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Chronic high-altitude exposure and the epidemiology of ischaemic stroke: a systematic review

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ABSTRACT

Introduction About 5.7% of the world population resides above 1500 m. It has been hypothesised 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 the association between long-term high-altitude exposure and ischaemic stroke.

Design A systematic review was performed from 1 January 1960 to 1 December 2021 to assess the possible link between high-altitude exposure and ischaemic stroke. The AMED, EMBASE, Cochrane Library, PubMed, MEDLINE, the Europe PubMed Central and the Latin-American bibliographic database Scielo were accessed using the University of Southampton library tool Delphis. In this review, we included population and individual-based observational studies, including cross-sectional and longitudinal studies except for those merely descriptive individual-based case reports. Studies were limited to humans living or visiting high-altitude locations for at least 28 days as a cut-off point for chronic exposure.

Results We reviewed a total of 1890 abstracts retrieved during the first step of the literature review process. The authors acquired in full text as potentially relevant 204 studies. Only 17 documents met the inclusion criteria and were finally included. Ten studies clearly suggest that living at high altitudes may be associated with an increased risk of stroke; however, five studies suggest that altitude may act as a protective factor for the development of stroke, while two studies report ambiguous results.

Conclusions This review suggests that the most robust studies are more likely to find that prolonged living at higher altitudes reduces the risk of developing stroke or dying from it. Increased irrigation due to angiogenesis and increased vascular perfusion might be the reason behind improved survival profiles among those living within this altitude range. In contrast, residing above 3500 m seems to be associated with an apparent increased risk of developing stroke, probably linked to the presence of polycythaemia and other associated factors such as increased blood viscosity.

Strengths and limitations of this study

► This review analyses the relationship between stroke and high-altitude exposure using published data.
► We report a quantitative analysis of the risk factors associated with ischaemic stroke at high altitude.
► One of the main limitations is the lack of average multicountry cohorts.
► Another limitation is that case reports were excluded from our analysis.

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 one in six men and one in five 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 7]

Stroke risk factors are often classified as traditional and non-traditional, and from this, they can be modifiable or non-modifiable.[8] In general terms, these risk factors have been classified as those which cause an ischaemic stroke or haemorrhagic stroke, being the most common and recognised as displayed in table 1.

INTRODUCTION

Stroke, also known as a cerebrovascular event, is a severe and often life-threatening medical condition that appears when the blood supply

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

Traditional risk factors	
Non-modifiable	**Modifiable**
Ischaemic stroke	
Age	
Sex	
Ethnicity	
Socioeconomic status	
Family history	
Thrombotic	
Arterial dissection	Waist circumference
	Alcohol misuse
	Obesity (BMI, WC, WHR)
	Diabetes
	Cigarette smoking
Embolic	
Atrial fibrillation	
Intracardiac thrombus	
Heart valve disease	Physical inactivity
Trauma and fractures	Apolipoprotein B/A1
Some types of surgeries	Hyperlipidaemia*
Systemic	
Post-traumatic hypovolaemia	
Acute systemic hypoxia	
ICH	
Vascular malformations	Hypertension
Bleeding diathesis	Cigarette smoking
Trauma	Obesity
	Waist to hip ratio
Haemorrhagic stroke	
SAH	
Cocaine abuse	Diet
Amphetamines	

*High low-density lipoprotein (LDL) serum levels.
BMI, body mass index; ICH, intracerebral haemorrhage; SAH, subarachnoid haemorrhage; WC, waist circumference; WHR, waist to hip ratio.

