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High Altitude Is Associated With Lower Stroke-Related Mortality: A 17-Year Nationwide Population-Based Analysis From Ecuador

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High Altitude Is Associated With Lower Stroke-Related Mortality: A 17-Year Nationwide Population-Based Analysis From Ecuador

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Abstract

Background:

Globally, 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 analysis 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 2001-2017. 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 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 (RR: 0.91 [0.88 - 0.95]) and women (RR: 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 (RR: 0.55 [CI95% 0.54 - 0.56]) and women (RR: 0.65 [CI95% [0.64 - 0.66]).

Conclusions:

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 the stronger effect between 2,000 m to 3,500 m.

Background

Cerebrovascular disease 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, In 2016, the global lifetime risk of stroke from the age of 25 years onward was approximately 25% among both men and women[2]. Stroke is the third leading cause of disability worldwide and affects people of all ages, though the causes of stroke a younger age are very different from those at older ages[3–6]. The risk of developing stroke increases with high blood pressure, atrial fibrillation, cigarette smoking, hyperlipidemia and diabetes mellitus[1]. Other modifiable factors are obesity, chronic kidney disease, excessive alcohol use, cocaine consumption, sedentarism, psychological stress and depression[7–9]. 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. [10–14].

Globally, at least 5.7% of the population live above 1,500 meters, with millions of people chronically exposed to high altitude. The association between high-altitude exposure and stroke is still unknown and the very few investigations available are still inconclusive[11, 12, 15]. 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[16]. The International Society of Mountain Medicine defines 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 [17].

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[18–20]. 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) [11, 12, 21, 22]. Paradoxical results were published by Faeh, et.al in 2009 [22]. They found a decreased risk of cardiovascular diseases (CVD) and stroke related mortality among those living in high altitude locations in Switzerland [22]. 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 [22]. Although this offers a new perspective of the potential protective effect of living at higher altitudes, the elevation range did not surpass 2,000 meters, making it difficult to extrapolate the results to other mountainous regions of the world. 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[23].

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 meters within the Ecuadorian highlands.

Methodology

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) including the following ICD-10 diagnoses: I60 subarachnoid haemorrhage (SAH), I61 intracerebral haemorrhage (ICH), I63 ischaemic stroke (IS) and I64 as not specified stroke.

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 2001-2017. 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 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.

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 people are Mestizo (79.3%), followed by Afro-Ecuadorians (7.2%), indigenous (7.1%), white or Caucasians descendants (6.1%) and other groups (0.4%)[24].

Exposure

The association between altitude exposure and stroke incidence and mortality was analysed. 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 to 2,500 m), high-altitude (2,500 to 3,500 m) and very high-altitude (3,500 to 5,500 m) was used to assess prevalence odds ratios by different elevations.

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 was retrieved from the National Institute of Census and Statistics (INEC) using the general hospital admission and the mortality databases for 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://www.ecuadorencifras.gob.ec/.

Inclusion criteria

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

Exclusion criteria

Patient without an ICD-10 diagnosis of stroke were not included[25]. 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.

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 was used as the standard population for the direct standardization[26]. 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 incidence and mortality. 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 if the data was performed using the SPSS statistics software for Mac (IBM Corp. 2014, version 24.0. Armonk, NY, USA) 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 (2365 Northside Dr. Suite 560, San Diego, CA 92108). The basic cartography maps were generated using QGIS Development Team 2.8 (Creative Commons Attribution-ShareAlike 3.0 licence 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.

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 altitudes develop stroke at a later age than the low altitude dwellers (Table 1).

Table 1 Age difference between altitude categories

	Mortality				Hospital Admission			
	Media	CI 95%	Median	CI 95%	Median	CI 95%	Median	CI 95%
	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]

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 [CI95% 11.5 - 21.4]) and women (16.2 / 100,000 [CI95% 11.7 - 20.8]) versus 10.6 / 100,000 [CI95% 6.9 - 14.3]) and women (12.3 / 100,000 [CI95% 8.45 - 16.9]) (Figure 1).

