Chandimandir, India. -Soldiers (22 to 48 y/o) -Clinical reports of 30 cases of stroke at high-altitude -4,270 m	-To determine the relationship between stroke and high-altitude.	-Information was prospectively collected from the Command Hospital in India -A detailed neurological and systemic examination was carried out for all the cases.	-Long-term stay at high-altitude was associated with higher risk of developing stroke. -Ischemic stroke was the most common among the type of strokes. -22 cases of IS, 2 ICH, 4 TIA and 2 had CVT - Out of 30 cases, 28 were of stroke in young, categorized as every case before the age of 45. - Polycythaemia with Hb ranging from 16.2 to 22 g/dL21 was seen in 21 of the 28 reported cases representing more than 75%. -Protein C and S deficiency was found in 1 case in each of the groups. - CT scan showed massive infarcts involving at least 50% of one cerebral hemisphere in 12 cases, demonstrating more severity. -Multiple infarcts were seen in one case.	-A detailed neurologica l and systemic examinatio n was carried out. -Cases were investigated with blood counts, lipid profile, cardiac evaluation, and CT scan/MRI. -Coagulation parameters were studied in some cases.	-They did not test for factor V or the Leiden coagulation factor. -They could not conclude that familial thrombophilia played a role in these high-altitude events, although is unlike this occur in this type of population.

Niaz et al. 2003	Stroke at high altitude: Indian experience	-The study was performed in Chandimandir, India -Sample was based on 30 men soldiers - Age ranged from 22 to 48 years. -Elevation: 4,200 m.	-To identify the presence of stroke using different clinical, imaging and laboratory assessment techniques to determine the presence or not of CVA.	-A cohort analysis of stroke prevalence and mortality from 1998-2000. - A detailed neurological and systemic examination was carried out. Cases were investigated with blood counts, lipid profile, cardiac evaluation, and CT scan/MRI. Coagulation parameters were studied in some cases.	-Stroke hospital admission rates was higher among high altitude residents (13.7/1000) versus low altitude (1.05/1000) -The mean high-altitude stay was 10.2 months -Age ranged from 22 to 48 years (mean 33.4 yr). -Soldiers had no pre-existing risk factors except for smoking (in four cases). -22 cases were ischemic stroke, 2 intracerebral haemorrhages and 4 were reported as TIA/RIND (transient ischemic attack/reversible ischemic neurological deficit). The authors reported 2 cases of cerebral venous thrombosis.	-This study is important since included otherwise healthy young soldiers and finding stroke among this group of people is not common. - Elevation was considerable high and the detailed neurological and systemic examination was carried out offered complete information about sociodemographic and clinically relevant data.	-The fact that not all the soldiers were given all the laboratory tests may have conferred some limitation on the work
Mahajan et. al 2004	Stroke at moderate altitude	-this study was performed in Himachal, Pradesh in the Sub-Himalayan ranges. -100 patients admitted to the hospital -age 20 to 85 years, -elevation: 2,200 m	To understand the clinical profile, presence of various risk factors for stroke at moderate altitude.	-A cross sectional analysis of stroke admission in a tertiary hospital from India	-Patients aged up to 45 years were defined as stroke in young. -Complete clinical, radiological and neurological examination was performed.	-This is the first study performed at a moderate altitude of 2,200 meters in India. -A complete analysis of stroke clinical features is presented	-No comments about the biological plausibility of the protective effect of altitude was made in the documents. -No control group was used to asses the differences with other populations. -The results were compared with other previously published report and no controlling was evidenced while using those reports.

Faeh et.al 2009	Lower Mortality from Coronary Heart Disease and Stroke at Higher Altitudes in Switzerland.	Men and women between 40 and 84 years. -259 to 1960 m.	Examine mortality from coronary heart disease (CHD) and stroke in its association with high-altitude living.	-A longitudinal analysis of mortality data from 1990 to 2000. Sociodemographic information, places of birth, residence and previously mobilization was obtained from the Swiss National Census-based record linkage study. - Data was obtained from the Swiss National Cohort, a longitudinal, census-based record linkage study.	-Living at higher altitude was associated with less CHD and less stroke mortality. -Mortality from CHD significantly decreased with increasing altitude as well as stroke (-12% per every 1,000 m	-First longitudinal study with individual data of a large homogeneous and representative population showing a protective effect of altitude on CVD mortality. - Consistent with results, other studies showed that the decrease in mortality with increasing altitude was stronger for CHD than for stroke.	The clinical risk factors of classic behaviour were not adjusted. -The variable for urbanity was artificial - The study not able to adjust for classic behavioural and clinical risk factors - The analysis cannot define causal relationships with risk factors or prove causal pathways for the effect of altitude.
Ezzati et.al 2011	Altitude, life expectancy and mortality from ischaemic heart disease, stroke, COPD and cancers: national population-based analysis of US counties	-Mortality and population data for 2001 through 2005. -12.1 million death records -Data from the National Centre of Health Statistics in US counties -500-1000 m -1000- 1500 m -1500 > m	Inspect the relationship of life expectancy and mortality from particular diseases in relationship to altitude.	-Ecological study of the association of mean county altitude with life expectancy and mortality from IHD, Stroke, COPD and cancer. -Results were adjusted for sociodemographic factors, migration, solar radiation, cumulative exposure to smoking and altitude.	- Counties above 1500 m had longer life expectances than those within 100m of sea level by 1.2 - 3.6 years for men and 0.5 -2.5 years for women. - Living at higher altitude may have a protective effect on IHD and a harmful effect on COPD. - The association between altitude and life expectancy for stroke and cancers were no statistically significant	- Is the first study to examine the relationship of altitude with life expectancy and with mortality from leading chronic diseases using consistent and comparable data and methods. - The large number of deaths in the vital registration data led to robust estimates of deaths rates and life expectancy.	- Data on how population and deaths are distributed by elevation within each county was not provided. -The lack of information about habits and risk factors might jeopardize the conclusions since people at high might be otherwise healthier even though high altitude maybe a risk.

Dhiman et. al 2018	The Evolving Pattern and Outcome of Stroke at Moderate Altitude	-Men and women with an average age of 62 years Sub-Himalayan region of India. -235 patients with stroke were consecutively admitted into a tertiary hospital. -2,000 m	The aim was to compare the clinical profile, risk factors, and outcome in hospitalized patients of stroke in a Tertiary Care Hospital situated at moderate altitude	-A prospectively collected Study in India. -A comparative analysis was performed with a previous study performed 15 years prior of the current study.	-Ischemic stroke was noted in 74%, and 26% had haemorrhagic stroke (HS). -Male accounted 58% of the cases and female for 42%. -Overall HS had poorer outcome. -There occurrence of stroke has decreased among hospitalized patients at moderate altitude.	The results of the present study were compared with the study conducted 15 years ago therefore a before and after analysis was possible.	-Elevation was assessed but no low altitude controls were presented or used. -The control group was from the same elevation, but no description of prior methodology was provided.
Khattar et.al 2019	Cerebral Venous Thrombosis at High-altitude: A Retrospective Cohort of Twenty-one Consecutive Patients	-The study cohort comprised 21 patients in Nepal. CVT was the diagnosis of interest. -elevation 3,048 m	Investigate the characteristics and treatment outcomes of patients who suffered CVT at high-altitude in eastern Nepal.	- Retrospectively reviewed all patients presenting with clinical and radiographic evidence of cerebral venous sinus thrombosis treated. - Neuroimaging evaluation and preoperative planning: Brain computed tomography (CT) was obtained in every patient prior to a definitive diagnosis.	21 patients of which 76% were men with an average age of 56. -men were found to have a higher risk for CVT at high-altitude -All patients presented with evidence of haemorrhagic conversion on the initial brain CT.	-A complete set of clinical data and outcomes were analysed.	-small sample size make it difficult to extrapolate the results -No controls at lower altitudes were used.

Discussion

The results from this review suggest that stroke seems to be more likely to occur in very high-altitude locations (>3,500 m) when the exposure is longer than 28 days, especially among younger people (< 45 y/o). On the other hand, when people live above 1,500 m and below 3,500 seems like there is a protective effect for stroke, probably triggered by better adaptation to hypoxia, efficient enough to reduce the likelihood of dying when compared to lower altitudes; nevertheless, no information is available about the exact point in which this protective effect become a risk factor.

It has been challenging to define how high altitude exposure can be defined and where the threshold is located in terms of mild or severe hypoxia [33]. For instance, Imray in 2011 uses a classification of high-altitude exposure according to the recommendations from the International Society of Mountain Medicine, a categorization that seems to be the most pragmatic [34]. The author defined low altitude everything located below 1,500 m, moderate or intermediate altitude between 1,500 to 2,500 m, high-altitude from 2,500 to 3,500 m, the very high-altitude from 3,500 m to 5,800, more than 5,800 extreme high-altitudes and above the 8,000 m is considered the death zone [34].