The risk of developing stroke increases with the presence of causal factors, which include arterial hypertension, atrial fibrillation, cigarette smoking, hyperlipidaemia, diabetes mellitus and acute infections such as COVID-19.[1 9] Other modifiable factors are obesity, chronic kidney disease, excessive alcohol and cocaine consumption, sedentarism, psychological stress or depression.[10–12] Other factors such as vitamin D or high altitude may play a role but have been less studied than the traditional vascular risk factors.[13–17]

Rationale for high-altitude exposure and stroke
Globally, at least 5.7% of the population lives above 1500 m; nevertheless, the association between high-altitude exposure and stroke has been poorly studied.[14 15 18] 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.[14 19–21] The few reports available suggest that living in high-altitude regions (>2500 m) increases the risk of developing thrombosis through hypoxia-driven polycythaemia which leads to a hypercoagulation unbalance, which have been associated with increased risk for the development of atherothrombotic stroke.[22–24]

Although most of the information comes from a case or case series reports, no cohort studies have been published in this area. The only available information came from very few cross-sectional analyses that have found a significant association between living in high-altitude regions and having a greater risk of developing stroke, especially among younger populations.[14 15 20 21]

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 ischaemic stroke.

METHODS
Research question
Does living at high altitude increase the risk of developing ischaemic stroke?

Study design
A systematic review was conducted including published scientific reports, including original research, abstracts, editorial and commentary letters. We have used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. No protocol was registered for this review since PROSPERO does not currently accept registrations for scoping reviews, literature reviews or mapping reviews.

Data source and search strategy
The literature review process was performed in English to cover the largest number of scientific databases and repositories containing academic literature from 1 January 1960 to 1 December 2021. 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.

The studies included are based on the following criteria:
Population: adults from both sexes, all ages and ethnic background.

Study designs: all epidemiological analyses including observational and experimental full research, abstracts, editorials or commentary letters.
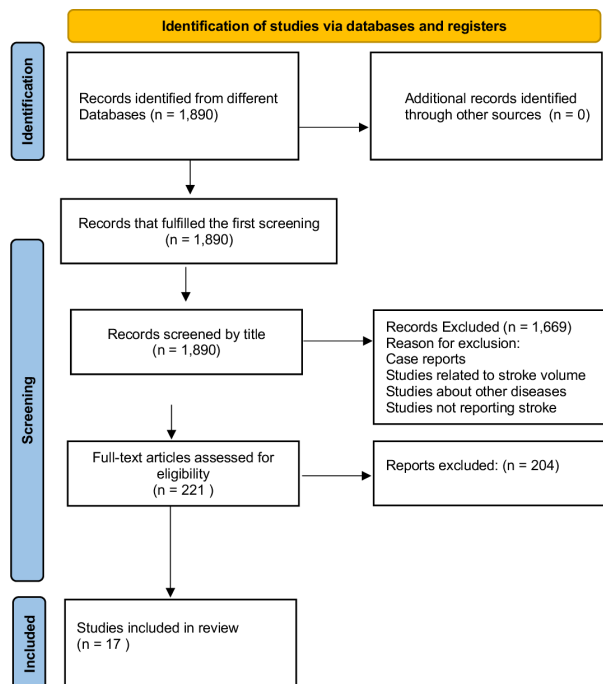
Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart diagram for reporting literature review search and meta-analysis.

Exposure: we included every elevation above 2000 m that was considered high altitude by the authors.

Outcome of interest: incidence and mortality rates.

Inclusion criteria

This systematic literature review included all scientific papers that were written in English and reported epidemiological findings on the impact of stroke in different populations exposed to moderate to high altitudes. We set the cut-off point of short or long-term exposure in 28 days based on previously published data.

The main inclusion criteria were:
► All manuscripts involving human subjects.
► All manuscripts that considered high altitude in the title or abstract and had the word stroke in the title.
► All studies published between 1 January 1960 and 1 December 2021.

The precise, full search strategy for all databases, registers and websites, including any filters and limits used, is described in the online supplemental file 1.

Exclusion criteria

Exclusion criteria included all reports of thrombosis, deep vein thrombosis or venous thrombosis (DVT).

List of the main exclusion criteria:
► Scientific papers concerning stroke that did not consider high altitude within the analysis.
► This literature review excluded all in vivo and in vitro studies.
► If the search term 'stroke' referred to cardiac output or stroke volume, the results were excluded.
► Case reports were excluded from the study.

