# Incidence, risk factors, prognosis, and health-related quality of life after stroke in a low-resource community in Chile (ÑANDU): a prospective population-based study

*Pablo M Lavados, Lorena Hoffmeister, Ana M Moraga, Angelica Vejar, Carolina Vidal, Constanza Gajardo, Bernardita Portales, Daniela San Martín, Eduardo Lopez, Alexis Rojo, Veronica V Olavarria, Juan Almeida, Alejandro M Brunser, Paula Muñoz Venturelli, Violeta Diaz, Arnold Hoppe, Claudio Sacks*

## Summary

**Background** Stroke is a leading cause of disability and death worldwide. The best estimates of local, national, and global burden of stroke are derived from prospective population-based studies. We aimed to investigate the incidence, risk factors, long-term prognosis, care, and quality of life after stroke in the Ñuble region of Chile.

**Methods** We did a prospective community-based study with use of multiple overlapping sources of hospitalised, ambulatory, and deceased cases. Standardised diagnostic criteria were used to identify and follow up all cases occurring in the resident population of the Ñuble region, Chile (in a low-income rural-urban population including predominantly people of Indigenous-European heritage), for 1 year. Participants were included if they had a clinical diagnosis of stroke confirmed according to the study criteria. All cases were adjudicated by vascular neurologists. Incidence rates of first-ever stroke were calculated from the population of Ñuble according to the 2017 national census.

**Findings** From April 1, 2015, to March 31, 2016, we ascertained 1103 stroke cases, of which 890 (80·7%) were first-ever incident cases. The mean age of patients with first-ever stroke was 70·3 years (SD 14·1) and 443 (49·8%) were women. A CT scan was obtained in 801 (90%) of 890 patients (mean time from symptom onset to scan of 13·4 h (SD 29·8). The incidence of first-ever stroke age-adjusted to the world population was 121·7 (95% CI 113·7–130·1) per 100 000. The age-adjusted incidence rates, per 100 000 inhabitants, by main pathological subtypes were as follows: ischaemic stroke (101·5 [95% CI 90·9–113·0]); intracerebral haemorrhage (17·9 [13·5–23·4]), and subarachnoid haemorrhage (4·2 [2·1–7·3]). The 30-day case-fatality rate was 24·6% (21·9–27·6). At 6 months after the stroke, 55·9% (432 of 773) of cases had died or were disabled, which increased to 61·0% (456 of 747) at 12 months. Health-related quality of life in survivors was low at 6 months, improving slightly at 12 months after the stroke.

**Interpretation** The incidence of stroke in this low-resource population was higher than our previous finding in northern Chile and within the mid-range of most population-based stroke studies. This result was due mainly to a higher incidence of ischaemic stroke, probably associated with increasing age and a high prevalence of cardiometabolic risk factors in the population studied. Our findings suggest that more should be done for the prevention and care of stroke in communities like the Ñuble population.

**Funding** The National Agency for Research and Development and the Technology-Health Research Fund, Clínica Alemana de Santiago, Boehringer Ingelheim, Bristol Meyers Squibb, The Herminda Martin Clinical Hospital of Chillán, Universidad Mayor, and Universidad de Concepción.



*Lancet Glob Health* 2021; 9: e340–51

Published Online January 7, 2021 https://doi.org/10.1016/S2214-109X(20)30470-8

**This online publication has been corrected. The corrected version first appeared at thelancet.com/lancetgh on April 14, 2021**