As humans acclimatize to high-altitude, adverse and often mild secondary effects can occur in response to hypoxia. Some of these adverse effects are linked to the increased blood viscosity due to polycythemia, augmented pulmonary arterial pressure, and sometimes, they are linked to a proposed hypercoagulation unbalance [20,22].

These consequences might be increasing the risk of forming an atherothrombotic plaque resulting in a stroke or myocardial infarction (MI) or venous-thrombotic events, resulting in deep venous thrombosis (DVT) or pulmonary embolism (PE) [35–37]. Although information about the time of exposure is scarce, the longer the exposure, the higher the risk [19,38].

Acute exposure to hypobaric hypoxia produces several compensatory physiological effects that can last hours, days, months, or years. The essential mechanisms are: increasing the heart and respiratory rates, a secondary polycythemia, haemoconcentration derived from reduced plasma volume caused by respiratory evaporative water loss and polyuria, and increased ventilatory response [33,39,40]. When acute exposure last longer than 28 days, more efficient and prolonged mechanisms take place, including sustained polycythemia, endothelium changes, reduced vascular resistance, nitric oxide-mediated hypotension, and angiogenesis [41–44]. Acute exposure to high-altitude hypoxia triggers a series of events that produce a hypercoagulable state [22]. This hypercoagulability state is boosted by dehydration, haemoconcentration, and polycythemia. When combined with dehydration (due to tachyphemia and extenuate physical activity) and limited mobilization (sleeping in tents and secluded spaces), these factors produce the perfect scenario for increasing vascular stasis and thrombosis [20,33,45].

When humans are exposed continuously to hypoxia, they develop adaptative mechanisms that are far more efficient than those observed in newcomers [46–49]. These last-longing mechanisms include anatomical (wider chests, shorter and lighter bodies, etc.), embryological (smaller fetus and placentas), circulatory (improved maximum flow output and higher pulmonary arterial pressure), and respiratory adaptations (improved hypoxic ventilatory response and oxygen diffusion capacities) [48,50–52]. Chronic exposure to hypobaric hypoxia leads to the development of more subtle compensatory mechanisms. These factors include long-term erythrocytosis, angiogenesis, capillary remodelling, and an improved ventilatory response [53–56] (Figure 2).

Once the general context of acute or chronic hypobaric hypoxia has been described, the main intrigue is which elevation is enough to generate compensatory mechanisms capable of reducing the risk of developing stroke and when these mechanisms become detrimental. After reviewing the current literature, the information available suggests that a window around 2,000 to 3,500 meters of elevation might be enough to generate some protective mechanisms (i.e., angiogenesis or vascular remodelling) against stroke [19,41,44].

In elevations below 2,000 meters, the degree of compensation might not be enough to ensure a protective effect, while above 3,500 meters, the adaptative compensatory mechanisms such as significant polycythemia and vascular stasis might increase the risk of thrombosis and, therefore, the risk of developing stroke [12,20,32] (Figure 2).

Figure 2 Proposed mechanisms and hypothesized physiopathology at low altitude (< 2,500 m), at high altitude (2,500-3,500 m) and very high altitude (>3,500 m). BP: Barometric pressure and O_2 *is the oxygen availability in relationship to sea level* FiO_2*. : Angiogenesis occurs at different elevations above sea level but during the hypoxic beneficial window, polycythemia and red blood cell as well as platelet adhesiveness is not significant as above 3,500 m, thus, the protective effect reaches its maximum. Above 3,500 m although angiogenesis is present, the significantly high hematocrit and polycythemia increase the risk of blood stasis and thrombogenesis.*

The information is still contradictory and opposed from one study to another. The few studies available have many limitations, and confounders' control was low in most of them. Nevertheless, very few studies that are better controlled and designed support some of our statements above. This report was designed to guide clinicians and researchers who are currently working with stroke and wanted to understand the role of elevation and hypobaric hypoxia for developing stroke while we suggest that further analysis and well-controlled studies are needed.

Limitations

Several limitations were found, including scarce information, conflicting results, and data lack when adjusting for confounders. In this sense, more research is needed to obtain a definitive answer; nevertheless, the information provided in this document can be used as an updated guide of the possible role of high-altitude exposure as a risk factor for developing a stroke.

Conclusions

It seems clear that short-term exposures to very high altitudes are a risk factor for developing a stroke, but when populations chronically reside between 2,000 to 3,500 meters, it seems like there is a protective effect, especially among native high-altitude dwellers. The available scientific literature suggests that above 3,500 to 4,000, the risk of developing stroke increases, especially if the exposure is acute among non-adapted populations.

When residing at moderate or high altitude (2,000-3,500 m), the suggestive protective effect might be due to increased perfusion within the tissues in response to hypoxia-triggered angiogenesis and vascular remodelling. Simultaneously, a hypercoagulable state might be responsible for the higher risk when exposed to very high or extreme altitudes.

Recommendations

Further investigations are needed to explore the role of socioeconomic variables and traditional risk factors among populations located at different elevations. Understanding the cultural and social differences between highlanders and lowlanders will permit more suitable and robust conclusions when elevation becomes a protective factor and when the parabola from lower risk to higher risk shifts above a certain altitude.

Abbreviations

ABP: Arterial Blood pressure

BMI: Body max index

BP: Barometric Pressure

COPD: Chronic obstructive pulmonary disease

CVD: Cerebro-vascular disease

CVT: Cerebro-venous thrombosis

CT: Computed tomography

HS: haemorrhagic stroke

IHD: Ischemic heart diseases

INEC: Ecuadorian Institute of Statistics and Census

IS: Ischemic stroke

ICD-10: 10th revision of the International Statistical Classification of Diseases and Related Health Problems

I60: Nontraumatic subarachnoid haemorrhage

I61: Nontraumatic intracerebral haemorrhage

I62: Cerebral infarction

I64: Other and unspecified nontraumatic intracranial haemorrhage

MRI: Magnetic Resonance Imaging

SES: Socioeconomic status

Availability of supporting data

All the information used for this analysis can be found online throughout the several medical databases available

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

EOP, SPC, EV, GV and PC contributed with the review of the bibliography and preparation of the manuscript, EV and EOP were in charge of the entire revision of the document and finalizing the version end of our manuscript

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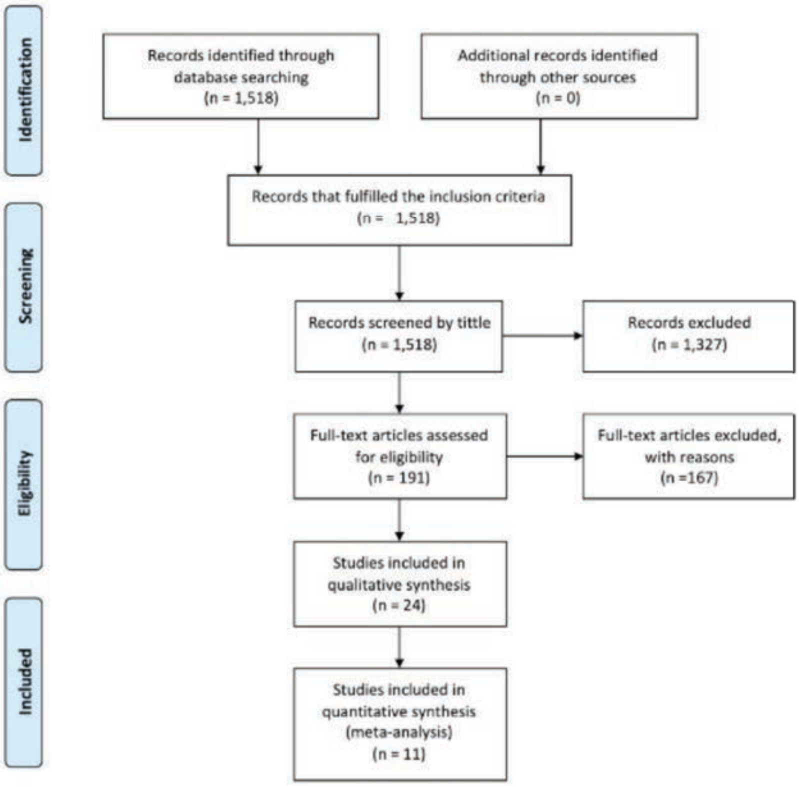

Figure 1

179x181mm (144 x 144 DPI)

4. Resumen global de los resultados

4.1 Resultados generales

En la sección de resultados específicos de nuestras dos poblaciones estudiadas se reclutaron con éxito 212 sujetos en total entre los pobladores de ambas comunidades. El 55% (n=117) correspondieron al grupo de baja altitud (Limoncocha) y el 45% (n= 95) fueron habitantes del grupo de gran altura (Oyacachi). En general, las mujeres representaron el 63% (n=134) de toda la cohorte y los hombres el 37% (n=78).