Bias assessment

In order to reduce risk of any type of bias, the data extraction process was performed by EO-P and SPC independently and in different times. To minimise errors while gathering information from any primary study, any disagreements were resolved after reaching consensus. In addition, while assessing the quality of primary studies, the Critical Appraisal Skills Programme (CASP) tool was used to reduce any tendency to search, interpret, favour or recall any information previously adopted by any of the authors of this work (online supplemental file 2).

Data synthesis

In this section, we completely reviewed all the manuscripts that met the inclusion criteria. With the information obtained, a quantitative analysis of the results using the CASP tool was performed. The information coming from each of the manuscripts was synthesised in two tables.

Patient and public involvement

No patient was 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.[25] 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.[14 15 20 21 26–36]

We included 1890 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 204 abstracts. In the end, we included 17 manuscripts within this literature review (figure 1).

Specific studies

Study 1: The first study published by Razdan *et al* in 1989 looked into the prevalence of stroke in elevations above 1500 m.[26] They found that the crude prevalence of stroke was higher than the populations residing below this elevation (table 2). The study was carried out in India and includes 91 cases of stroke; the sample included men and women between 5 and 65 years old.[26]

Study 2: In 1990, Annobil *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 disease and stroke.[27]

Study 3: In 1994, García reported the prevalence of risk factors of developing stroke at 2500 m in a community in

Table 2 Critical appraisal and summary of the literature

Author (year)	Title	Sample, setting and elevation	Aim	Design, type and length of exposure	Main findings
Razdan et al[26] (1989)	Cerebrovascular disease in rural Kashmir, India	▲ The study was performed in Kuthar Valley, India. ▲ Elevation: 1530 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.	▲ 91 cases of stroke were detected. ▲ Crude prevalence rate of 143/100 000. ▲ Proportion in men (69, 23%) and women (30, 77%).
Annobil et al[27] (1990)	Cerebrovascular accidents (strokes) in children with sickle cell disease residing at high and low altitudes of Saudi Arabia	▲ The study was performed in Saudi Arabia. ▲ 8 stroke cases. ▲ Elevation: 3000 m.	▲ To compare the clinical and radiological indications of stroke in patients with sickle cell 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.	▲ The incidence of stroke in children with sickle cell disease is similar regardless of elevation.
Garcia[28] (1994)	Cerebrovascular disease: risk factors analysis of natives living at high-altitude	▲ The study was performed in Peru. ▲ 50 patients with a confirmed diagnosis of stroke and 52 healthy patients. ▲ Elevation: 2500 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) and random population (controls).	▲ Atherosclerosis was the most important risk factor for CVD in the highland natives.
Jaillard et al[20] (1995)	Prevalence of stroke at high altitude (3380 m) in Cuzco, a town of Peru A population-based study	▲ The study was performed in Peru. ▲ 3246 subjects interviewed. ▲ Elevation: 3800 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, polycythaemia, high consumption of alcohol and area of residence were associated with higher stroke prevalence.
Jha et al[14] (2002)	Stroke at high altitude: Indian experience	▲ The study was performed in India. ▲ Elevation: 4270 m.	▲ To determine the relationship between stroke and high altitude.	▲ Information was prospectively collected from the Command Hospital in India.	▲ Long-term stay at high altitude was associated with higher risk of developing stroke.
Niaz and Nayyar[15] (2003)	Cerebrovascular stroke at high altitude	▲ The study was performed in Chandimandir, India. ▲ Elevation: 4200 m.	▲ To identify the presence of stroke using different clinical, imaging and laboratory assessments.	▲ A cohort analysis of stroke prevalence and mortality from 1998 to 2000.	▲ Stroke hospital admission rates were higher among high-altitude residents (13.7/1000) versus low- altitude residents (1.05/1000).
Mahajan et al[29] (2004)	Stroke at moderate altitude	▲ This study was performed in Himachal Pradesh in the sub-Himalayan ranges. ▲ Elevation: 2200 m.	To understand the clinical profile, and 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 examinations were performed.
Faeh et al[21] (2009)	Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland	▲ The study was performed in Switzerland. ▲ 1 641 144 Swiss and foreign nationals born in Switzerland. ▲ Elevations: 259–1960 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.	▲ Living at higher altitude was associated with less CHD and less stroke mortality.
Ezzati et al[30] (2012)	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 2001–2005. ▲ 12.1 million death records. ▲ Elevations: 500–1000 m, 1000–1500 m, >1500 m. ▲ The study was performed in the USA.	Inspect the relationship of life expectancy and mortality in particular diseases in relation to altitude.	▲ Ecological study of the association of mean county altitude with life expectancy and mortality from IHD, stroke, COPD and cancer.	▲ Counties above 1500 m had longer life expectancies than those within 100 m of sea level by 1.2–3.6 years for men and 0.5–2.5 years for women.

