Prevalence and risk factors of stroke in high-altitude areas: a systematic review and meta-analysis

Bo Zheng,1 Yuding Luo,1,2 Yan Li,1 Gangfeng Gu,1 Junyao Jiang,1 Chuanli Chen,1 Zhao Chen,1 Jian Wang 1

ABSTRACT

Objective The primary objective of this study is to investigate the prevalence and risk factors of stroke in high-altitude areas through a comprehensive systematic review and meta-analysis.

Design This study adopts a systematic review and meta-analysis design.

Data sources A thorough search was conducted on databases including PubMed, Web of Science, Embase, Cochrane Library, MEDLINE and SCOPUS, covering the period up to June 2023.

Eligibility criteria Studies reporting the prevalence of stroke in high-altitude areas and exploring related risk factors were included, regardless of whether they involved clinical samples or the general population. Studies with incomplete, outdated or duplicate data were excluded.

Data extraction and synthesis We performed eligibility screening, data extraction and quality evaluation of the retrieved articles. Meta-analysis was employed to estimate the prevalence and risk factors of stroke in high-altitude areas. The Newcastle-Ottawa Scale was used to assess the risk of bias.

Results A total of 17 studies encompassing 8566042 participants from four continents were included, with altitudes ranging from 1500 m to nearly 5000 m. The pooled prevalence of stroke in high-altitude areas was found to be 0.5% (95% CI 0.3%–7%). Notably, the prevalence was higher in clinical samples (1.2%; 0.4%–2.5%) compared with the general population (0.3%; 95% CI 0.1%–0.6%). When considering geographic regions, the aggregated data indicated that stroke prevalence in the Eurasia plate was 0.3% (0.2%–0.4%), while in the American region, it was 0.8% (0.4%–1.3%). Age (OR, 14.891), gender (OR, 1.289), hypertension (OR, 3.158) and obesity (OR, 1.502) were identified as significant risk factors for stroke in high-altitude areas.

Conclusions The findings of this study provide insights into the pooled prevalence of stroke in high-altitude areas, highlighting variations based on geographic regions and sampling type. Moreover, age, gender, hypertension and obesity were found to be associated with the occurrence of stroke.

STRENGTHS AND LIMITATIONS OF THIS STUDY

This study represents the first meta-analysis to estimate the prevalence of stroke in high-altitude areas. By consolidating and analysing existing research, it provides a valuable contribution to the field.

This study encompasses studies conducted in diverse locations and includes various sample types. By incorporating a wide range of data, it enhances the generalisability and applicability of the findings.

The study considers relevant risk factors associated with stroke in high-altitude areas. By considering these factors, it adds depth to the analysis and provides a more comprehensive understanding of the topic.

A notable limitation of this study is the presence of significant heterogeneity among the included articles. This variability may introduce uncertainties and impact the reliability of the conclusions drawn. It is important to interpret the findings with caution considering this potential limitation.

INTRODUCTION

Stroke, also known as cerebral stroke or cerebrovascular accident (CVA), is an acute cerebrovascular disease characterised by a vascular cause that leads to a neurological deficit and focal brain injury in the central nervous system. The vascular causes of stroke include cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage.1 In 2019, stroke was identified as the second-leading cause of death and the third-leading cause of death and disability combined.2 Epidemiological data suggest that more than 16 million individuals experience a stroke or CVA annually. Among different types of cerebrovascular disorders, cerebral infarction accounts for 48.4%, cerebral haemorrhage for 37.2%, subarachnoid haemorrhage for 9.8% and cerebral embolism for 4.6%. It has been observed that individuals residing in high-altitude areas have a higher prevalence of various cerebrovascular disorders, with ischaemic cerebrovascular diseases being the most common.3

Previous studies have reported a significantly increased risk of cerebrovascular
disease among people living above 4500 m above sea level compared with those in lower-lying areas, with a tenfold increase in risk.\(^4\)\(^5\) Prolonged stays in high-altitude areas contribute to thrombosis risk due to hypoxia-induced polycythaemia, which triggers an imbalance in hypercoagulation and can result in atherothrombotic stroke.\(^6\)\(^7\) Additionally, the low oxygen concentrations in high-altitude environments can cause hypoxic injury to the cerebral vascular wall, leading to cerebral vasodilation, increased blood volume, irregularities in cerebral circulation and ultimately, stroke occurrence.\(^8\) However, comprehensive studies reporting the prevalence of stroke in high-altitude areas are limited.