4.2 Diferencias de edad y sexo

Dentro de nuestra cohorte, las mujeres del grupo de baja altitud tenían una media de 4 años más (41,0 [30,0-59,0]) que las mujeres del grupo de gran altura (36,0 [29,0-48,0]), sin embargo, esta diferencia no fue estadísticamente significativa (p: 0. 121).

Los hombres de baja altitud tenían una media de 5 años más (42,0 [30,0-52,0]) que los hombres que vivían a gran altitud (36,0 [25,0-57,0]), sin embargo, esta diferencia tampoco fue estadísticamente significativa (p: 0,420).

4.3 Diferencias antropométricas

4.3.1 Peso (Kg) e Índice de Masa Corporal (IMC).

En relación con el peso, encontramos que las mujeres que viven en las grandes alturas son en promedio 1.9 kilos más livianas (60,84 Kg ± 8,333 Kg) que las que las que viven a bajas (62,75 ± 14,44Kg), sin embargo, esta diferencia no fue estadísticamente significativa (p: 0,374). Los hombres que viven en altitudes elevadas son un 20,7% más ligeros que sus homólogos de altitudes bajas (valor p <0,0001) (Tabla 1).

Tabla 3 Análisis sociodemográfico, antropométrico y de factores de riesgo de las cohortes baja y alta.

		Mujer				Hombre			
		Baja Altura	**Altas Alturas**	**(%) Diff**	**Sig.**	**Baja Altura**	**Altas Alturas**	**(%) Diff**	**Sig.**
Edad (mediana) (IQR)		41.0 (30.0-59.0)	36.0 (29.0-48.0)	13.0	0.121	42.0 (30.0-52.0)	36.0 (25.0-57.0)	15.4	0.420
Edad Categorías	Adulto Joven	45 (57.0)	41 (73.2)	9.3	0.086	24 (54.5)	27 (67.5)	11.7	0.475
	Adulto	19 (24.1)	11 (19.6)	53.3	0.086	15 (34.1)	10 (25.0)	40.0	0.475
	Anciano	15 (19.0)	4 (7.1)	115.8	0.086	5 (11.4)	3 (7.5)	50.0	0.475
Peso (Kg) - M ± SD		62.75 ± 14.44	60.84 ± 8.33	3.1	0.374	74.26 ± 10.83	60.34 ± 8.71	20.7	**0.000**
Altura (cm) - M ± SD		149.22 ± 7.01	152.61 ± 8.62	2.3	0.333	159.90 ± 6.39	155.51 ± 9.93	2.8	**0.019**
IMC - M ± SD		27.90 ± 5.10	26.10 ± 3.10	6.7	**0.022**	29.00 ± 4.20	24.90 ± 2.90	15.2	**0.000**
IMC	Bajo Peso	0 (0.0)	0 (0.0)	0.0	**0.036**	0 (0.0)	0 (0.0)	0.0	**0.000**
	Normal	25 (32.1)	20 (35.7)	22.2	**0.036**	5 (12.5)	21 (53.8)	123.1	**0.001**
	Sobrepeso	31 (39.7)	29 (51.8)	6.7	**0.036**	22 (55.0)	16 (41.0)	31.6	**0.002**
	Obesidad	12 (15.4)	7 (12.5)	52.6	**0.036**	7 (17.5)	2 (5.1)	111.1	**0.003**
	Obesidad Extrema	10 (12.8)	0 (0.0)		**0.036**	6 (15.0)	0 (0.0)		**0.004**

En términos de sobrepeso, las mujeres que viven en altitudes elevadas tienen una mayor proporción (51,8%) de sujetos con sobrepeso que las que viven en altitudes bajas (39,7%); sin embargo, en el caso de los hombres, esta relación se invierte, ya que los que viven en altitudes bajas tienen una mayor proporción (55%) de sujetos con sobrepeso que los que viven en altitudes elevadas (41%).

En cuanto a la obesidad, el grupo de baja altitud, tanto en hombres como en mujeres, tiene una mayor proporción de sujetos obesos (16,4%) que los sujetos que viven a gran altitud (8,8%), siendo estas diferencias estadísticamente significativas (tabla 1). En cuanto a la obesidad extrema, sólo encontramos 10 mujeres y 6 hombres con obesidad extrema (IMC > 40), perteneciendo todos ellos al grupo de baja altitud (tabla 1).

4.3.2 Estatura (cm)

En cuanto a la estatura, las mujeres del grupo de gran altitud son 3,3 cm más altas (152,6 cm ± 8,62 cm) que las del grupo de baja altitud (149,2 cm ± 7,01 cm), aunque esta diferencia no fue estadísticamente significativa (valor p 0,333). Entre los hombres, sin embargo, los habitantes de las zonas altas son 4,3 cm más bajos (155,5 cm ± 9,93 cm) que los de las zonas bajas (159,9 cm ± 6,39 cm), siendo esta diferencia estadísticamente significativa (valor p 0,019).

4.3.3 Características antropométricas

Las mujeres de las bajas alturas son más bajas (- 2,3%) y más pesadas (+ 3,1%) que las que viven a gran altura (Tabla 1). La altura de los hombros (-0,3%), el perímetro torácico (-0,7%) y el perímetro de la cintura (-9,1%) también eran menores en el grupo de baja altitud. A la vez encontramos que la circunferencia de la cabeza es significativamente menor entre las mujeres de baja altitud (- 3,6%) y las que viven en altitud. El perímetro cefálico también era menor en los hombres de baja altitud (-2,7%).

4.3.4 Composición corporal

En relación con el % de musculo, las mujeres que viven a grandes alturas tienen menos masa muscular (-24,8%) que sus pares de baja altitud, mientras que los hombres de las zonas elevadas tienen una masa muscular significativamente mayor (+ 13,5%) que sus homólogos de bajas alturas. El % de grasa corporal es menor entre las mujeres de baja altitud (-15,5%) y no se encontraron diferencias entre los hombres.

4.4 Diferencias psico-emocionales y de autopercepción de salud

4.4.1 Cuestionario SF-36

Las puntuaciones globales del cuestionario SF-36 muestran que, en todos los casos, los participantes que vivían a bajas alturas obtuvieron una puntuación mayor que los que vivían a gran altitud y, tras utilizar una corrección de Bonferroni, el nivel de significación alcanzado fue de p = 0,006. La mediana y el rango intercuartil de las puntuaciones para cada dominio y para la puntuación total del SF-36 fue mayor en los pobladores de las bajas alturas. Las pruebas de Wilcoxon Rank test, para comparar las puntuaciones por altura indicaron que las puntuaciones fueron significativamente diferentes para las dimensiones "Limitación del rol por problemas emocionales" (p = 0,007), "Vitalidad" (p = 0,005), "Salud mental" (p = 0,002), "Funcionamiento social" (p = 0,005) y "Salud general" (p = 0,031).

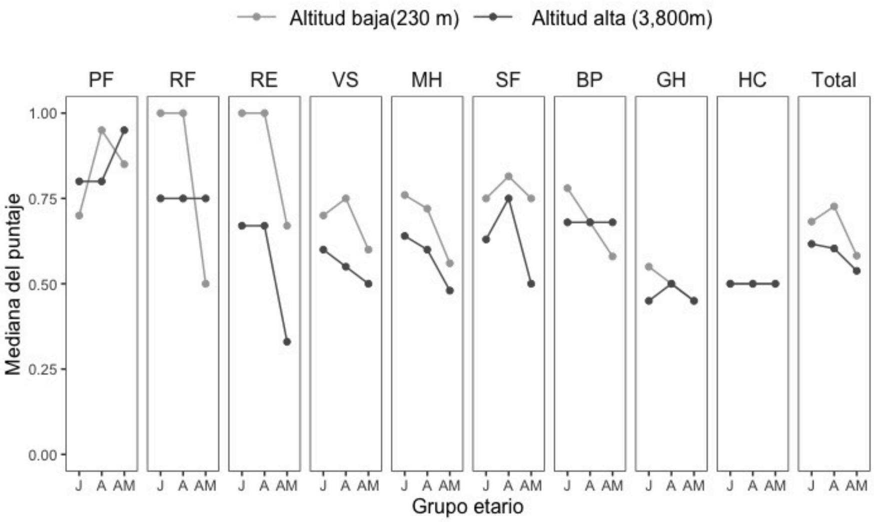

Figura 8 Resultados del SF-36 entre pobladores de Oyacachi versus Limoncocha

4.4.2 Optimismo

En relación con las principales diferencias dentro del espectro del optimismo, observamos que las poblaciones que residen por sobre los 3,800 metros tiene una ligera disminución dentro de la escala de optimismo LOT-r sin embargo esta diferencia no fue estadísticamente significativa.