Continued

Table 2 Continued

Author (year)	Title	Sample, setting and elevation	Aim	Design, type and length of exposure	Main findings
Dhiman et al[31] (2018)	The evolving pattern and outcome of stroke at moderate altitude	▲ The study was performed in India. ▲ Men and women with an average age of 62 years in sub-Himalayan region of India. ▲ 235 patients with stroke were consecutively admitted into a tertiary hospital. ▲ Elevation: 2000 m.	The aim was to compare the clinical profile, risk factors and outcome in hospitalised patients who had a 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 to the current study.	▲ Ischaemic stroke was noted in 74%, and 26% had haemorrhagic stroke (HS). ▲ Men accounted for 58% of the cases and women for 42%. ▲ Overall HS had poorer outcome. ▲ The occurrence of stroke has decreased among hospitalised patients at moderate altitude.
Khattar et al[32] (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: 3048 m.	Investigate the characteristics and treatment outcomes of patients who suffered from CVT at high altitude in eastern Nepal.	▲ Retrospectively reviewed all patients presenting with clinical and radiographic evidence of cerebral venous sinus thrombosis treated.	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.
Lu et al[33] (2020)	Characteristics of acute ischemic stroke in hospitalized patients in Tibet: a retrospective comparative study	▲ The study was performed in Tibet and Beijing. ▲ 236 and 1021 inpatients with acute ischemic stroke from People's Hospital of Tibet Autonomous Region and Peking University First Hospital. ▲ Elevations: 40 and 3650 m above sea level.	This study aimed to analyse the clinical characteristics of patients with AIS at high-altitude regions through a hospital-based comparative study between Tibet and Beijing.	▲ Hospital-based comparative study.	▲ In Tibet, patients with AIS were relatively younger, and anterior circulation infarctions were more common. ▲ Young adult stroke, erythrocytosis and hyperhomocysteinaemia were more frequent among the patients from the People's Hospital of the Tibet Autonomous Region (PHOTAR).
Burtscher et al[34] (2021)	Does living at moderate altitudes in Austria affect mortality rates of various causes? An ecological study	▲ The study was performed in Austria. ▲ 467834 deaths. ▲ Elevations: <251 m, 251–500 m, 501–750 m, 751–1000 m, 1001–2000 m.	This study tested the hypothesis that living at moderate altitudes (up to 2000m) is associated with reduced mortality from all causes.	An ecological study.	▲ The Autonomous Sensory Meridian Response (ASMR) neurological evaluation for residents living in higher (>1000m) versus lower (<251 m) altitude regions (with agriculture employment below 3%) were 485.8 vs 597.0 (rate ratio 0.81, 95% CI 0.72 to 0.92; p<0.001) for men and 284.6 vs 365.5 (rate ratio 0.78, 95% CI 0.66 to 0.91; p=0.002) for women.
Ortiz-Prado et al[35] (2021)	Stroke-related mortality at different altitudes: a 17-year nationwide population-based analysis from Ecuador	▲ The study was performed in Ecuador. ▲ A total of 38 201 deaths and 75 893 hospital admissions due to stroke. ▲ Elevations: low altitude (<1500m), moderate altitude (1500–2500m), high altitude (2500–3500m), very high altitude (3500–5500m).	Elucidate the association between stroke and altitude using four different elevation ranges.	▲ An ecological analysis of all stroke hospital admissions, mortality rates and disability-adjusted life-years in Ecuador was performed from 2001 to 2017.	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, 95% CI 0.88 to 0.95) and women (OR 0.83, 95% CI 0.79 to 0.86).