The objective of this study is to estimate the overall prevalence of stroke in high-altitude areas, analyse subgroups contributing to prevalence variability, and identify risk factors associated with stroke occurrence.

**METHODS**

**Literature search strategy**

A comprehensive literature search was conducted using several databases, including PubMed, Web of Science, Embase, Cochrane Library, MEDLINE and SCOPUS. The search strategy employed a combination of relevant keywords such as “stroke” and “high altitude”, along with their synonyms and controlled language terms. Detailed information regarding the search strategy can be found in online supplemental table S1. In addition, the reference lists of retrieved articles were manually examined to identify any additional relevant publications. No language restrictions were applied during the search process.

**Study selection**

After removing duplicate studies, the titles and abstracts of articles were independently screened by two reviewers based on predefined inclusion and exclusion criteria. Full-text articles were obtained for further evaluation if at least one reviewer deemed the abstract eligible for inclusion. Each publication underwent a thorough assessment by both reviewers to determine its final inclusion in the study. Any disagreements between the reviewers were resolved through extensive discussion until a consensus was reached.

The inclusion criteria for this study were as follows: (1) studies reporting the prevalence of strokes in high-altitude areas; (2) studies investigating risk factors or not; (3) studies based on clinical samples or the general population. The exclusion criteria were as follows: (1) studies with incomplete data; (2) studies with outdated or duplicate data.
Data extraction

We conducted the literature search, and data were extracted from each article using a standardised form. The extracted data included information such as the first author, publication year, geographic region, sampling type, events, sample size, gender, diagnostic method, age, altitude and population characteristics. Altitude classification in the meta-analysis followed internationally accepted standards: 1500–3500 m as high altitude, 3500–5500 m as ultrahigh altitude and above 5500 m as extremely high altitude. Preliminary studies were cross-checked to ensure data consistency and eliminate discrepancies.

Assessment of risk of bias

The quality assessment of each included study was performed by two reviewers using the Newcastle-Ottawa Scale for observational cohort and cross-sectional studies. In cases of disagreement, a third researcher served as an arbitrator to resolve any disputes regarding the study's quality. The Newcastle-Ottawa Scale assigns a total value of 9 points to the assessment items, except for the comparability of cases and controls item, which receives a rating of 2 points. Compliance with the assessment items is scored as 1, while partially or non-compliant items receive a score of 0. Higher cumulative scores indicate lower research bias in the study.

Statistical analysis

To combine individual rates for analysis, a double inverse sine transformation was used. The heterogeneity of the trials was assessed using Cochrane's Q statistic, and the degree of variability was evaluated using the I² statistic. When significant heterogeneity was detected (I²>50%) by Cochrane’s Q statistic, pooled prevalence and 95% CIs were calculated using a random-effects model; otherwise, a fixed-effects model was employed. Sensitivity analysis was conducted to explore the potential sources of heterogeneity. Funnel plots and Egger tests were performed to assess the presence of bias in the meta-analysis results. In cases where bias was detected, the trim-and-fill method was applied to evaluate the stability and reliability of the results. Data analysis was performed using STATA software V.17.0 and Comprehensive Meta-Analysis software (V.3.0).

Figure 2  Forest plots of the prevalence of stroke at high altitude areas.
RESULTS

Study selection and characteristics

From the initial 5761 papers identified in the literature search, 4012 duplicates were removed. After screening the titles and abstracts, 692 papers were deemed ineligible. Following further evaluation and selection, a total of 17 papers4 10–25 that met the inclusion criteria were included in our quantitative synthesis (figure 1). The characteristics of the included studies can be seen in online supplemental table S2.