See **Comment** page e235

**Department of Neurology and Psychiatry, Clínica Alemana de Santiago** (P M Lavados MD, V V Olavarria MD, J Almeida MD, A M Brunser MD, P Muñoz Venturelli PhD, V Diaz MD, A Hoppe MD) **and Clinical Studies Centre and Bioethics Centre, Institute of Science and Medical Innovation** (B Portales ST, P Muñoz Venturelli), **Universidad del Desarrollo, Clínica Alemana, School of Medicine, Santiago, Chile; School of Public Health, Universidad Mayor, Santiago, Chile** (L Hoffmeister PhD, C Vidal MSc); **School of Public Health and School of Medicine, Universidad de Concepción, Concepción, Chile** (A M Moraga MD); **Herminda Martin Clinical Hospital of Chillán, Ñuble Health Service, Chillan, Chile** (A Vejar MD, C Gajardo RN, D San Martín RN, E Lopez MD, A Rojo MD); **Neurology Service, Hospital Padre Hurtado, Santiago, Chile** (J Almeida); **Department of Neurology, School of Medicine, Universidad de Valparaíso, Valparaíso, Chile** (C Sacks MD); **The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia** (P Muñoz Venturelli)

## Introduction

According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), stroke represented 9·1% of all deaths in Chile in 2017, being the second most common cause of overall and premature deaths in Chile in 2017. It also represented the third most common cause of deaths and disability combined in Chile in 2017.[1] This burden, measured as disability-adjusted life-years, has been decreasing consistently in the past few decades, even though the prevalence of vascular risk factors has remained stable or even increased (eg, obesity).[2,3]

As in most diseases, stroke burden is heterogeneous. This heterogeneity has been shown at national, regional, and continental levels.[2] We have previously described substantial regional variations in stroke burden in Chile. Stroke mortality and case-fatality rates are particularly high in the central-southern regions, and lower in the northern and southern regions.[4,5] The heterogeneity was investigated in an ecological study describing significant differences in the prevalence of poverty, sedentary lifestyles, obesity, and diabetes between regions.[6] Substantial variability in hospital stroke care has also been described in Chile, which could affect case-fatality rates.[7]

The best estimates of both incidence and outcomes come from population-based studies providing reliable data for evidence-based health-care policy.[8] Unfortunately,

Correspondence to:
Dr Pablo M Lavados, Department of Neurology and Psychiatry, Clínica Alemana de Santiago, Universidad del Desarrollo, Clínica Alemana, School of Medicine, Santiago 7650567, Chile
**plavados@alemana.cl**

## Research in context

### Evidence before this study

We searched PubMed and Google Scholar from database inception until July 31, 2020, for articles in any language on incidence, prognosis, and health-related quality of life after stroke at a population level with the search terms "stroke and epidemiology", "stroke and incidence", "population and stroke and incidence", "community and stroke and incidence", "intracerebral haemorrhage and incidence and population", "intracerebral haemorrhage and incidence and community", "subarachnoid haemorrhage and incidence and population", "subarachnoid haemorrhage and incidence and community", "stroke burden", "stroke and case fatality and population", stroke and case fatality and community", "stroke and risk factors and community", "stroke and risk factors and population", "stroke and prognosis and population", "stroke and prognosis and community", "stroke and quality of life and population", and "stroke and quality of life and community". Previous data for incidence and prognosis of total stroke at a population level in Chile were based on a single study done 20 years ago in a predominantly urban community in the northern desert coast region. Another incidence study from 15 years ago in a central valley of Chile investigated only subarachnoid haemorrhage. This paucity of repeated unbiased population-based studies meeting the ideal criteria not only in Chile but also in Latin America and many geographical regions in the world makes estimations of burden difficult and prone to bias. Regionally, only Brazil with an ongoing study in Joinville and the recently published study in Matao has provided measurements of population incidence in different time periods using similar methods.

### Added value of this study

This study adds prospective, unbiased, population-based information for stroke incidence, prognosis, and effects on health-related quality of life at 6 months and 12 months in an underserved mixed rural-urban population in Chile with a high vascular risk. Our previous similar study in Chile was from a smaller, wealthier, urban coastal population, which had a lower overall vascular risk. This study also adds more information on long-term prognosis as it extends follow-up from 6 months to 12 months. Data for health-related quality of life after stroke at a population level have only been collected in a few similar studies, mostly in high-income populations in Australia, Europe, New Zealand, and the USA. This information is valuable for the unbiased estimation of the global burden of stroke in Chile and globally.