Continued

Peru; nevertheless, the study focused on the association between risk factors and stroke and not in the relationship with elevation.[28] In this study, the author discusses cerebrovascular events in people living above 2500 m but does not analyse the role of hypoxia as a triggering or protective factor. We came to this work because it was conducted at high altitudes and had stroke as an outcome; nevertheless, no comments about hypoxia were given in this study.

Study 4: In 1995, Jaillard *et al* published one of the most cited stroke documents at high altitude. A document from Peru described the results from a 'door to door' survey in Cuzco, a city located at 3380 m above sea level. In this study, men and women over 15 years of age were included and classified as 97% mestizos, 1.3% white, 1.1% Quechua and 0.1% Aymara, and 0.2% were from other racial groups. They reported a crude prevalence rate of 6.47 per 1000 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.[20]

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 who came from lower altitudes (<3000 m) and higher altitudes (>3000 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 (9 months on average). The hospital admission rate at high altitude was reported to be 12 times greater (12.8/1000) than at lower altitudes (1.0/1000), this result being statistically significant.[14]

Study 6: In 2003, Niaz and Nayyar conducted a case–control study to describe the prevalence of stroke above 4571 m in India. They included 4000 soldiers (20–40 years old) 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 standardisation of the sample was provided, the researchers concluded that living at elevations above 4500 m was associated with 10 times more risk of developing stroke. The authors concluded that chronic (>28 days) hypobaric hypoxia exposure is associated with a higher risk of developing stroke, with massive ischaemic stroke being the most frequent presentation.[15]

Study 7: In 2004, Mahajan *et al* conducted a cross-sectional study in Himachal Pradesh, India, and among 100 patients between men and women some had risk factors such as hypertension or smoked from urban and rural areas hospitalised in a tertiary-level hospital located at an altitude of 2200 m. They reported that the incidence of stroke was lower when compared with previously published studies from India. Although

Table 2 Continued

Author (year)	Title	Sample, setting and elevation	Aim	Design, type and length of exposure	Main findings
Liu *et al*[36] (2021)	Acute ischemic stroke at high altitudes in China: early onset and severe manifestations	▲ The study was performed in China. ▲ 892 cases of first-ever acute ischemic strokes at altitudes of 20, 2550 and 4200 m in China (697 cases from Penglai, 122 cases from Huzhu and 73 cases from Yushu).	Describe and investigate the characteristics of acute ischemic stroke at different altitudes in China.	Ecological study.	▲ Ischaemic strokes at high altitudes were characterised by younger ages (69.14±11.10 vs 64.44±11.50 vs 64.45±14.03, p<0.001) and larger infarct volumes (8436.37±296 150.07 mm³ vs 17 213.16±470 440.74 mm³ vs 42 459±845 290.83 mm³, p<0.001).

AIS, acute ischemic stroke; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; CVT, cerebral venous thrombosis; IHD, ischaemic heart disease.