Assessment of bias risk

The bias risk of each included article was evaluated using the Newcastle-Ottawa Scale. The average score for each article was over 6 points, indicating overall fair quality. Only one article was assessed as being of poor quality, while the remaining 16 papers adhered to the standards for research of fair quality (online supplemental table S3).

Prevalence of stroke

In our meta-analysis, a total of 36582 stroke events from the included samples were analysed. The pooled stroke incidence was found to be 0.5% (0.3%–7%) (figure 2). The data exhibited significant statistical variability, with

<table>
<thead>
<tr>
<th>Table 1: Subgroup analyses</th>
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<tr>
<td>Group</td>
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<tr>
<td>High</td>
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<tr>
<td>Very high</td>
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<tr>
<td>Sampling type</td>
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<td>Clinical sample</td>
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<td>Diagnostic method</td>
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<td>Physician</td>
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<tr>
<td>Questionnaire</td>
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<td>Geographic location</td>
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<tr>
<td>Eurasia</td>
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<tr>
<td>America</td>
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Figure 3 Funnel plot of effect sizes for included studies.
Table 2  Risk factors of stroke prevalence in high altitude areas

<table>
<thead>
<tr>
<th>No.</th>
<th>Risk factor</th>
<th>Studies (n)</th>
<th>OR</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Older age</td>
<td>5</td>
<td>14.891</td>
<td>13.303</td>
<td>16.668</td>
<td>46.950</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>Female gender</td>
<td>7</td>
<td>1.289</td>
<td>1.263</td>
<td>1.316</td>
<td>24.122</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>Hypertension</td>
<td>2</td>
<td>3.158</td>
<td>2.729</td>
<td>3.654</td>
<td>15.444</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>Obesity</td>
<td>2</td>
<td>1.502</td>
<td>1.306</td>
<td>1.726</td>
<td>5.722</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

an I² statistic of 99.942%. Sensitivity analysis, excluding studies with a significant risk of bias, confirmed the reliability of the results (online supplemental figure S1).

Publication bias
Publication bias was assessed using a funnel plot and Egger’s test. The results from figure 3 and online supplemental figure S2 did not provide clear evidence of publication bias. However, it is important to note that the high heterogeneity observed should not be disregarded, despite the apparent symmetry of the funnel plot.

Subgroup analyses
Subgroup analyses were conducted to examine the impact of altitude, sampling type, diagnostic method and location on stroke prevalence (table 1). The pooled prevalence of stroke in clinical samples was higher at 1.2% (0.4%–2.5%) compared with the general population at 0.3% (95% CI 0.1%–0.6%). When considering geographic regions, the aggregated data indicated that stroke prevalence in the Eurasia plate region was 0.3% (0.2%–0.4%), while in the American region, it was 0.8% (0.4%–1.3%). However, no significant variations in prevalence were observed in the subgroups categorised by altitude or diagnostic method (online supplemental figures S3–S6).

Risk factors
Individuals above the age of 50 years had a significantly higher risk of stroke in high-altitude areas (OR, 14.891). Females exhibited a higher risk of stroke compared with males (OR, 1.289). The presence of hypertension and obesity was associated with 3.158-times and 1.502-times greater risk of stroke, respectively (table 2). Subgroup analysis of age and gender revealed prevalence differences based on altitude (online supplemental figures S7 and S8).

DISCUSSION
We conducted a pooled analysis of stroke prevalence in high-altitude areas using data from studies that included both clinical samples and the general population. Our analysis, based on 17 studies and a total of 36,582 stroke events, estimated an overall prevalence of 0.5% for stroke in high-altitude areas. We observed significant variations in prevalence across different sampling types and geographic locations among the included studies. Among the analysed risk factors, older age, female gender, hypertension and obesity were found to be associated with an increased risk of stroke occurrence.