### Implications of all the available evidence

Even though Chile has made substantial progress in stroke prevention and care legislation, our data suggest that more should be done or that this legislation needs more time to show effects in communities like the Ñuble population. Our data also specifically point to the absence of specific legislation in the identification and treatment of atrial fibrillation to prevent embolic strokes as denoted by the low use of oral anticoagulation.

few studies meet the standard or advanced criteria for ideal stroke incidence studies and in many cases, when available, they are outdated.[9] The only community incidence study of all stroke types in Chile (the PISCIS study in the northern coastal region of Iquique)[10] is from nearly two decades ago and in a predominantly urban area that had a lower vascular and cerebrovascular risk.

The Ñuble Cerebrovascular Attack Incidence and Death Community Surveillance Study (ÑANDU) is a community-based prospective study investigating incidence, risk factors, long-term prognosis, care, and quality of life after stroke in the central Ñuble region of Chile. We aimed to assess the incidence of first-ever and total stroke, previously known vascular risk factors, 30-day case-fatality rates, prognosis, and quality of life at 6 months and 12 months after stroke.

## Methods

### Study design and participants

This community-based prospective study (ÑANDU) was organised according to the WHO STEPwise approach to stroke surveillance expanded data collection. Accordingly, we prospectively ascertained all fatal and non-fatal strokes, hospital admissions, and community events, for 1 year.[11]

The region of Ñuble is in the central plains of Chile, which extend around 13 180 km² from the Pacific Ocean to the Andes. According to the 2017 National Census, the region had 483 521 inhabitants; 30·6% lived in rural areas.[12] This region is low income, with 16·1% living below the poverty line according to income compared with the national average of 8·6%.[13] As for most of the country, health care in the region is mainly provided by the public health system, 80% of the population being affiliated to this health system. At the time of this study, the regional public hospital system included one large 470 bed general hospital with continuous CT scan availability and a dedicated stroke unit; one medium-size 116 bed hospital with continuous CT scan availability and a preferred stroke unit; and five small community hospitals of less than 100 beds each. There were four community family health centres, two outpatient clinics, and six walk-in ambulatory-only emergency clinics. Additionally, one small private hospital of 46 beds with continuous CT and MRI was available. There were 517 doctors in the region, many of whom had afternoon private practices.

We prospectively screened multiple overlapping sources for possible stroke cases. We checked emergency consultations, hospital admissions, and discharge

diagnosis lists each day in each hospital in the region. Weekly checks were also done on discharge diagnosis lists from hospitals in the large nearby Concepción province in case any patients with a known residence in Ñuble had been admitted. Weekly checks were also done of intensive or intermediate care units, internal medicine, and other relevant medical wards, as well as outpatient clinics, CT scans, and carotid duplex orders in the two larger hospitals in the region (within a specified timeframe of days of weeks [hot pursuit]). Monthly checks of all hospital discharges in Ñuble during the study period were also done with use of the National Statistic Hospital Discharge Registry system to identify cases based on categories I60–I69 and G45 of the International Classification of Diseases (ICD), tenth revision (over a longer timeframe [cold pursuit]).

We also did weekly checks of all death certificates of residents in the Ñuble region through the national death registry to identify individuals who were not admitted to hospital. We included all ICD-10 I60 to I69 codes as primary diagnoses, and reviewed all other diagnoses in the death certificate, including all those with an incident stroke. We excluded cases who died because of a stroke occurring before the study period. We cross-checked all individuals who had a stroke and died with the national discharge registry database from 2010 to 2016 to ensure identification of first-ever strokes. We prevented double-counting by identifying cases with their national identification number in the screening log.

Patients were ascertained from April 1, 2015, to March 30, 2016. Follow-up continued until March 30, 2017, for the last patient identified. Because of the large size and geographical extension of the population studied, budget constraints only allowed us to perform the study for 12 months, with another 12 months' follow-up.