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.[21] They reported that mortality from stroke decreased at 12% per 1000 m gained in elevation. The effect of altitude on the cardiovascular and cerebrovascular diseases 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 259–1960 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.[21]

Study 9: An ecological study presented by Ezzati *et al* in 2012 was used in the National Elevation Dataset, National Centre for Health Statistics and US Census. The authors analysed the crude association of mean county altitude with life expectancy and mortality from ischaemic heart disease (IHD), stroke, chronic obstructive pulmonary disease and cancers. Living at higher altitudes showed a beneficial association with IHD mortality, but the results were not statistically significant for stroke.[30]

Study 10: A prospectively collected study in India published by Dhiman *et al*[31] reported the evolving pattern and outcome of stroke at moderate altitude. This prospective, observational study was carried out at 2000 m above sea level and included the clinical features and risk factor profile of 235 patients diagnosed with a stroke between men and women with an average age of 62 years. 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 hospitalised patients compared with the 2004 report.[29 31]

Study 11: An ecological study design in Nepal published by Khattar *et al* in 2019 demonstrated that ischaemic stroke is most likely to occur at elevations above 3000 m, and although this diagnosis is not technically considered as stroke, the physiopathology of it might indicate some relationship with the development of ischaemic cerebrovascular events, despite some of these findings that targeted high altitude as a possible risk factor for developing stroke in 2009[32] (table 2). The study included 21 patients with stroke, 76% were men with a mean average age of 56 years, medical comorbidities included hypertension and diabetes was reported.

Study 12: A hospital-based comparative study in Tibet and Beijing with 236 and 1021 patients, respectively, with acute ischaemic stroke published by Lu *et al* in 2020 demonstrated that patients diagnosed with acute ischaemic stroke located at 3650 m (Tibet) above sea level were younger than those who lived at 40 m (Beijing) above sea level (p<0.001); also, in Tibet, there was a higher proportion of cerebrovascular accidents in young adults, which may be associated with erythrocytosis.[33]

Study 13: An ecological study published by Burtscher *et al* in 2021 carried out in Austria demonstrated that mortality for all causes including stroke decreases as height increases, demonstrating a linear association; the mortality rate was lower around 15%–20% in those who live at altitudes ranging from 1000 to 2000 m. It is important to note that the causes of death most affected by height are cardiovascular diseases and cancer, since at higher altitudes people have a lower mortality rate from these diseases.[34]

Study 14: An ecological analysis of all stroke hospital admissions, mortality rates and disability-adjusted life-years in Ecuador published by Ortiz-Prado *et al* in 2021 demonstrated that high-altitude populations had lower stroke mortality in men (OR 0.91, 95% CI 0.88 to 0.95) and women (OR 0.83, 95% CI 0.79 to 0.86) and had a significant lower risk of getting admitted to the hospital when compared with the low-altitude group in men (OR 0.55, 95% CI 0.54 to 0.56) and women (OR 0.65, 95% CI 0.64 to 0.66).[35]

Study 15: An ecological study carried out in China published by Liu *et al* demonstrated that ischaemic strokes at high altitudes were characterised by younger ages and larger infarct volumes; also risk factors such as atherosclerosis, diabetes mellitus, coronary heart disease and hyperlipidaemia were significantly lower than those in high-altitude areas.[36]

DISCUSSION

The results from this review suggest that stroke seems to be more likely to occur in very high-altitude locations (>3500 m) when the exposure is longer than 28 days, especially among younger people (<45 years old). On the other hand, when people live above 1500 m and below 3500 m, it 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 with lower altitudes; nevertheless, no information is available about the exact point in which this protective effect becomes 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.[37] For instance, Imray *et al* in 2011 used a classification of high-altitude exposure according to the recommendations from the International Society of Mountain Medicine, a categorisation that seems to be the most pragmatic.[38] The authors defined low altitude as everything located below 1500 m, moderate or intermediate altitude between 1500 and 2500 m, high altitude from 2500 to 3500 m, the very high altitude from 3500 to 5800 m, extremely high altitude more than 5800 m and death zone above 8000 m.[38]