4.5 Capacidad pulmonar y volúmenes ventilatorias

4.5.1 Resultados espirométricos y ventilatorios medidos

El grupo de gran altitud tiene una mayor Capacidad Vital Forzada (CVF) y un mayor volumen espiratorio forzado en el primer segundo (FEV_1). El FEV1, sin embargo, estas diferencias no son significativas. La relación FEV_1/FVC fue inferior en el grupo de gran altitud, así como las mediciones del flujo espiratorio forzado (Tabla 2).

4.5.2 Resultados espirométricos predictivos

Los valores predichos demuestran que los habitantes de las zonas altas tienen una mayor CVF tanto para los hombres como para las mujeres. Asimismo, cuando se compara con los valores predichos, el VEF1 fue mayor para ambos sexos, aunque sólo fue significativo entre las mujeres.

Tabla 4 Resultados Espirométricos en pacientes de Oyacachi versus Limoncocha

Indicador Espirométrico	Sexo	Baja Altura	Gran Altura	Diff. Media	Sig.
FVC (L)	Mujer	2.6187	2.939	-0.3203	0.789
	Hombre	3.5362	3.957	-0.4208	0.720
FEV_1 (L)	Mujer	2.5541	2.7251	-0.171	0.794
	Hombre	3.3505	3.602	-0.2515	0.396
FEV_1/FVC ratio	Mujer	95.4385	92.761	2.6775	0.354
	Hombre	94.927	91.3533	3.5737	0.391
FEF25-75%	Mujer	3.9028	3.9478	-0.045	0.781
	Hombre	4.7384	4.5457	0.1927	**0.017**
FEF25-75% - 85%	Mujer	1.8954	1.7346	0.1608	0.536
	Hombre	2.4084	1.862	0.5464	**0.008**
PEF L/s	Mujer	5.6669	5.8726	-0.2057	0.655
	Hombre	7.8292	7.8143	0.0149	0.906

4.6 Diferencias Hematológicas y de Perfil lipídico

4.6.1 Diferencias en las constantes vitales según el sexo y la elevación

Encontramos que la presión arterial tiende a ser más alta entre los hombres (106/75 mmHg) que en las mujeres (102/70 mmHg), sin embargo, esta pequeña diferencia no fue significativa. La presión arterial media (PAM) y la presión arterial sistólica fueron un 6,2% y un 7,5% más bajas en los hombres del grupo de gran altitud en comparación con los del grupo de baja altura, siendo estas diferencias estadísticamente significativas (valor p 0,01 y 0,029) (Figura 9).

Figura 9 Toma de Muestra de Sangre entre pobladores de Oyacachi 3,800 m

4.6.1 Recuento sanguíneo completo, análisis bioquímico y análisis de riesgo cardiovascular

No se observaron diferencias en el recuento de glóbulos blancos entre el grupo de baja y gran altura. En cuanto al recuento de glóbulos rojos y las características microscópicas, se observó que los habitantes de las grandes alturas tienen un mayor recuento de glóbulos rojos, hematocrito y hemoglobina, aunque tienen glóbulos rojos más pequeños que contienen menos hemoglobina por eritrocito.

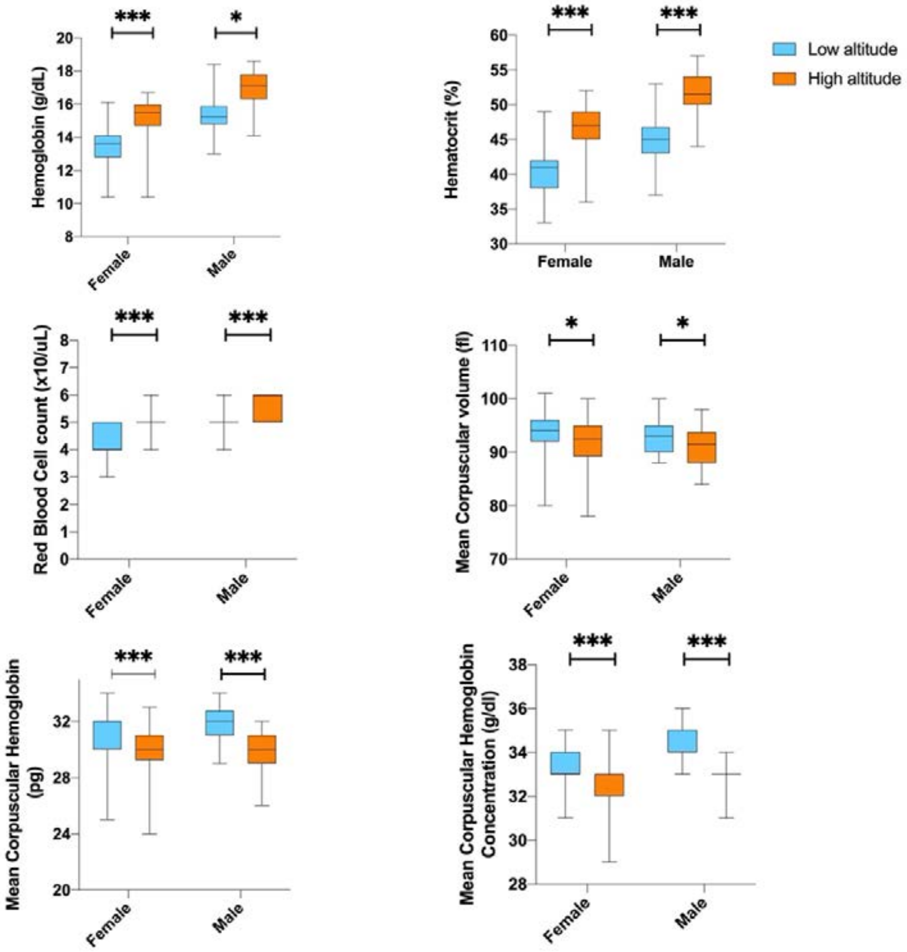

Figura 10 Diferencias hematológicas entre pobladores de las grandes alturas versus bajas alturas

5. Discusión

En el campo de la fisiología y la medicina de la altura, el entender el comportamiento epidemiológico de distintas enfermedades en poblaciones ubicadas a distintas alturas geográficas, nos puede dar una perspectiva nueva sobre el impacto que la hipoxia hipobárica podría tener como factor protector o como factor de riesgo (Faeh D et al., 2009; Damodar et al., 2018; Ortiz-Prado et al., 2021a).

Aunque existe mucha información publicada sobre los efectos de la altura y la hipoxia hipobárica sobre los distintos aspectos fisiológicos del cuerpo humano, la descripción epidemiológica a nivel poblacional ha sido reportada en menor proporción. Una de las razones principales de esta tendencia podría basarse en que, a nivel global, muy pocos países tienen poblaciones representativas que residen en rangos de altura amplios como los vistos en los Andes latinoamericanos (Tremblay and Ainslie, 2021).

En ese sentido, hemos analizado algunas enfermedades a nivel epidemiológico en un país como el Ecuador que tiene un rango de 221 ciudades (cantones) ubicadas desde los 0 m hasta los 4,300 m sobre el nivel del mar (Figura 2).

5.1 Impacto de la altura sobre la distribución epidemiológica de las enfermedades

En esa lógica, hemos identificado un grupo de enfermedades crónico-degenerativas como el accidente cerebrovascular o el cáncer que tienen una elevada prevalencia y por tanto pueden proporcionar un gran número de casos, para establecer su vínculo con la altura (Salazar-Vega et al., 2019; Ortiz-Prado et al., 2021a). A la vez, hemos estudiado el impacto que podría tener la altura con la tasa de suicidios como un indicador indirecto de los efectos que la altura podría tener en la esfera psico-emocional (Ortiz-Prado et al., 2017) y finalmente hemos analizado la relación que podría tener la altura sobre las enfermedades infectocontagiosas, caso en el que por razones coyunturales evidentes hemos elegido al COVID-19 (Ortiz-Prado et al., 2021c).

Con la oportunidad geográfica y demográfica que tenemos en el Ecuador, hemos identificado ciertas enfermedades que no han sido estudiadas anteriormente en el país dentro del contexto de la altura.