To ensure referral of all possible patients who had a stroke occurring during the study period, we sent letters and emails to local physicians, held meetings with private health centres, and together with the local health service organised a monthly stroke seminar held at the public general hospital (Herminda Martin Clinical Hospital of Chillán) from 2014 to 2016, open to primary care, emergency, inpatient, and ambulatory care personnel of the public health sector in the region, as well as the students and faculty of the universities who worked in the local health sector. This meeting was not mandatory, but all personnel and students could attend the meetings in their working hours.

A public stroke prevention and symptom recognition awareness campaign was also launched during the study period, including flyers, newspapers, and local television interviews and World Stroke Day activities in Chillán, the regional capital city. Social networks were used too, including a project webpage and a Facebook page, providing information about the study, a dedicated contact telephone number and email for referrals, and stroke care and prevention tips for physicians, health personnel, local authorities, and the general public. We also organised a stroke awareness and prevention programme with workers from one of the largest food industries in the region. Regular meetings with the hospital directors and local health authorities were held before and throughout the study period to inform them about the project and to organise the transfer of all local important administrative data regarding stroke cases. Similarly, we lectured about stroke epidemiology and care in local university meetings during the study period.

All cases identified as possible strokes were reviewed by the field investigator (AMM) and one of two trained study nurses (CG, DSM) and, if confirmed according to the study definitions, were contacted to obtain informed consent directly or from their next of kin. Study data were collected and managed using REDCap electronic data capture tools hosted at Universidad Mayor. Once consent was obtained, the study nurses extracted all the relevant medical and imaging information and registered it on an online electronic case report form in the RECap platform. Doubtful or difficult cases were discussed with one of the field neurologists (AV, AR, or EL).

In all consented cases, clinical data for the electronic case report form and imaging or imaging reports were subsequently centrally reviewed by one vascular neurologist (VVO, JA, AMB, PMV, VD, or PML), and adjudicated according to the study definitions. All identified but not confirmed cases and those centrally adjudicated as stroke mimics were reviewed again by three senior vascular neurologists (PML, AH, and CS). Severity of all ischaemic strokes according to the National Institutes of Health Stroke Scale score was retrospectively adjudicated on the basis of documented clinical history and physical examinations by one senior vascular neurologist (PML).[14,15] Severity of intracerebral haemorrhage, subarachnoid haemorrhage, cerebral sinus venous thrombosis, and undetermined stroke type is described according to the admission Glasgow Coma scale scores.

We extracted data for and recorded all relevant clinical, neuroradiological, radiological, cardiac, and laboratory tests, as well as management and outcomes that were recorded in the patient clinical notes. No tests or examinations were done beyond usual clinical practice. Causes of death were divided into neurological, infectious, cardiovascular, cancer, and other.

Stroke cases were defined as rapidly developing clinical signs of focal disturbance of cerebral or retinal function with no apparent cause other than that of vascular origin. Pathological and ischaemic clinical subtypes were defined according to standard definitions suggested by the American Heart Association and American Stroke Association as described in the appendix (p 3).

See Online for appendix

Vascular risk factors were defined as described in the appendix (p 4). Dependency was defined according to the modified Rankin scale score as described in the appendix (p 5). Health-related quality of life was assessed with the