Age and Sex-adjusted stroke mortality and stroke admission rates by age groups

Stroke mortality rates are significantly lower among younger population (< 40 years of age) in both groups (low vs high), nevertheless, mortality increases from 40 to 50 years of age in more than 200% for both groups.

Stroke hospital admission rates are also higher among lowlanders and increases significantly after the 50’s (Figure 2).

Difference in Mortality and hospital admission rates in age and sex-stratified populations

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).

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	Diff	(n)	Age-Adjusted Rates	Diff
Man						
Low Altitude (<1,500)	11,241	57.9	Ref	25,003	305.4	Ref
Moderate Altitude (1,500-2,500)	1,887	55.6	-2.3	4,412	255.9	-49.4
High-altitude (2,500-3,500)	5,674	44.4	-13.5	9,921	196.8	-108.6
Very High-altitude (3,500-5,500)	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)	13,344	56.3	Ref	29,652	291.6	Ref
High-altitude (>2,500)	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)	9,770	53	Ref	20,371	251.6	Ref
Moderate Altitude (1,500-2,500)	2,222	57.2	4.2	4,657	259.2	7.6
High-altitude (2,500-3,500)	6,690	54.8	1.8	11,096	200.7	-50.9
Very High-altitude (3,500-5,500)	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)	12,183	52.6	Ref	25,312	246.5	Ref
High-altitude (>2,500)	6,855	56.9	4.3	11,012	208.5	-38.0
Total	**19,038**	**N/A**	**4**	**36,324**	**N/A**	**-37.9**

Stroke mortality and hospital admission relative risk at low (<2,500 m) and high (>2,500 m) altitude

In the last 17 years of available data, we can observe that hospital admission is less likely to occur in the highlands for men RR: 0.69 CI95% [0.68 - 0.71] and women RR: 0.83 CI95% [0.83 - 0.86], while at 2,500 m of elevation and above, mortality risk was only reduced among men RR: 0.84 CI95% [0.81 - 0.87] but no among women 1.08 CI95% [1.05 - 1.12].

Stroke mortality and hospital admission relative risk at four different elevation ranges

Populations from very high-altitudes 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 CI95% [0.54 - 0.56] when compared with the low altitude group OR: 0.65 CI95% [0.64 - 0.66]) (Figure 3).

Burden of disease 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. Living at higher altitudes is associated with lower YYL per 100,000 people (Table 3).

Table 3 Burden of stroke and years of life lost prematurely due to stroke in Ecuador from 2001-2017.

Altitude	Population	Deaths	Deaths per 1000 pop (95% C.I.)	YLL	YLL per 1000 pop. (95% C.I.)
Low Altitude	8,941,296	3,543	0.40 (0.38 - 0.41)	75,823	8.48 (8.42 - 8.54)
Moderate Altitude	1,424,273	537	0.38 (0.35 - 0.41)	11,004	7.73 (7.58 - 7.87)
High Altitude	4,360,711	1,249	0.29 (0.27 - 0.30)	21,698	4.98 (4.91 - 5.04)
Very High Altitude	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)

Discussion

Our study is the first to describe the burden of stroke at four different elevation ranges. Ecuador is unique for this type of analysis since it has populations residing from sea level to very high altitudes. 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 decreases the risk of 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.

Our results suggest that living at higher altitudes decreases the risk of stroke due to the significant lower rates of stroke admissions and mortality. Our results are similar to those reported in Switzerland in 2009, this was the only publication similar to ours that longitudinally compare stroke mortality at high-altitude[22].

To date the burden of stroke has not been reported by altitude level. Our data suggest that living at higher altitudes decreases the risk of stroke after adjusting for population, age, and sex.

