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Population-based stroke incidence estimates in Peru: Exploratory results from the CRONICAS cohort study

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Summary

Background—Limited information exists about the incidence of first-ever stroke at the population level, particularly in low- and middle-income countries (LMIC). Longitudinal data from the CRONICAS Cohort Study includes both altitude and urbanization and allows a detailed assessment of stroke incidence in resource constrained settings. The aim of this study was to estimate the incidence and explore risk factors of first-ever stroke at the population level in Peru.

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Declaration of Competing Interests
No conflict of interest to declare.

Data sharing statement
Due to data restrictions, datasets used for the present analysis could be available from the corresponding author on reasonable request. Proposals may be submitted up to 36 months following article publication. Only individual participant data that underlie the results reported in this article, after de-identification will be available.

Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lana.2021.100083.

Methods—Stroke was defined using a standardised approach based on information from cohort participants or family members. This information was adjudicated centrally by trained physicians using common definitions. Time of follow-up was calculated as the difference between date of enrolment and the reported date of the stroke event. Unstandardised and age-standardised, first-ever stroke incidence rate and 95% confidence intervals (95% CI) were calculated. Generalized linear models, assuming Poisson distribution and link log, were utilized to determine potential factors to develop stroke.

Findings—3,601 individuals were originally enrolled in the cohort and 2,471 provided data for the longitudinal analysis. The median time of follow-up was 7.0 (range: 1 - 9) years, accruing a total of 17,308 person-years. During followup, there were 25 incident cases of stroke, resulting in an age-standardised incidence of stroke of 98.8 (95% CI: 63.8 – 154.0) per 100,000 person-years. After adjustment by age and sex, stroke incidence was higher among people with hypertension (incidence risk ratio (IRR) = 5.18; 95% CI: 1.89 – 14.16), but lower among people living at high altitude (IRR = 0.09; 95% CI: 0.01 – 0.63).

Interpretation—Our results indicate a high incidence of first-ever strokes in Peruvian general population. These results are consistent with the estimates found in previous LMIC reports. Our study also found a contributing role of hypertension, increasing the risk of having a first-ever stroke. This work further advances the field of stroke epidemiology by identifying high altitude as a factor related to lower incidence of stroke in a longitudinal study. However, this information needs to be considered with cautions because of the study limitations.

Abstract

This translation in Spanish was submitted by the authors and we reproduce it as supplied. It has not been peer reviewed. Our editorial processes have only been applied to the original abstract in English, which should serve as reference for this manuscript.

Existe información limitada sobre la incidencia del accidente cerebrovascular (ACV) a nivel poblacional, especialmente en los países de ingresos bajos y medios (PIBM). Los datos longitudinales del estudio de cohorte CRONICAS incluyen tanto la altitud como la urbanización y permiten una evaluación detallada de la incidencia de ACV en entornos con recursos limitados. El objetivo de este estudio fue estimar la incidencia y explorar los factores de riesgo del primer ACV a nivel poblacional en Perú.

El accidente cerebrovascular se definió utilizando un método estandarizado basado en la información de los participantes de la cohorte o de familiares. Esta información fue adjudicada centralmente por médicos entrenados usando definiciones estándar. El tiempo de seguimiento se calculó como la diferencia entre la fecha de enrolamiento y la fecha reportada del evento de ACV. Se calculó la tasa de incidencia del primer ACV no estandarizada y estandarizada por edad y los intervalos de confianza al 95% (IC 95%). Se utilizaron modelos lineales generalizados, asumiendo la distribución de Poisson y el link log, para determinar los factores potenciales para desarrollar un accidente cerebrovascular.

3.601 individuos se reclutaron originalmente en la cohorte y 2.471 proporcionaron datos para el análisis longitudinal. La mediana del tiempo de seguimiento fue de 7,0 (rango 1 - 9) años, haciendo un total de 17 308 personas-año. Durante el seguimiento, se produjeron 25 casos incidentes de ACV, lo que dio lugar a una incidencia estandarizada por edad de 98,8 (IC 95%:

63,8-154,0) por 100.000 personas-año. Tras el ajuste por edad y sexo, la incidencia de ACV fue mayor entre las personas con hipertensión (riesgo relativo (RR) = 5,18; IC 95%: 1,89 – 14,16), pero menor entre las que vivían a nivel de altura (RR = 0,09; 95% CI: 0,01 – 0,63).