5.1.1 Enfermedades crónico degenerativos

Las implicaciones epidemiológicas de vivir o visitar zonas montañosas se ha descrito desde los años 700 D.C (West, 2006). Reportes históricos que provienen de los primeros médicos tibetanos, ya mencionaban la presencia de afecciones médicas causadas por residir a grandes alturas. Estos documentos señalaban como prevalentes la presencia de enfermedades pulmonares, la lepra, algunas enfermedades venéreas, posiblemente la difteria, la rabia y algunas enfermedades del aparato genitourinario (Pingree, 1974).

En épocas más contemporáneas, el interés de estudiar enfermedades crónico-degenerativas como la diabetes, la enfermedad cardiovascular o la enfermedad cerebrovascular han tomado más relevancia en el estudio de la medicina de alta montaña. Parecería ser que el vivir en zonas montañosas y ubicadas en lugares remotos de las principales cadenas montañosas del mundo podrían estar ligados a la aparición o reducción de ciertos factores de riesgo que podrían asociarse con la aparición de dichas enfermedades o la disminución del riesgo de padecer una (Puri et al., 1986; Wu et al., 2007; Aryal et al., 2017).

Por ejemplo, varios estudios realizados en poblaciones que residen en los Andes suramericanos han sugerido que tanto la enfermedad coronaria, como el infarto agudo de miocardio son relativamente poco frecuentes entre los habitantes de las zonas altas (Ramos et al., 1967). Reportes similares se han descrito en distintas zonas del planeta incluidas las zonas montañosas de Tian Shan y Pamir en Asia Central. Los reportes de dichas regiones también sugieren que las enfermedades cardiovasculares degenerativas son raras (Mirrakhimov, 1978).

La exposición repentina a grandes alturas donde la PO_2 arterial disminuye activa varios mecanismos complejos y adaptativos destinados a salvaguardar la homeostasis bajo condiciones ambientales extremas, como la hipoxia y las bajas temperaturas. La exposición a corto plazo va seguida de una hiperglucemia transitoria, desencadenada principalmente por la activación del sistema simpático, mientras que la exposición a largo plazo da lugar a una disminución de las concentraciones de glucosa en plasma, mediada por la mejora de la sensibilidad a la insulina y el aumento de la eliminación periférica de glucosa (Koufakis et al., 2019). A largo plazo, se ha estudiado en varias ocasiones la presencia de alteraciones en el metabolismo de los carbohidratos. En términos de hipoglucemia, no hay pruebas directas de que la altura provoque una baja de glucosa plasmática a largo plazo, pero exposiciones agudas junto al ejercicio extenuante puede provocar hipoglicemia entre montañistas. Al contrario, la exposición a largo término puede aumentar la producción de varias hormonas relacionadas con el estrés que pueden aumentar los niveles séricos de glucosa, pero paradójicamente, aunque los resultados son escasos, la diabetes mellitus tipo I y II parecerían ser menos prevalente que en las zonas ubicadas a nivel del mar (Woolcott et al., 2014).

De la misma forma, varios reportes sugieren que el vivir en zonas montañosas se asocia a mejores perfiles lípidos que aquellas personas que residen a nivel del mar, o que estos perfiles empeoran una vez que pobladores de las grandes alturas, migran a zonas más bajas (Santos et al., 2001; Aryal et al., 2017; Ortiz-Prado et al., 2021b). Algunos reportes como los elaborados por Siqués et al., sugieren que aquellos nativos de zonas bajas tienen cambios en su composición lipídica una vez que se exponen de forma aguda a zonas montañosas por encima de los 3,000 m (Siqués et al., 2007).

La función renal a largo plazo puede verse afectada entre personas no correctamente adaptadas a la altura, presentando alteraciones bioquímicas en los niveles plasmáticos de marcadores de la función renal (Brito et al., 2007).

5.1.1.2 Accidente cerebrovascular en el Ecuador

En relación al accidente cerebrovascular, nuestros resultados sugieren que vivir a mayor altitud se asocia con una reducción del riesgo de desarrollar un ictus, evidenciado por las tasas significativamente menores de ingresos a los hospitales y por la notable reducción en términos de mortalidad entre aquellos pobladores que residen a las grandes alturas (Ortiz-Prado et al., 2021a).

Estos resultados son similares a los reportados en Suiza, cuando Faeh et al., comparó longitudinalmente la mortalidad por el ACV en la altura y encontraron un descenso de la mortalidad, tanto por patología cardiaca como por ACV en un rango de altitudes desde 259 m hasta 1.960 m (Faeh D et al., 2009). Estos resultados fueron más evidentes en los hombres que en las mujeres, y la asociación negativa entre la altitud y la enfermedad fue más fuerte para la cardiopatía que para el accidente cerebrovascular (Faeh et al., 2009). Otro estudio epidemiológico publicado recientemente por Bürtscher et al. en este mismo año 2021 proporcionó datos adicionales que apoyan la afirmación de que vivir a una altitud moderada

(1.000-2.000 m) se asocia con una reducción de la mortalidad por causa cardiovascular, esta vez en pobladores de regiones montañosas de Austria (Burtscher et al., 2021).

Si bien el vivir en la altura parecería asociarse con una reducción del riesgo de morir por un ACV, en términos de otras causas de muerte como el suicidio, el vivir a grandes alturas podría estar asociado con un riesgo mayor de muerte (Brenner et al., 2011; Ortiz-Prado et al., 2017).

5.1.2 Alteraciones psico-emocionales y psiquiátricas

Los efectos que podría tener el vivir permanentemente a grandes alturas sobre alguno de los espectros emocionales, psicológicos y psiquiátricos asociados con el estado de ánimo se han estudiado poco. Estos reportes sugieren que el vivir a grandes alturas se asocia a mayores tasas de suicidio (Brenner et al., 2011; Reno et al., 2018).

Si bien se ha especulado con el papel que la exposición a hipoxia (y la potencial disminución en la disponibilidad de oxígeno a nivel cerebral) podría jugar en este fenómeno, es bastante más posible que los desencadenantes correspondan a otras causas. Por ejemplo, las condiciones meteorológicas asociadas a la gran altura pueden afectar sin duda a los hábitos culturales y, concretamente, a la forma de socializar de las personas. Las personas que viven a gran altitud pasan más tiempo dentro de sus casas debido al clima más duro, lo que sin duda afecta a su esfera psicológica a través del riesgo de mayor aislamiento social y puede trascender a su estado emocional . Parece que en nuestras poblaciones estudiadas el efecto de la altitud es diferente según el género, probablemente esto sea debido a las diferencias de género en la asignación de las tareas realizadas día a día, especialmente porque las mujeres tienden a permanecer en casa la mayor parte del día y también pueden tener menos interés o posibilidades de acceso a la información, o de más oportunidades de desarrollo, lo que puede dar lugar a una visión más pesimista del mundo.

Aunque los Estados Unidos de Norteamérica no tiene grandes grupos poblacionales viviendo por sobre los 2,500 m de altura, ellos han realizado un buen número de estudios que buscan analizar la asociación entre altura y suicidio (Haws et al., 2009; Betz et al., 2011; Kim et al., 2011; Ha and Tu, 2018). En todo Estados Unidos, el riesgo de suicidio parece ser significativamente mayor entre las personas que viven a mayor altitud, según sugieren un puñado de investigaciones (Oquendo et al., 2001; Searles et al., 2014; Fontanella et al., 2015; Ha and Tu, 2018).

5.1.2.1 Suicidio y altura en el Ecuador

El suicidio es un problema de salud bastante grave, a menudo poco atendido, y que está rodeado de ciertos mitos, tabúes y estigmas. Según la Organización Mundial de la Salud son alrededor de 800.000 personas las que se suicidan cada año en todo el mundo (OPS, 2014). El suicidio tiene un elevado número de factores de riesgo asociados a su incidencia. Las tasas de suicidio a nivel global varían de una región a otra, afectando más a hombres que a mujeres que residen en grandes urbes (Mueller et al., 2015).

Las diferencias epidemiologias no se limitan solamente al sexo, la edad o el lugar donde residen los sujetos que terminan con su vida por la vía del suicidio. El rol del medio ambiente y del clima ha sido estudiado varias veces y cada vez tenemos más evidencia de que el medio ambiente puede influenciar el estado de ánimo de las personas, aumentando el riesgo de suicidarse en algunas circunstancias (Brenner et al., 2011). Aunque no hay mucha investigación sobre este tema, se especula que la altitud, la hipoxia, el frio o alguna otra característica de las poblaciones de las grandes alturas puede aumentar los trastornos psiquiátricos, los cambios de humor, el riesgo de depresión y el riesgo de cometer un suicidio (Kramer et al., 1993; Virués-Ortega et al., 2006; Gamboa et al., 2011; Aquino Lemos et al., 2012; Reno et al., 2018).