A possible explanation for the decreased risk of stroke in this population maybe due to physical activity, smoking rates, incidence of obesity, and diet. These risk factors may play a role explaining the lower mortality and hospital admission rates due to stroke among highlanders. Specific data about risk factors could not be analysed due to the lack of data in the national databases.

In terms of our findings, we observed consistent dose-response relationship between high-altitude and a reduced risk of developing stroke between 2,000 up to 3,500 meters of elevation. Beyond this point, other factors might be involved in a reduction of this hypothesized protective effect. For instance, brain angiogenesis is a common finding among acclimatized and adapted brain to high-altitude[27–29]. This is the postulated most important protective factor when reducing the size of a stroke and when improving recovery after a ischemic episode at high altitude[29–32]. Nevertheless, above this point, high haematocrit levels due to a significant polycythaemia causing thicker blood overcome this protective factor, reducing blood flow, and causing statis as well as thrombogenesis[33–36]. Although no data from human studies available our results support the plausible relationship of a “protective window” that lays between 2,000 m to 3,500 m of elevation and anything below this point progressively loses the hypostatized protective effect while anything above 3,500 confronts angiogenesis and vascular remodelling versus high-altitude triggered thrombogenesis.

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[37]. These behaviors might contradict the paradoxically lower mortality of stroke among highlanders[38] People in the coast region seem to have higher consumption of carbohydrates (36 % versus 30%) and have inferior access to health services (24 versus 32 health centres per every 100,000 people) than the persons in the highlands[39]. 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 (236,9 / 100,000), situation that is similar to other studies [40, 41]. Other risk factors such as hypertension, obesity and sedentarism have been showed to be less prevalent among high-altitude dwellers according to some of the available published data[42–44].

Although some of the risk factors are might be less prevalent among highlanders, other factors such as; higher platelet adhesiveness, polycythaemia, hypoxemia may play a role increasing the risk of developing stroke in altitudes beyond 3,500 m[18, 45–47].

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[13, 22, 48, 49].

Limitations

The main limitation of this analysis is that some residual risk factors such as educational attainment, SES, BMI, BP, smoking, diabetes and polycythaemia were not controlled since data is available. 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.

Conclusions

This is the first epidemiological study that explored the risk of developing 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 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 the stronger effect between 2,000 m to 3,500 m and beyond this point, the hypostatised protective effect starts to compete against polycythaemia and high viscosity blood, to well-known thrombogenic factors.

The results and the available literature suggest that high-altitude residents, probably due to their increased cerebral microvasculature have better perfusion protecting the brain in some degree, against hypoxia. 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.

Declarations

Ethics approval and consent to participate

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

Consent for publication

N/A

Availability of data and materials

All the information used for this analysis can be retrieved from the National Institute of Census and Statistics (INEC) at the following repository: https://aplicaciones3.ecuadorencifras.gob.ec/sbi-war/

Competing interests

The authors declare no competing interests.

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Authors' contributions

EOP contributed towards the conception and design of the whole project, obtained full access to the data from the National Institutes of Statistic in Ecuador, and was primarily accountable for all aspects of work, ensuring integrity and accuracy of the research as well as of the drafting of the manuscript, and the final responsibility for the decision to submit for publication.

SC, EV and AB contributed towards data acquisition and the revision of the available literature review

KSR, LGB and MC contributed to the statistical analysis and the internal validity of the study and the initial drafting of the manuscript.

ARH undertook the burden of disease analysis and the economic impact of stroke at different altitudes in Ecuador.

PSE, AB, GV and PR critically reviewed and edited the manuscript, providing input towards the reporting of the data, and its interpretation.