Los resultados indican una alta incidencia de ACV en la población general. Estos resultados son consistentes con las estimaciones encontradas en informes anteriores de PIBM. En consonancia con la literatura publicada, nuestro estudio también encontró un papel contribuyente de la hipertensión, aumentando el riesgo de tener un primer ACV. Nuestro estudio supone un avance en el campo de la epidemiología del ACV al identificar la altitud como un factor relacionado con una menor incidencia en un estudio longitudinal. Sin embargo, esta información debe de tomarse con precaución debido a las limitaciones del estudio.

Keywords

Stroke; Incidence; Peru; Risk Factors; Hypertension

Introduction

Stroke imposes major societal and economical burdens and is a major cause of death and disability worldwide, with 87% of all stroke deaths occurring in low- and middle-income countries (LMIC).[1,2] Previous studies in LMIC have reported stroke incidence rates varying from 73 to 165 per 100,000 person-years, with rates of fatality due to stroke ranging between 18% and 35%;[3,4] but in general, such data are scarce and most reports include hospital-based or registry estimations.

According to the report of the Global Burden of Stroke, age-standardised stroke incidence cases in 2016 was between 90 and 150 per 100,000 cases in Latin America. Also, the Andean countries (Peru, Bolivia and Ecuador) since 1990 had a 54.9% reduction in stroke-related deaths, with a reduction in 20.5% incident cases and 57.1% in years of life lost.[5] A sub-analysis of the INTERSTROKE study including only Peruvian participants with a first-ever stroke,[6] found a mortality rate of 21% after one year.[7] As the world's population ages, including large numbers in LMIC, the probability of having stroke also increases.[8] Estimations of stroke incidence derived from population-based studies in LMIC are rare but needed to understand stroke burden.

Previous cross-sectional studies were conducted in high altitude population from Latin America,[9–11] and some of them reported that high altitude is a risk factor for ischemic stroke;[12,13] nevertheless, these were case-control or hospital-based studies and not longitudinal ones. In Peru, as in other countries, high altitude is associated with rural areas[14,15] and these areas have usually low prevalence of cardiovascular risk factors.[16] Due to this controversy, we plan to explore the association between incidence of stroke and high altitude using a cohort study conducted in settings with different altitude and degree of urbanization.

Therefore, this study aimed at estimating the incidence and explore the risk factors of first-ever stroke at the population level in Peru.

Materials and Methods

We followed the Standards of Reporting Neurological Disorders (STROND).[17]

Study design and setting

Longitudinal information of the CRONICAS Cohort Study was used. The CRONICAS Cohort Study is an ongoing prospective study conducted in four Peruvian sites with varying degrees of altitude and urbanization: Pampas de San Juan de Miraflores, in Lima, a highly-urbanized area located at the sea level; Puno, located at 3825 meters above sea level, contributed with two sites one urban and one rural; and Tumbes, a semiurban setting in the coastal North of Peru, also at sea level.[18] The study sites are resource-constrained settings as they are situated in low-income areas of Peru.

Study population and sampling

Subjects were selected using a single-stage random sampling procedure. Individuals aged ≥35 years, permanent residents in the study areas, were potentially eligible. At each site, a sex and age (35-44, 45-54, 55-64, and 65+ years) stratified sample was taken from the most updated census available. Only one subject per household was considered eligible and invited to the study. Further details about the sampling procedure are described elsewhere.[18]

Baseline and Follow-up assessment

Enrollment started in September 2010 and follow-up was conducted, on average, seven years after initial assessment (an additional follow-up was conducted in 2013). At baseline, a survey was conducted to collect socio-demographic, clinical and anthropometric information. During followup, events of interest (i.e., stroke) were recorded.