En uno de los primeros estudios que buscaban analizar la distribución epidemiológica del suicido en el Ecuador, nuestro equipo reportó que los habitantes de la altura tienen tasas más altas de suicidio que sus pares de la costa (Ortiz-Prado et al., 2017). Según el último Censo Nacional, esta población vulnerable tiene menos acceso a una vivienda adecuada, a la educación y a la atención sanitaria (INEC, 2010).

En nuestro trabajo Carchi y Azuay, dos de las provincias con mayores tasas de suicidio, experimentaron una emigración masiva de sus jóvenes adultos hacia Estados Unidos y Europa en el año 2000 (Boccagni, 2013). Los patrones de inmigración son variables que aumentan el riesgo de suicidio debido a la aparición de familias desintegradas y niños que se criaron solos, hacen a este grupo particularmente vulnerable a la depresión, al abuso de drogas y probablemente a un mayor riesgo de suicidio (Ide et al., 2012; Milner et al., 2012).

5.1.3 Enfermedades infectocontagiosos

En el campo de la fisiología de la altura, el rol de la hipoxia ha sido analizado desde hace siglos como un factor precursor o protector de distintas enfermedades infecciosas. En teoría, los drásticos cambios fisiológicos que se producen durante la aclimatación pueden modificar los mecanismos de defensa innatos contra la infección microbiana, pero hay pocos datos que examinen sistemáticamente esas interacciones.

Durante los siglos XVIII y XIX, varios científicos y médicos de la época informaron de epidemias de viruela en las regiones montañosas de Lhasa. Para 1925 se ha estimado que al menos 7,000 personas murieron en Lhasa y sus alrededores. Debido a la prevalencia de la viruela en el Tíbet, en el siglo XVIII, los chinos colocaron una tablilla en Lhasa con instrucciones sobre cómo frenar la enfermedad, que en dicha época se presentaba en estas zonas montañosas (West et al., 2007).

En épocas más contemporáneas, las infecciones entéricas que son la principal causa de enfermedad entre los viajeros, han sido también estudiadas entre zonas montañosas del planeta (Basnyat et al., 2001; Ericsson et al., 2001). Por ejemplo, el 10% de las evacuaciones en helicóptero dentro de la cadena montañosas de los Himalaya se deben a complicaciones derivadas de enfermedades diarreicas (Dawadi et al., 2020).

Otras infecciones pueden ser más prevalentes en zonas montañosas. Por ejemplo, la infección por rabia, listeria, shigelosis o leptospirosis ha sido una grave preocupación para quienes se aventuran en zonas elevadas de América Latina o Asia (Ericsson et al., 2001).

A pesar de tener la capacidad analítica para identificar tendencias entre poblaciones ubicadas a diferentes alturas que van desde los 0 m hasta los 5,500 m, en Latinoamérica, los estudios son escasos. En ese sentido, iniciar trabajos que busquen determinar la carga epidemiológica a distintas alturas son fundamentales para entender si existen o no, diferencias fisiológicas que podrían tener las infecciones en relación con la altura.

5.1.3.1 COVID-19 y altura

La pandemia de COVID-19 sigue creando una presión sin precedentes en los sistemas sanitarios de todos los países del mundo. Hasta septiembre de 2021, se han notificado más de 220 millones de casos en todo el mundo, y se han registrado oficialmente al menos 4,5 millones de muertes por COVID-19 (Bashir et al., 2020; Coccia, 2020; JHU, 2020).

Varios factores ambientales y sociales se han asociado a una menor o mayor tasa de mortalidad relacionada con el COVID-19 y a la transmisibilidad del virus SARS-CoV-2 (Bashir et al., 2020; Coccia, 2020). Entre los factores ambientales, la exposición a grandes alturas ha generado controversia y ha intrigado a la comunidad científica por sus posibles beneficios a través de la hipoxia en términos de infección, prevalencia y mortalidad por COVID-19 (Millet et al., 2021).

En este contexto, varios autores han tratado de determinar la posible relación entre la mortalidad generada por el virus CoV-2 del SRAS y su transmisibilidad y el hecho de vivir en regiones situadas a gran altitud (Arias-Reyes et al., 2020; Woolcott and Bergman, 2020; Ortiz-Prado et al., 2021d; Zubieta-Calleja et al., 2021).

Algunos grupos de investigación han establecido que vivir a gran altura podría estar relacionado con la reducción de la mortalidad, la morbilidad y la mejora de la tasa de supervivencia relacionada con los pacientes confirmados con la infección por el SARS-CoV-2 (Arias-Reyes et al., 2020; Kong et al., 2020; Zubieta-Calleja et al., 2021)

Aunque vivir a gran altura puede estar asociado a una menor incidencia de COVID-19 y aparentemente a una menor mortalidad, la fisiopatología o los factores ambientales que están detrás de esta asociación todavía se están estudiando (Pun et al., 2020). Por ejemplo, se ha hipotetizado el efecto de vivir a gran altura y la expresión del receptor ACE-2, pero no hay pruebas definitivas que apoyen esta afirmación (Joyce et al., 2020). Por otro lado, la adaptación a la altura, la mayor resistencia a la hipoxia, así como la influencia del medio ambiente (radiación UV, ozono o frío) como factores de protección no se han relacionado aún con una mayor supervivencia (Cardenas et al., 2021).

A pesar de no disponer de información adicional sobre otros factores y cofactores, el estudio del exceso de mortalidad a diferentes alturas añade novedad a la literatura actual. Además, el uso del exceso de mortalidad por todas las causas proporcionará una poderosa herramienta para evaluar rápidamente estimaciones no sesgadas de la carga real de mortalidad por COVID-19 en Ecuador. Proponemos un enfoque innovador que utiliza valores medios en simulaciones utilizando la técnica de "bootstraping" para replicar el mecanismo de generación de datos de las series de mortalidad-tiempo y así obtener estimaciones más sólidas de las muertes esperadas para cuantificar el exceso de mortalidad en Ecuador en función de la altitud. En nuestro conocimiento, este es el primer estudio que utiliza un rango de altitud tan extenso, basado en una amplia clasificación de altitudes bajas y elevadas (2.500 m como punto de corte), así como dos clasificaciones ampliamente aceptadas por los expertos en fisiología de la altitud y medicina de montaña.

5.2 Impacto de la altura sobre el estado físico-emocional de los pobladores que residen en altitudes mayores a los 2,500 m

5.2.1 Parámetros hematológicos, perfil lipídico y análisis de riesgo cardiovascular

Nuestro estudio entre dos poblaciones genéticamente idénticas pero que residen a diferentes alturas demuestra que los parámetros hematológicos, bioquímicos y algunos clínicos difieren entre las dos poblaciones (Ortiz-Prado et al., 2021b).

Algunas de las diferencias que hemos encontrado, especialmente las distinciones antropométricas se deben probablemente a los procesos adaptativos de las distintas poblaciones (Julian and Moore, 2019). Al analizar los datos, observamos que, en general, las mujeres de Oyacachi (3,800 m) son ligeramente más livianas y más altas que las mujeres de las tierras bajas (Merrill, 2020). Por otro lado, los hombres de altitudes elevadas son significativamente más bajos de talla y más livianos que los hombres de las tierras bajas (Figura 11).