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Figures

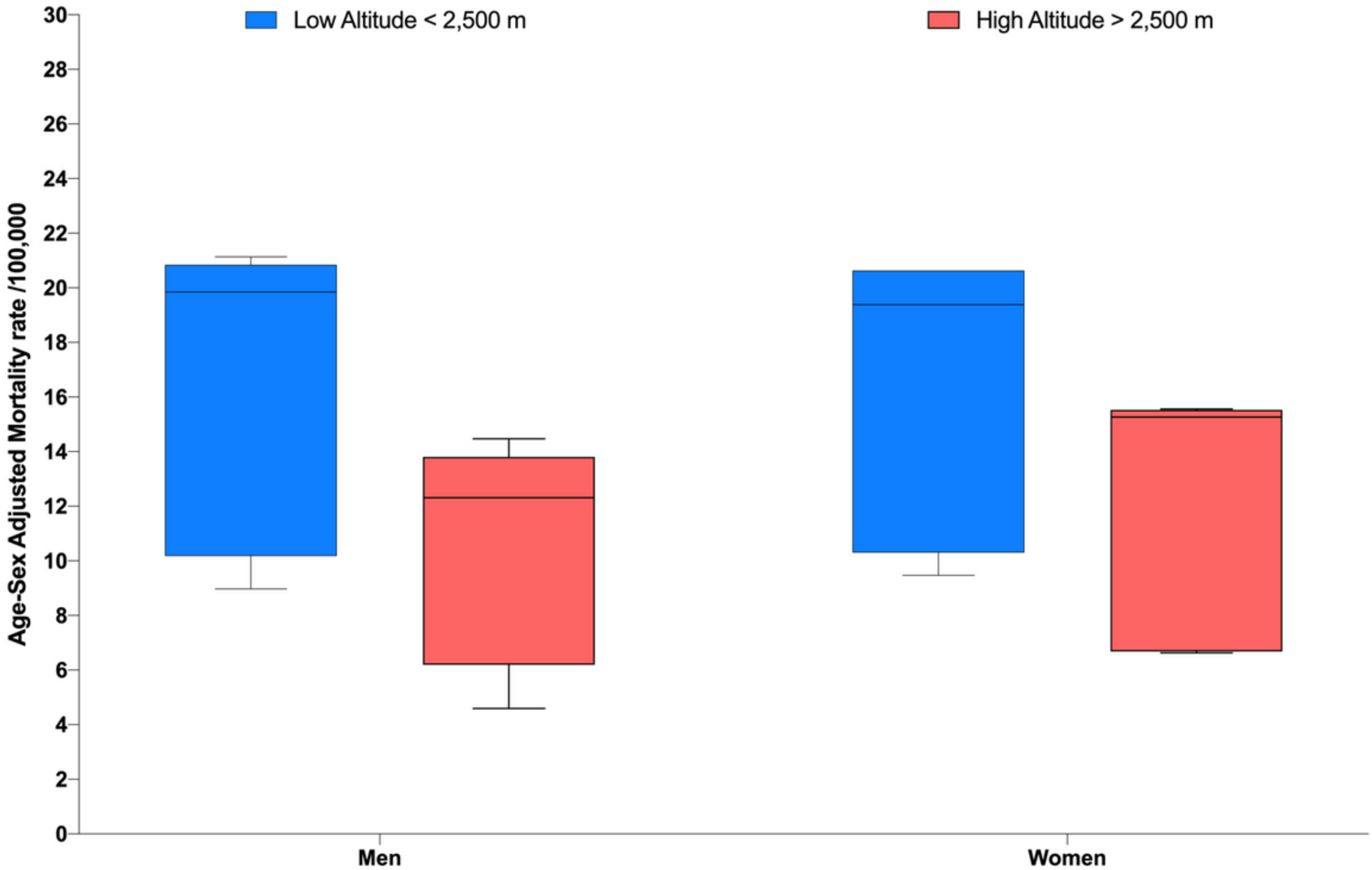

Figure 1

Overall age and sex-adjusted mortality rate by sex and elevation exposure