Variable definitions

The outcome was incidence of stroke. The events were collected using standardised case-reports forms from the participants or family members. This information was adjudicated centrally by trained physicians using common definitions as previously described.[19] A definite stroke case was defined as "*an acute focal neurological deficit diagnosed by a physician and thought to be of vascular origin (without other cause such as brain tumor) with signs and symptoms lasting ≥ 24 hours*", whereas a possible stroke case was defined as an "*event with a history of sudden onset of focal neurological deficit of one or more limbs, loss of vision or slurred speech lasting about 24 hours or more*". These definitions (definite and possible) and the approach for case adjudication were used to define the outcome in this study and they have been used by the PURE Study in previous reports.[19,20]

For this assessment, time of follow-up was calculated as the difference between date of enrollment and date of stroke when reported or date of last visit to confirm the absence of stroke (censoring date).

Other variables assessed at baseline as potential risk factors for stroke were sex, age (<45, 45-54, 55-64, and ≥65 years), education level (primary or less vs. secondary or more), socioeconomic status was assessed through a wealth index based on the possession of household resources and household facilities (like radio, types of television, refrigerator, between others),[21] and was divided into tertiles (low, middle and high socio–economic status), study site (urban, semiurban, and rural), altitude level (sea level/high altitude), smoking (never vs. ever), obesity (body mass index ≥30 kg/m^2), hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or previous physician diagnosis and current pharmacological treatment), and type 2 diabetes mellitus (fasting glucose ≥126 mg/dL or self-report of physician diagnosis and currently receiving anti-hyper-glycemic drugs).

Statistical analysis

Statistical analysis was conducted in STATA v14.0 for Windows (Stata Corp, College Station, TX, US). Population characteristics were tabulated. Unstandardised and age-standardised, using WHO world standard population, first-ever incidence rate of stroke per 100,000 person-years of follow-up and 95% confidence intervals (95% CI) were calculated excluding those who self-reported having stroke at baseline. Incidence rates were obtained by potential risk factors and study sites. Generalised linear models, assuming Poisson distribution and link log, were utilised to determine potential risk factors associated with stroke. Poisson regression models took into account follow-up length as this may differ by participant in the cohort. Crude and age- and sex-adjusted analyses were conducted to estimate the incidence risk ratio (IRR) and their 95% CI. Also, the attributable risk of hypertension for having a stroke was estimated from the adjusted model.

Ethics

Ethical approval for the study was obtained from the Institutional Review Board at Universidad Peruana Cayetano Heredia and Asociación Benéfica PRISMA, in Peru, and the Johns Hopkins University, in the US. Also, informed consent was obtained before starting cohort evaluation.

Role of the funding source: Funders had no role in study design, data collection, data analysis, interpretation, or writing of the report.

Results

A total of 3,601 individuals were originally enrolled in the cohort, but 2 (0.1%) were excluded because incomplete data related to stroke. In addition, a total of 16 (0.4%; 95% CI: 0.3% - 0.7%) individuals self-reported a previous episode of stroke at baseline, and were excluded from further analyses.

During the follow-up phase, 909 (24.8%) individuals were lost to follow-up and 203 (5.6%) died. Thus, only 2,471 records were further analysed. There were differences in age, educational level, study site and altitude between those included in the analyses and those lost to follow-up, however, no differences were observed in terms of hypertension and diabetes frequency (Supplementary Material 1). Participants at baseline had a mean age of 55.7 (SD ±12.7) years, and 1,841 (51.4%) were females. The characteristics of the study population are reported in Table 1. Median time of follow-up was 7.0 (range: 1 – 9) years, accruing a total of 17,308 years of follow-up.

A total of 25 incident cases of stroke were reported (12 definite and 13 possible), translating into a crude first-ever stroke incidence of 144.4 (95% CI: 97.6 – 213.8) per 100,000 person-years. When WHO standard population was used, age-standardized incidence of stroke was 98.8 (95% CI: 63.4–154.0) per 100,000 person-years. Also, age-standardized incidence of stroke by age and sex is available in Supplementary Material 2.