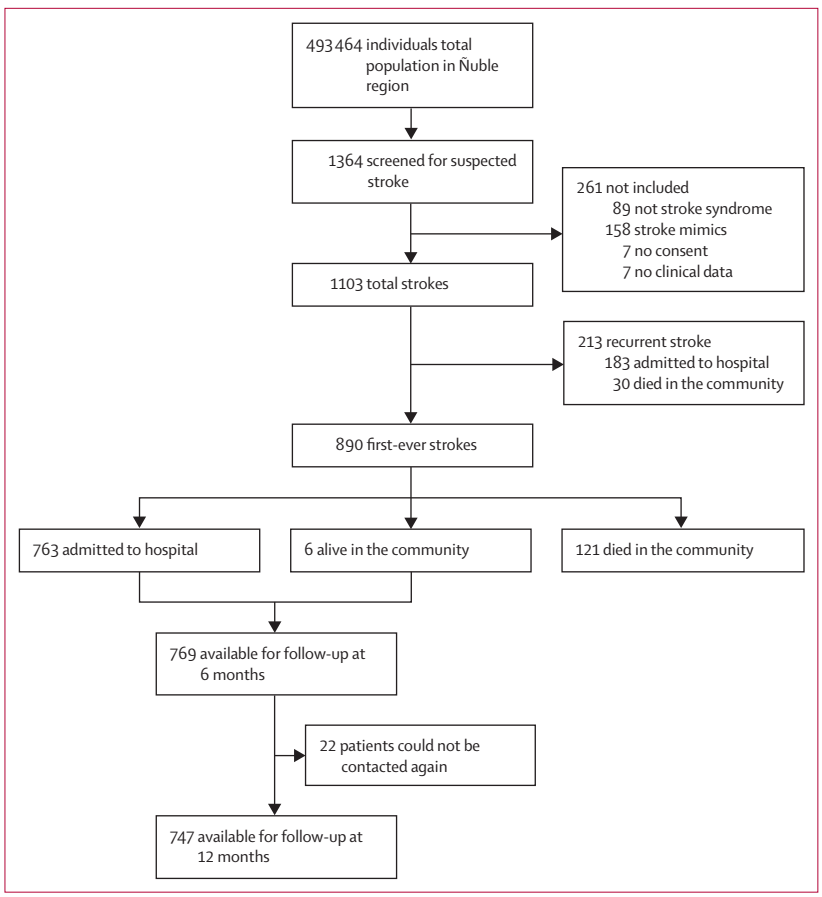


*Figure:* **Study profile**

EuroQoL Group 5-Dimension Self-Report Questionnaire, which has been shown to be valid after stroke, as described in the appendix (p 5).

Patients were followed up at 1, 6, and 12 months after the stroke by trained personnel who undertook a telephone interview with the patient, their next of kin, or caregiver with a standard questionnaire. This interview was requested in patients who were known to be alive. To ensure that we did not call patients who had died or their family members or caregivers, we checked death certificates weekly for all ascertained cases during the study period. Information about recovery, dependency, health-related quality of life, dwelling, secondary prevention medications, use of health-care and rehabilitation facilities, stroke recurrence, and cost was obtained in all followed-up cases.

The study was approved by the scientific ethics committee of the Universidad del Desarrollo, Clínica Alemana School of Medicine in Santiago, and the local scientific ethics committee of the Herminda Martin Clinical Hospital in Chillán, Ñuble region. According to the local ethics committee decision, written informed consent was obtained in all cases included in the analysis, except those identified through death certificates.

We calculated crude incidence rates using the 2017 national Census data projection for 2015. Incidence rates for first-ever strokes were age-adjusted to Chilean, European, and world populations by the direct method.

### Statistical analysis

We calculated 95% CIs for crude rates—adjusted and specific—for age and sex. Normality distribution was checked and, when appropriate, the Byar Poisson approximation method for small samples was used to calculate 95% CIs of age-specific and adjusted incidence rates.[16] Proportions were compared with the $\chi^2$ test or Fisher's exact test for proportions or student's $t$ test for continuous variables when appropriate. All tests were two-tailed and p values of 0·05 or less were considered statistically significant.

This study is reported according to the Standards of Reporting of Neurological Disorders guidelines.[17] We used SPSS, version 24.0 for statistical analysis.

### Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data reported in the study and the corresponding author had final responsibility for the decision to submit for publication.

## Results

During the study period from April 1, 2015, to March 31, 2016, 1364 patients were identified as having had a possible stroke. Of these, 261 (19·1%) were excluded by the field investigators, local neurologists, or the adjudication committee. The reasons for exclusion were an absence of appropriate clinical data to establish a clinical diagnosis in seven cases (six insufficient data and one early death), seven patients rejected the invitation to participate, 158 stroke mimics, and 89 cases in which the patient did not have stroke symptoms, but had been labelled as having had a stroke in administrative datasets (figure).