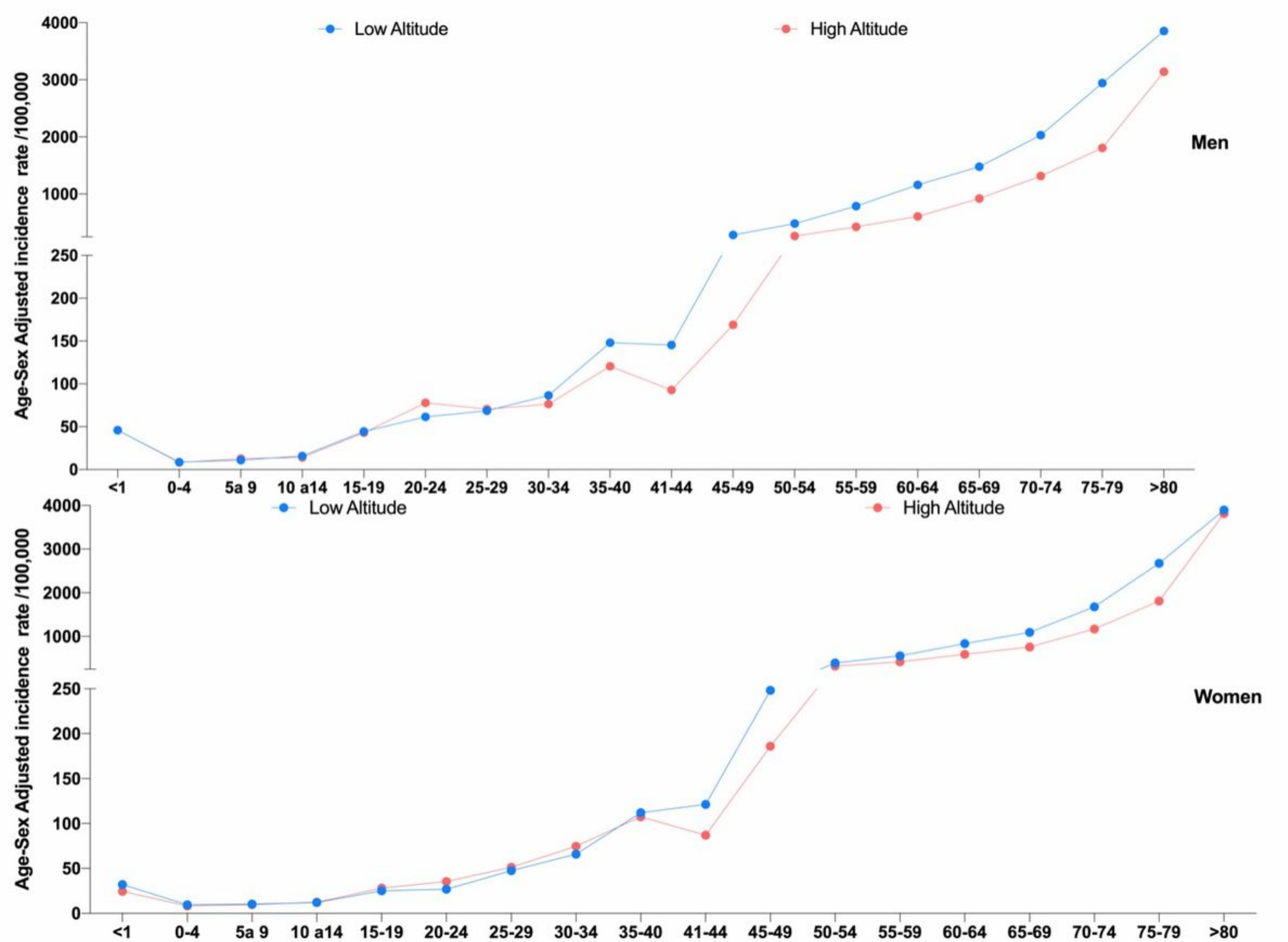

Figure 2

Age-sex adjusted hospital rate due to stroke by age group in the low and high-altitude.