In an unadjusted model (Table 2 and Supplementary Material 3), stroke was positively associated with older age ($p<0.001$), primary or less education level ($p=0.005$), and hypertension ($p<0.001$), but was negatively associated with living at high altitude ($p=0.014$). After adjustment by age and sex (Table 2), the incidence risk rate of stroke in people with hypertension was 5.2 times higher compared to people without hypertension; whereas, high altitude was a protective factor in comparison to living at the sea level (IRR 0.09; 95% CI: 0.01 – 0.63). Based on the adjusted model, the population attributable risk of hypertension for having a first-ever stroke was 54.8%.

Discussion

Drawing from observations generated through a random sampling frame at baseline across a diversity of geographical sites, our results indicate a high incidence of first-ever strokes in the general population. Our results are consistent with the estimates found in previous LMIC reports.[4,22] In line with the reported literature, our study also found a contributing role of hypertension, increasing the risk of having a first-ever stroke.[6,23] Our study further advances the field of stroke epidemiology identifying high altitude as a factor related to lower incidence of stroke in a longitudinal study which, in contrast to other cross-sectional, case-control and hospital-based studies,[9–13] raises questions as to whether is the high altitude or the rural/urban context that drives this observation.

A report using the Global Burden Diseases Data Visualization of 2017 identified an age-adjusted incidence rates per 100,000 person-years of 104.8 (95% CI: 97.6 – 112.3) and a prevalence of 991.9 (95% CI: 941.6 – 1044.7) per 100,000 individuals in Latin America.[24] Also, a systematic review estimated that prevalence of stroke ranged from 0.2% to 0.7%, a similar magnitude as in our baseline evaluation despite of being self-reported.[25] Another systematic review reported a 42% reduction in stroke incidence in high-income countries in the last four decades, whereas this increases 100% in LMICs.[4] As a consequence, our standardized estimates are greater than those reported in Australia, United Kingdom and France, similar to those reported by Chile and Georgia, and lower to those reported by Japan and India.[4]

Hypertension is an important risk factor for stroke according to our bivariable model and this association was significant after adjusting by age and sex. The INTERSTROKE study reported that blood pressure levels ≥140/90 mm Hg was the most important of the modifiable risk factors for stroke.[26] In addition, this study estimated the attributable risk of hypertension for having a stroke in 48%, value that is slightly lower in comparison to our findings of 54.8%. Also, the INTERHEART study found that about 70% and 80% of strokes could be prevented by antihypertensive medication. This finding is important as in Peru as well as many other LMICs, the rate of hypertension awareness is close to 50%, and hence untreated individuals with hypertension are a group of concern.[27–29] As a result, it is possible that the number of cases with stroke may increase in the next years if strategies to diagnose and manage hypertension are not appropriately implemented.

An age ≥65 years was also found to increase the risk of stroke. It is described that the incidence of stroke double every ten-years since the age of 45[30] and this study found that incidence rate increased as age increased. Also, comorbidities are common in elderly, including hypertension and type 2 diabetes mellitus, two of the main factors of stroke. Regarding level of education, a previous report of Brazil found an inverse correlation between years of education and stroke incidence.[31] This report also found that more education level is associated with lower stroke incidence. Education level is a proxy of socioeconomic status, and it appeared to explain differences in stroke incidence among different districts in Brazil. Because of low levels of schooling in previous decades in Latin America countries, a greater age was associated with lower educational levels in our sample, and the association between education and stroke disappear after controlling by age and sex.

Additionally, a recent report used the socio-demographic index (a compilation of factors that included education, lagged distributed income and total fertility rate) to group countries and they showed that age-standardized incidence declined from 1990 to 2016 globally in 8%, in all country groups except in the middle group.[5]