The varying nature of the data collection, including both clinical data and population-based surveys, contributed to considerable variability in the estimates across studies. For instance, the prevalence of stroke was reported to be 4.06% in US dialysis patients residing in high-altitude areas,19 which was 200 times higher than the prevalence in the general population of the Chinese plateau (0.02%).22 Subgroup analysis based on sampling type revealed a fourfold higher prevalence in clinical samples, suggesting that individuals with underlying diseases are at a higher risk of stroke. Additionally, we observed a lower prevalence estimate in the Eurasia plate (0.3%), with only one study from Europe included.16 Out of the 12 studies, four reported a stroke prevalence of less than 0.2%, while all 5 studies from the American regions reported higher prevalence rates. We conducted further subgroup analyses based on altitude and diagnostic method to explore possible sources of heterogeneity but found no significant variation. Although some research suggests an increased risk of stroke with residence above 3500 m,2 our findings did not align with this trend. Extreme natural environments can have adverse effects on individuals; however, relevant dietary and lifestyle factors may offset these impacts. Notably, studies by Ortiz-Prado et al and Liu et al comparing stroke prevalence between high and very high altitudes found that high altitudes exhibited even higher prevalence rates than very high altitudes (0.72% vs 0.22%; 0.03% vs 0.02%),22 25

Globally, there were approximately 12.2 million new stroke cases and 101 million people living with stroke aftermath in 2019, resulting in an economic burden of US$861 million.2 26–28 Based on the global population of 7.7 billion in 2019, the stroke prevalence we observed in high-altitude areas exceeded the world average. The lower partial pressure of oxygen in high-altitude regions may play a significant role in inducing abnormal conditions such as loss of muscle mitochondrial density and intestinal barrier dysfunction, leading to the development of certain diseases, including hypertension and hyperlipidaemia, which increase the risk of stroke.29–31 It has been reported that elevated systolic blood pressure, poor diet and high body mass index are leading risk factors globally,32 partially aligning with the results observed in high-altitude areas. While our analysis focused on individual risk factors such as age, gender, hypertension and obesity, it is important to acknowledge that healthcare
and economic conditions can also impact stroke prevalence. It has been reported that 89% of stroke deaths and disability occur in low-income and middle-income countries, and up to 85% of all strokes can be prevented.\textsuperscript{33}–\textsuperscript{37} In addition, dietary factors may play a crucial role in stroke prevention, with increased consumption of fruits and vegetables, particularly citrus fruits and juices, as well as cruciferous and green leafy vegetables, showing strong protective effects.\textsuperscript{33,38}

To the best of our knowledge, this is the first systematic review and meta-analysis focusing on the prevalence of stroke and related risk factors in high-altitude areas. We also provided subtype prevalence based on altitude, sampling type, diagnostic method and geographic location. However, our study has several limitations. First, significant heterogeneity was observed across the included studies, with sampling type being a major contributing factor. Despite conducting subgroup analyses, the pooled prevalence within each subgroup remained heterogeneous. Second, the sample sizes varied greatly across continents, introducing potential sampling bias and affecting the generalisability of the results. Third, the limited research available from Europe, North America and Africa restricts the accessibility of global prevalence and the magnitude of stroke in high-altitude areas.

In conclusion, our meta-analysis revealed a higher prevalence of stroke in high-altitude regions, with variations observed among different sampling types and geographic locations. Older age, female gender, hypertension and obesity emerged as risk factors in populations residing in high-altitude areas. To reduce the occurrence of stroke in these areas, it is crucial for governments to enhance local medical and economic conditions and encourage individuals to prioritise self-healthcare.

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Contributors All authors had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. JW designed the study, YLuo, JJ, CC and ZC acquired the study data. GG and YLi analysed and interpreted the data. BZ wrote the first draft of the manuscript. All authors revised the manuscript and approved it for publication. JW is guarantor of the review.

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Patient consent for publication Not applicable.

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