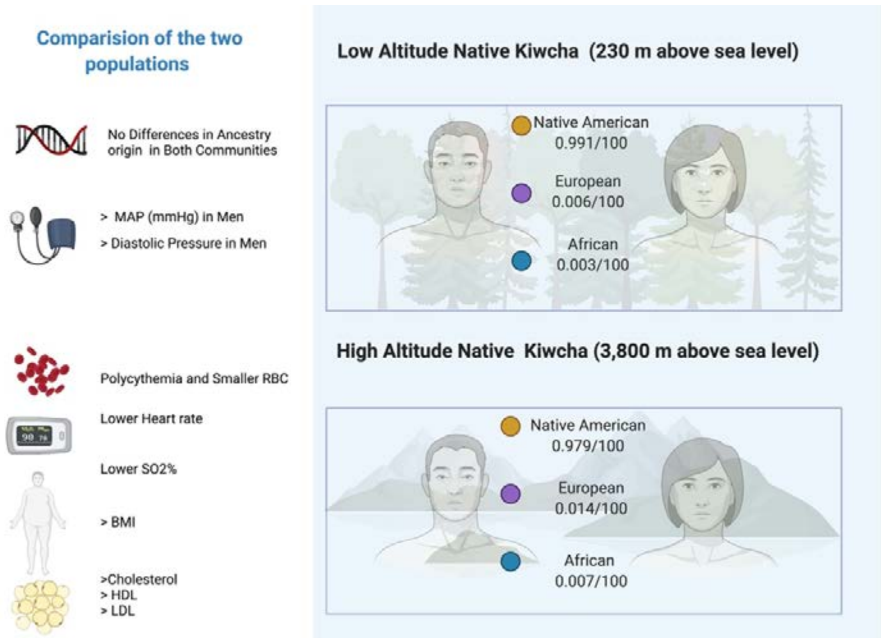

Figura 11 Diferencias principales entre dos poblaciones indígenas que residen a diferentes alturas

Nuestros hallazgos son similares a los reportados en Bolivia por Leatherman et al., en 1984 luego de estudiar a 138 hombres de las zonas rurales montañosas de Bolivia (3.700 m), concluyendo que los hombres de las zonas elevadas son más bajos y más livianos que sus homólogos de tierras bajas (Leatherman et al., 1984). A la vez, Toselli et al., en 2001 describió que los individuos son más bajos de talla en las zonas montañosas en relación con su masa corporal que los habitantes de las tierras bajas (Toselli et al., 2001). Sin embargo, en contraste con los resultados anteriores, Khalid en 1995 no detectó ninguna diferencia estadísticamente significativa cuando observó que los residentes de las zonas altas de Arabia Saudí eran significativamente más pesados y más altos que el grupo de control de las tierras bajas (Khalid, 2008). Estas diferencias entre dos poblaciones (la andina y la saudí) podrían demostrar diferencias en cuanto al tiempo de adaptación entre los dos grupos, algo que se ha descrito ampliamente con anterioridad (Moore et al., 1998; Beall, 2007; Tyagi et al., 2008). Por otra parte, las mujeres de grandes alturas presentan una mayor proporción de obesidad que sus pares de las tierras bajas, posiblemente debido a las condiciones culturales que obligan a las mujeres a quedarse en casa cocinando mientras los hombres salen de sus casas a trabajar (Khalid, 2008; Lin et al., 2018).

5.2.2 Optimismo y autopercepción

Los efectos de la exposición crónica a grandes alturas sobre el sistema nervioso central y el desarrollo cognitivo han sido estudiados anteriormente (Aquino Lemos et al., 2012; Wehby, 2013; Yan, 2014; Hu et al., 2016). La mayoría de los estudios se han realizado en modelos animales y han demostrado que la maduración del tejido neurológico y la replicación celular podrían verse afectadas durante la hipoxia hipobárica simulada (Floyd et al., 2020). En humanos, los estudios sobre el funcionamiento neuropsicológico son escasos. En pequeñas cohortes, se ha informado de que los niños nacidos por encima de los 4.000 m de altitud están menos atentos y responden menos a los estímulos visuales y auditivos que los niños nacidos a menor altitud (Saco-Pollitt, 1981). La evaluación neuropsicológica entre los niños y adolescentes de gran altitud indicó una reducción menor de la velocidad psicomotora con el aumento de la altitud (Hogan et al., 2010).

A pesar de esta evidencia, los efectos a largo plazo de la hipoxia crónica en el comportamiento humano y las actitudes hacia la vida rara vez se han estudiado (Kious et al., 2018). Se ha planteado la hipótesis de que vivir a gran altura puede tener un efecto sobre el metabolismo de la serotonina, reduciendo la síntesis del 5-hidroxitriptófano (5-HTP), lo que disminuye los niveles de serotonina en el sistema nervioso central (Kious et al., 2018). Los resultados de Kious y sus colaboradores podrían orientar nuestra comprensión de cómo la baja producción de serotonina podría estar relacionada con los síntomas del estado de ánimo que son comunes entre las personas que residen a gran altura (Kious et al., 2018). También se ha informado de que la química del cerebro parece estar alterada debido a la exposición a largo plazo a una mayor altitud (Shi et al., 2014; Hwang et al., 2019). DelMastro y colaboradores también informaron de correlaciones significativas entre la altitud y la sintomatología depresiva y ansiosa, así como los problemas de sueño (DelMastro et al., 2011).

El lapso de tiempo entre la exposición a la altitud y la presencia de efectos medibles aún no está claro. Algunos informes sugieren que incluso las visitas de corta duración a lugares de gran altitud podrían tener un impacto negativo en la salud mental. Por ejemplo, Barbara Shukitt-Hale y Harris R. Lieberman describieron en 1996 los efectos de la altitud sobre el rendimiento cognitivo y los estados de ánimo, y señalaron que una exposición de un mes de duración a la altitud era suficiente para aumentar la inestabilidad emocional (Shukitt-Hale and Lieberman, 1996). Se informó de síntomas psicóticos entre alpinistas sanos durante la exposición a una altitud muy elevada durante períodos de tiempo relativamente cortos (Brugger et al., 1999; Firth and Bolay, 2004; Hüfner et al., 2018).

La relación entre la exposición crónica a la hipoxia de gran altitud y la depresión o el suicidio se ha notificado en menos ocasiones (Gamboa et al., 2011; Ortiz-Prado et al., 2017; Reno et al., 2018). Algunas investigaciones anteriores también han descrito efectos adversos en poblaciones que residen en climas duros o poco acogedores (Kurlansik and Ibay, 2012; Melrose, 2015). El trastorno afectivo estacional es una condición en la que la autopercepción de la vida puede deteriorarse en climas más fríos (Kurlansik and Ibay, 2012). El hecho de que vivir a mayor altitud se asocie a menudo con climas más fríos podría estar relacionado con esta respuesta negativa hacia la vida entre los montañeses, sin embargo, este vínculo no se ha estudiado previamente.

5.2.3 Análisis comparativo de los parámetros de función pulmonar y espirometría

En nuestro estudio encontramos que los habitantes de las zonas altas tienen mayores capacidades pulmonares, de forma similar a los resultados publicados por otros autores (Brutsaert et al., 1999; Kiyamu et al., 2015; Weitz et al., 2016; López Jové et al., 2018a). Descubrimos que las personas que viven en altitudes elevadas tienen una capacidad vital forzada mayor que las que viven en altitudes bajas, y esta diferencia es estadísticamente significativa tanto para los hombres como para las mujeres.

El hecho de tener una mayor capacidad vital forzada está probablemente relacionado con los cambios anatómicos derivados de siglos de adaptación (Fiori et al., 2000b; Moore, 2001; Havryk et al., 2002a; Talaminos-Barroso et al., 2020). Algunas de estas adaptaciones anatómicas evolutivas (tórax más ancho y profundo) confieren a estas poblaciones unos pulmones más grandes, lo que se traduce en una mayor capacidad para albergar más aire. Un tórax más ancho y un mejor rendimiento pulmonar van acompañados de una mayor velocidad de espiración. El FEV1, también era mayor en los que vivían a gran altura, sin embargo, la mayor capacidad pulmonar también se relacionaba con una relación FEV1/FVC ligeramente inferior.

Estos hallazgos se han correlacionado incluso con hallazgos similares reportados en personas que ascienden rápidamente a elevaciones significativas. Sharma et al., en 2007 encontraron que a 3.450 m la CVF tuvo un aumento inicial del 9% en las primeras 24 horas, seguido de una disminución significativa de la CVF, así como del FEF1 y de la ventilación voluntaria máxima. A 5.350 m se produjo un aumento del 21% de la CVF en las primeras 48 horas, con una disminución posterior al igual que con los otros valores medidos (Sharma and Brown, 2007).

En relación a las principales diferencias entre grupos étnicos, Havrick et al., en el 2002 en su estudio demuestra que la población Sherpa presentaba valores espirométricos mucho mayores en comparación con los valores predichos para Caucásicos de su mismo sexo, edad y estatura en especial FEV_1 y FVC, (Havryk et al., 2002b). Lo que podría deberse a la adaptación física y evolución genética de generaciones que han habitado estas zonas geográficas por muchos años (Havryk et al., 2002b).

El incremento de la función respiratoria con cambios tanto morfológico como de mecánica respiratoria es un ejemplo de la adaptación en poblaciones que han vivido por generaciones a grandes alturas como lo es la tibetana. Permitiéndoles obtener mayores volúmenes pulmonares y una mejor capacidad de difusión (Gilbert-Kawai et al., 2014).