High altitude in our study sample was a protective factor for stroke incidence. One explanation could be related to lower cardiovascular risk factors in high altitude in comparison to sea level,[32] e.g., in China, symptomatic carotid artery subjects from a high-altitude area have lower plaque burden and less calcification in the carotid artery compared to those from an area near sea level. In addition, authors reported that people that lives at different altitude levels may have differences in diet, environment and genetic inheritances in the country.[33] These findings were also found in the CRONICAS cohort and reported previously.[34] Additionally, half of the high-altitude population in our study sample live in rural areas where diet and physical activity patterns differs from the urban areas.[35,36] Besides, a cross sectional study from 1988 in the city of Cuzco, Peru at 3400 meters above sea level found that living in an urban vs. a rural area was a risk factor for stroke (odds ratio 4.3; 95% CI: 1.0 – 19.2).[11] However, our results are controversial in comparison to other studies, e.g., in Saudi Arabia in an age- and sex- matched case-control study of stroke cases, the frequency of thrombotic stroke at high altitude was 93.4% as compared to 79.3% at low altitude ($p<0.05$), whereas the proportions of other types of stroke were similar between the two settings. The population from high-altitude city had a higher odds ratio for hypertension (OR: 4.4, 95% CI: 1.6 - 10) in comparison to sea level (OR: 2.1, 95% CI: 1.9 – 3.9), even when the high-altitude city was a less dense city (48 inh/km^2) compared to the low altitude city, the capital of Saudi Arabia (2240 inh/km^2). Additionally, researchers showed the association of polycythaemia and stroke in the high altitude population.[12] Another case-control study from India found that the risk of stroke was 10 times greater at high altitude (4500 meters above sea level) in comparison to sea level in 4000 healthy male individuals in each setting from the military army during one year.[13]

Other factors related to the weather and environment such as temperature[37–39] and air pollution[40] could be related with stroke. Also, these factors differ in high altitude vs. sea level settings. However, the evidence is not clear and some controversy exists about the association of these factors and stroke.

Prevention of stroke is sorely needed in many LMICs where weak and fragmented healthcare systems, together with reduced resources, imposes major societal and familial burden as well as limited post-stroke care. The burden of stroke is heavy in terms of reduced quality of life, increase years of life lost, morbidity and mortality in the most vulnerable populations.[41]

This study has some limitations that merit discussion. First, the small number of events is a weakness that did not allow us to adjusted by time-varying variables; nevertheless, this is one of the few studies in Latin America contributing stroke-related findings with a population basis across a diversity of sites, thus extending the knowledge of the epidemiology of stroke in the region. It is also worth mentioning that despite small numbers, it was possible to adjust our models by some co-variables. Despite of using a standardized approach to detect cases of stroke, access to diagnosis may differ by study site. Thus, healthcare and diagnosis access may be more limited in rural Puno compared to highly-urbanized Lima, with the subsequent underestimation of stroke incidence. In addition, this study did not include transit ischemic acute attacks because they are classified under other denomination in the International Classification of Diseases. Also, other limitation is the high rate of lost to follow-up and deaths (31%) that could introduce bias in our study results, especially because lost to follow-up subjects was greater at high altitude in comparison to sea level (44.3% vs 21.9%, $p<0.001$ respectively). Additionally, the cause of death was unknown and some of them could be due to stroke. The exclusion of these records may underestimate the population-based incidence of stroke. Also, some additional differences between those participants that were included in the analysis and those that were not included were identified (Supplementary Material 1). Finally, we did not have a confirmatory imaging of stroke and we did not differentiate between haemorrhagic and ischemic stroke.

In summary, our results show that the rate of first-ever stroke were high compared to high-income countries but similar to that of other LMIC scenarios. Preventive efforts should emphasize subgroups of individuals with hypertension, elderly and people that live at sea level. These results are useful to expand the understanding of stroke epidemiology in LMIC and resource-constrained settings, and potentially guide allocation of resources for stroke prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Context

Evidence before this study

Population-based studies to determine the incidence of stroke and their related factors are scarce in low- and middle- income countries and the Latin America region. Most of the existing studies are from Brazil, and Peru did not have a formal evaluation of the stroke incidence.

Added value of this study

Drawing from observations generated through a random sampling frame at baseline across a diversity of geographical sites, our results indicate a high incidence of first-ever strokes in the general population. After adjustment by age and sex, stroke incidence was greater among those with hypertension, but the incidence was lower among people living at high altitude.