As humans acclimatise 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 polycythaemia, augmented pulmonary arterial pressure and, sometimes,
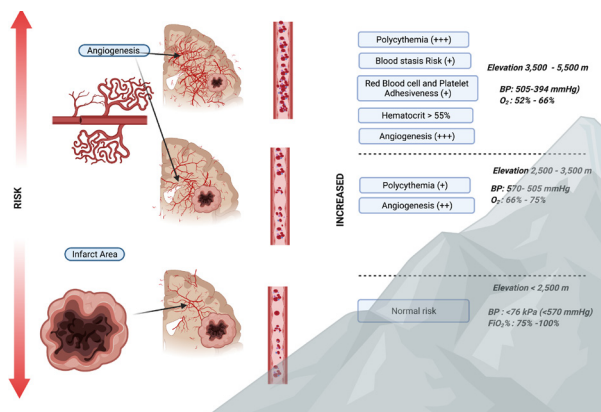
Figure 2 Proposed mechanisms and hypothesised physiopathology at low altitude (<2500 m), high altitude (2500–3500 m) and very high altitude (>3500 m). O_2 is the oxygen availability in relationship to sea level. FiO_2: angiogenesis occurs at different elevations above sea level but during the hypoxic beneficial window, polycythaemia and red cell as well as platelet adhesiveness are not significant as above 3500 m, thus the protective effect reaches its maximum. Above 3500 m, although angiogenesis is present, the significantly high haematocrit and polycythaemia increase the risk of blood stasis and thrombogenesis. BP, barometric pressure.

they are linked to a proposed hypercoagulation unbalance.[22 24]

These consequences might be increasing the risk of forming an atherothrombotic plaque resulting in a stroke or myocardial infarction or venous thrombotic events, resulting in DVT or pulmonary embolism.[39–41] Although information about the time of exposure is scarce, the longer the exposure, the higher the risk.[21 42]

Acute exposure to hypobaric hypoxia produces several compensatory physiological effects that can last for hours, days, months or years. The essential mechanisms are: increasing the heart and respiratory rates, a secondary polycythaemia, haemoconcentration derived from reduced plasma volume caused by respiratory evaporative water loss and polyuria and increased ventilatory response.[37 43 44] When acute exposure lasts longer than 28 days, more efficient and prolonged mechanisms take place, including sustained polycythaemia, endothelium changes, reduced vascular resistance, nitric oxide-mediated hypotension and angiogenesis.[45–48] Acute exposure to high-altitude hypoxia triggers a series of events that produce a hypercoagulable state.[24] This hypercoagulable state is boosted by dehydration, haemoconcentration and polycythaemia. When combined with dehydration (due to tachyphemia and extenuating physical activity) and limited mobilisation (sleeping in tents and secluded spaces), these factors produce the perfect scenario for increasing vascular stasis and thrombosis.[22 37 49]

When humans are exposed continuously to hypoxia, they develop adaptive mechanisms that are far more efficient than those observed in newcomers.[50–53] These long-lasting 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).[52 54–56] 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[57–60] (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 2000–3500 m of elevation might be enough to generate some protective mechanisms (ie, angiogenesis or vascular remodelling) against stroke.[21 45 48]

In elevations below 2000 m, the degree of compensation might not be enough to ensure a protective effect, while at above 3500 m, the adaptive compensatory mechanisms such as significant polycythaemia and vascular stasis might increase the risk of thrombosis and, therefore, the risk of developing stroke[14 22 32] (figure 2).

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 lack of data 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

This review suggests that the most robust studies tend to advocate that prolonged living at higher altitudes reduces the risk of developing stroke or dying from it. 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, residing at high-altitude locations, especially above 3500 m, is associated with an apparent increased risk, probably linked to 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 exposed to very high altitudes. It seems clear that short-term exposures to very high altitudes are a risk factor for developing a stroke. The available scientific literature suggests that above 3500–4000 m, the risk of developing stroke increases, especially if the exposure is acute among non-adapted populations.

It is important to note that one of the main limitations presented by some of the studies analysed was the lack of analysis of risk factors related to stroke; in addition, the level of education, socioeconomic level or living conditions of the participants were not analysed. We also highlight that certain risk factors such as diabetes, arteriosclerosis, coronary heart disease or hyperlipidaemia have a lower prevalence in people living in high-altitude areas

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.

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