Hace 60 años Pugh sugirió que los Sherpas tenían un incremento en el consumo máximo de oxigeno debido a un intercambio gaseoso más eficiente secundario a una capacidad de difusión más grande (Pugh, 1962). Desde entonces en varios estudios ya se ha demostrado que existe una mayor capacidad de difusión en comparación con poblaciones sobre el nivel del mar, como consecuencia de un menor gradiente de oxigeno alveolo – arterial (Zhuang et al., 1996) (Chen et al., 1997)

Entre estudios realizados en la población andina podemos destacar un estudio muy interesante de López et al., en el 2018, en el que establece ecuaciones de predicción espirométrica para la población andina de grandes alturas, en su estudio demuestra que los valores espirométricos en esta población son mayores a los normales en comparación a las ecuaciones para la gente sobre nivel del mar. Además, propone la formulación de una ecuación de referencia para los habitantes del altiplano andino ya que siguiendo las ecuaciones formuladas para la gente sobre nivel del mar se puede subestimar la presencia de patrones espirométricos restrictivos o la severidad de patrones obstructivos. Siendo así de suma importancia incorporar valores de referencia con ecuaciones realizadas en poblaciones de mismo nivel de altura. Se comparó además sus ecuaciones de predicción espirométricas con las obtenidas en estudios de poblaciones de los Himalaya, encontrándose diferencias significativas (López Jové et al., 2018b).

Entre los estudios más significativos en la población latinoamericana en la altura tenemos el aporte de Pérez et al., con el estudio PLATINO conducido en 5 grandes ciudades en el cual se destaca la importancia de la etnia para ser consideradas en el análisis de parámetros estandarizados de espirometría (Pérez-Padilla et al., 2006). En su estudio observamos que la población de américa latina es similar a la americana de origen mexicano, y norteamericana blanca del estudio NHANES III (Hankinson et al., 1999)., y en un 20% superior a la población negra (Pérez-Padilla et al., 2006). Por lo que, se esperaría que la función pulmonar sea variable en américa latina por las diferentes etnias y latitudes, factores a considerar en futuros análisis.

5.2.4 Diferencias antropométricas y de composición corporal

Los resultados de nuestro estudio son los primeros que comparan las diferencias antropométricas en una población indígena adulta de genotipo controlado que vive a baja (230 m) y alta altitud (3.800 m). Al analizar los datos, observamos que, en general, las mujeres de gran altitud son ligeramente más ligeras y más altas que las mujeres de las tierras bajas, sin embargo, los hombres de gran altitud son significativamente más bajos y más ligeros que los hombres de baja altitud. Nuestros hallazgos son similares a los reportados en Bolivia por Leatherman et al. en 1984 (Leatherman et al., 1984). Entre los quechuas, un grupo nativo similar de Perú, Toselli et al., en 2001 encontraron individuos más bajos a gran altura en relación con su masa corporal (Toselli et al., 2001). Sin embargo, en contraste con los hallazgos anteriores, Khalid et al. no detectó estos resultados en 1995 cuando demostró que los residentes de gran altitud de Arabia Saudí eran significativamente más pesados y altos que el grupo de control de baja altitud (Khalid, 1995). Sin embargo, en contraste con los hallazgos anteriores, Khalid et al. no detectó estos resultados en 1995 cuando demostró que los residentes de gran altitud de Arabia Saudí eran significativamente más pesados y altos que el grupo de control de baja altitud (Moore et al., 1998, 2011; Beall, 2007; Tyagi et al., 2008; Moore, 2017b).

Se ha planteado la hipótesis de que al menos el 5% de los nativos de altura de Perú poseen un gen recién descubierto llamado *FBN1*. Este gen parece estar asociado a favorecer a los nativos andinos de gran altitud con una baja estatura y posiblemente una piel más gruesa (Pennisi, 2018). Es bien sabido que los habitantes de las grandes altitudes y los animales que viven en ellas suelen ser más pequeños, una respuesta evolutiva a la escasez de alimentos u oxígeno, así como una piel más gruesa, que puede ayudar a proteger el cuerpo de la intensa radiación UV en esos lugares (West, 2012; Pennisi, 2018).

Es bien sabido que el peso de los recién nacidos es significativamente menor entre los neonatos de gran altitud que los del nivel del mar (Al-Shehri et al., 2005; Hoke and Leatherman, 2019), una situación que puede prolongarse no sólo durante el embarazo, sino también durante los primeros años de la infancia y la adolescencia (Lichty et al., 1957; Iannotti et al., 2009; Moore et al., 2011).

El hecho de que los recién nacidos sean más pequeños tiene que ver con un proceso adaptativo que pretende reducir el consumo de oxígeno por parte del feto, siendo más eficiente la entrega de oxígeno a un organismo más pequeño a través de una placenta más pequeña (Krüger and Arias-Stella, 1970; Zamudio, 2003; Dolma et al., 2021).

Los humanos expuestos crónicamente a grandes alturas han compensado la reducción de la presión parcial de oxígeno (APO_2) con cambios anatómicos y morfofuncionales (Ortiz-Prado et al., 2019b). Por ejemplo, se han descrito tórax más grandes, más anchos y más profundos entre los habitantes de las tierras altas cuando se les ha comparado con los habitantes de las tierras bajas (Beall, 1982; Brutsaert et al., 1999; Moore, 2017b). Esto se debe probablemente a la mayor capacidad pulmonar de los seres humanos a gran altura, especialmente los que residen en el nuevo mundo (Fiori et al., 2000a; Weitz et al., 2002). Aunque esta afirmación se ha demostrado anteriormente, en nuestro estudio no encontramos diferencias estadísticamente significativas en los diámetros del tórax, aunque las mujeres parecen tener un tórax ligeramente mayor, que sus homólogas de las tierras bajas.

6. Conclusiones

a) A nivel epidemiológico, el suicidio parecería ser más frecuente en poblaciones que residen a grandes alturas (publicación 4.5).

b) Las causas detrás de este aparente aumento en los suicidios Aún no se conocen, pero podemos especular que se debe a la exposición crónica a un mal clima, que obliga a permanecer mayor tiempo dentro de nuestras burbujas familiares y en espacios cerrados (publicación 4.5).

c) El accidente cerebrovascular en poblaciones situadas las grandes alturas parecerían ser menos prevalente en comparación con las poblaciones que residen a menor altura (publicación 4.4).

d) Nuestros resultados sugieren que vivir a mayor altitud ofrece una reducción del riesgo de morir por un accidente cerebrovascular, así como una reducción de la probabilidad de ser ingresado a un hospital por la misma causa, siendo el efecto más evidente entre los 2.000 y los 3,500 m de altura (publicación 4.4).

e) El estudio de la presión parcial de oxígeno (PO_2) en los seres humanos incluye una serie de factores metodológicos, fisiológicos y clínicos. Nuestra publicación es la primera que proporciona una revisión profunda de la literatura e identifica de forma sistemática y clara cuál es la PO_2 en los distintos tejidos del cuerpo humano (publicación 4.6).

f) Las diferencias antropométricas entre poblaciones genéticamente comparables que viven a diferentes altitudes varían según el sexo, demostrando que la población de gran altitud es en general más ligera y baja que sus controles de baja altitud. Los hombres a gran altitud, probablemente debido a las cargas de trabajo extenuantes, son más ligeros y tienen cuerpos más musculosos que sus homólogos de las tierras bajas. El diámetro del tórax y la longitud biaxial no eran mayores entre los habitantes de las alturas, como esperábamos. Por último, encontramos que la edad corporal es significativamente mayor que su edad real entre las poblaciones de gran altitud, mientras que las poblaciones de baja altitud tienen una edad corporal más joven que su edad real, posiblemente relacionada con las condiciones climáticas y sociodemográficas encontradas en estos lugares. (publicación 5.2).

h) Los residentes de las grandes alturas tienen mayor capacidad pulmonar que sus pares de la Amazonia ecuatoriana, lo que indica una mayor capacidad pulmonar (publicación 5.1).

i) Observamos que las poblaciones que residen a grandes alturas presentan diferencias en cuanto a la percepción de su propio estado de salud cuando comparamos con sus pares amazónicos de baja altura (publicación 4.2).

j) Los indígenas de altura son más propensos a reportar estados de salud desfavorables representados por puntuaciones más bajas en todas las dimensiones del SF-36, en comparación con sus homólogos de baja altitud (publicación 4.2).

k) Los indígenas que viven a gran altitud son significativamente más propensos a informar de alteraciones en la salud emocional, la vitalidad y la salud general que los que viven a baja altitud (publicación 4.2).

l) Los efectos de la altitud parecen ser diferentes en función del sexo, las mujeres se ven más afectadas en dimensiones más relacionadas con los hábitos culturales, como el funcionamiento social y el optimismo; mientras que los hombres se ven afectados en dimensiones de vitalidad, salud mental y salud general (publicación 4.2).

7. Referencias

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