Implications of all the available evidence

Stroke is a public health problem in Peru and worldwide. Risk factors such as hypertension need to be managed in order to avoid first-ever strokes, and these actions have to be emphasised to promote an appropriate management of high blood pressure in Peru.

Table 1:

Characteristic of the study population at baseline

Variable	N (%)
Female sex	1,841 (51.4%)
Age (≥65 years)	892 (24.9%)
Education level (primary or less)	1,635 (45.7%)
Socioeconomic status	
Lowest	1,213 (33.9%)
Middle	1,181 (32.9%)
Highest	1,189 (33.2%)
Study site	
Urban	1,853 (51.7%)
Semiurban	1,030 (28.8%)
Rural	700 (19.5%)
Site altitude	
High altitude	1,462 (40.8%)
Risk factors	
Ever smoke	1,509 (42.2%)
Obesity	861 (26.8%)
Diagnosis of hypertension	635 (19.7%)
Diagnosis of diabetes mellitus	218 (7.0%)

Results may not add due to missing values.

Table 2:

Incidence of stroke by risk factors: crude and adjusted models

Variable	Incidence rates per 100,000 person-years*	IRR (95% CI)	Age- and sex-adjusted IRR (95% CI)
Sex			
Female	132.6 (75.3 – 233.4)	1	.
Male	157.7 (91.6 – 271.7)	1.19 (0.54 – 2.61)	.
Age			
< 45 years	24.6 (3.5 – 174.3)	1	.
45 – < 55 years	68.7 (22.2 – 213.1)	2.8 (0.29 – 26.9)	.
55 – 65 years	124.4 (55.9 – 276.9)	5.07 (0.61 – 42.1)	.
≥ 65 years	372.0 (224.3 – 617.1)	**15.16 (2.00 – 114.75)**	.
Education level			
Secondary or more	64.5 (28.9 – 143.6)	1	1
Primary or less	237.5 (151.5 – 372.3)	**3.68 (1.47 – 9.21)**	2.15 (0.81 – 5.68)
Socioeconomic status			
Lowest	110.7 (49.7 – 246.4)	1	1
Middle	116.9 (55.7 – 245.1)	1.06 (0.36 – 3.14)	1.25 (0.41 – 3.82)
Highest	203.5 (115.6 – 358.3)	1.84 (0.69 – 4.89)	2.36 (0.85 – 6.52)
Study site			
Urban	132 (73.6 – 239.8)	1	1
Semiurban	210.8 (122.4 – 363.1)	1.59 (0.71 – 3.54)	1.56 (0.69 – 3.47)
Rural	34.9 (4.9 – 248.3)	0.26 (0.03 – 2.04)	0.27 (0.03 – 2.12)
Site altitude			
Low altitude	209.1 (140.2 – 311.9)	1	1
High altitude	17.2 (2.4 – 121.8)	**0.08 (0.01 – 0.61)**	**0.09 (0.01 – 0.63)**
Smoking			
Never	141.4 (83.7 – 238.7)	1	1
Ever smoke	149.1 (82.6 – 269.2)	1.05 (0.48 – 2.32)	1.03 (0.42 – 2.51)
Obesity			
No	139.4 (85.4 – 227.5)	1	1
Yes	182.8 (91.4 – 365.6)	1.31 (0.56 – 3.06)	1.54 (0.65 – 3.62)

Variable	Incidence rates per 100,000 person-years*	IRR (95% CI)	Age- and sex-adjusted IRR (95% CI)
Diagnosis of hypertension			
No	62.6 (31.3 – 125.1)	1	1
Yes	508.4 (311.5 – 829.9)	**8.13 (3.48 – 18.96)**	**5.18 (1.89 – 14.16)**
Diagnosis of diabetes mellitus			
No	153.1 (100.8 – 232.5)	1	1
Yes	182.9 (45.8 – 731.6)	1.19 (0.28 – 5.08)	0.95 (0.22 – 3.97)

IRR = incidence risk ratio, 95% CI = 95% Confidence interval.

Socioeconomic status in tertiles, Obesity defined as body mass index ≥30 kg/m^2.

*WHO world standard population.