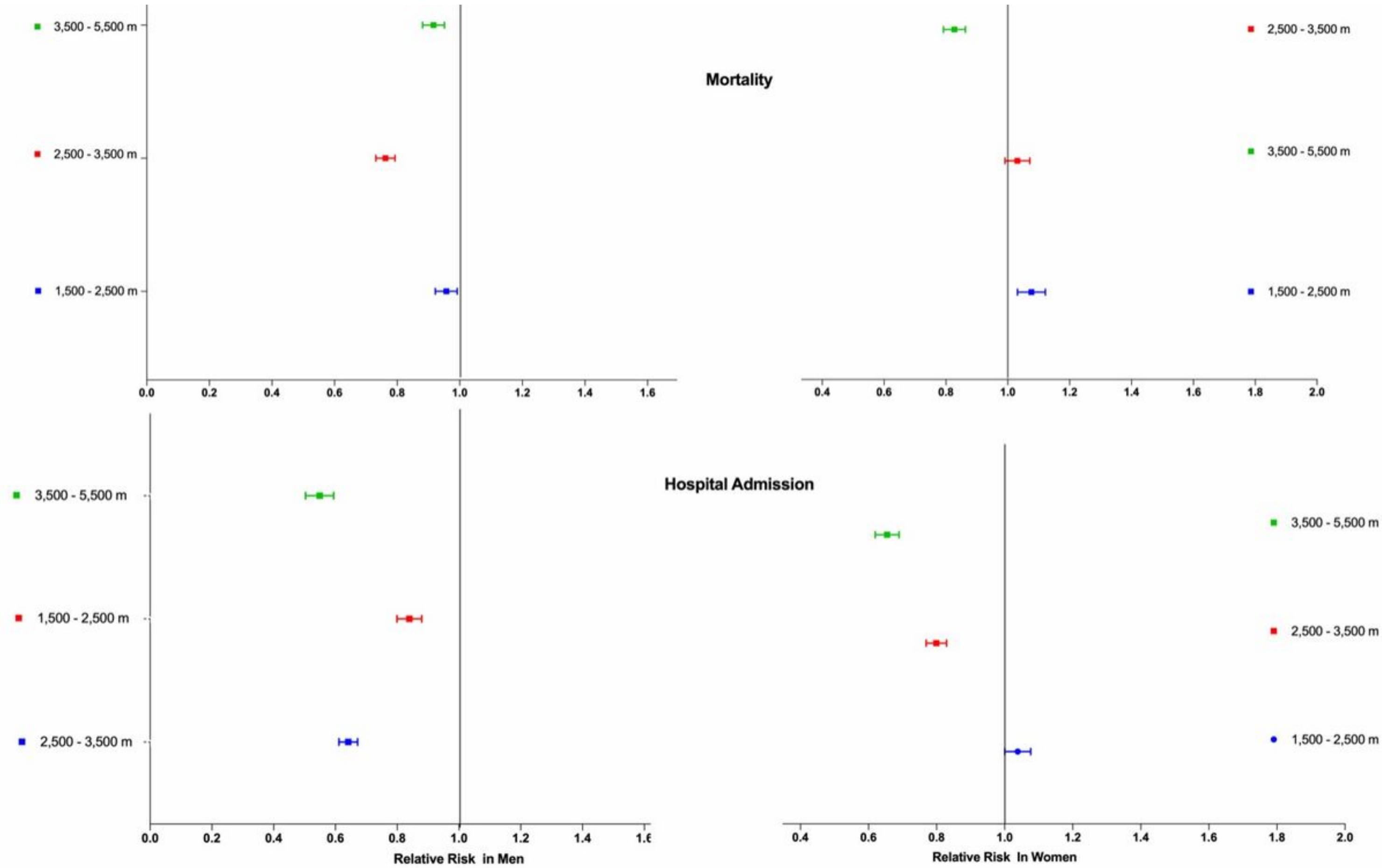

Figure 3

Relative for mortality and hospital admissions in men and women living at 4 different elevation. Low altitude was used as a reference variable.