Of the 1103 total stroke cases, 890 (80·7%) were judged to have had a first-ever stroke, and 213 (19·3%) a recurrent stroke. Of the patients with a first-ever stroke, 763 (85·7%) were identified in a hospital setting, six (0·7%) were identified in private ambulatory clinics, and 121 (13·6%) were identified through the national death registry.

The mean age of patients with first-ever stroke was 70·3 years (SD 14·1) and 443 (49·8%) were women; women had a slightly older mean age than men (71·8 years [SD 14·6] *vs* 68·8 years [13·4]). Of all first-ever strokes, 289 (32%) of 890 occurred in patients younger than 65 years; 623 (70%) had 12 years or less of education and 272 (31%) were residents of rural areas (data not shown).

In 801 (90%) of 890 patients with first-ever stroke, a non-contrast brain CT scan was obtained in 567 (64%) patients

within 2 days, with a mean time from symptom onset to imaging of 13·4 h (SD 29·8). An MRI was obtained in ten (1%) patients and a lumbar puncture in just one (<1%) patient. No autopsies that resulted in a stroke diagnosis were done during the study period. All other cases for patients without a CT or MRI were labelled as undetermined stroke type. The main reason for not doing a CT scan were deaths due to stroke in the community or patients being too ill upon arrival to the emergency department of the two hospitals with CT scans available.

Of the 890 patients with first-ever stroke, we recorded 639 (72%) ischaemic strokes, 111 (12%) intracerebral haemorrhages, 47 (5%) subarachnoid haemorrhages, four (<1%) cerebral sinus venous thromboses, and 89 (10%) undetermined stroke types. The median National Institutes of Health Stroke Scale score for cerebral infarctions was 5 (IQR 3–11). The median Glasgow Coma scale values were 11 (IQR 7–15) for intracerebral haemorrhage, 14 (11–15) for subarachnoid haemorrhage, and 15 (10–15) for cerebral sinus venous thrombosis (data not shown).

The crude annual incidence of total stroke was 229·4 per 100 000 population (95% CI 210·7–249·4; appendix p 15). The crude annual incidence of first-ever stroke was 180·4 per 100 000 (168·7–192·6; table 1) and the crude annual incidence of recurrent stroke was 43·2 per 100 000 (37·4–49·0). The age-adjusted incidence rate to the Chilean population of 2017 for first-ever stroke was 163·4 (152·9–174·6), total stroke was 202·2 (190·4–214·5), and recurrent stroke was 38·7 per 100 000 (35·0–42·5; table 1, appendix p 15). The incidence of first-ever stroke was 121·7 per 100 000 (95% CI 113·7–130·1) when age-adjusted to the world population and 254·1 per 100 000 (237·4–271·7) when age-adjusted to the European population.

The age-specific and sex-specific first-ever incidence rates per pathological subtype are presented in table 2. Incidences increased progressively with each decade of life in all pathological subtypes. Men had higher overall incidence rates of ischaemic strokes, while women had higher rates of subarachnoid haemorrhage. In the case of intracerebral haemorrhage, the total incidences were similar but heterogeneous between sexes, being higher in young men and older women.

The overall 30-day case-fatality rate of first-ever stroke was 24·6% (95% CI 21·9–27·6; table 3). Intracerebral haemorrhage and subarachnoid haemorrhage had very high case-fatality rates, with roughly 50% of cases dying during the first month after symptom onset. The rates were higher in men than women, with slight differences according to pathological subtype, and increased substantially with age.

The frequency, incidence, severity, and prognosis of ischaemic stroke clinical syndromic subtypes according to the Oxfordshire Community Stroke Project classification are shown in the appendix (p 3). The most frequent were partial anterior circulation infarction (36%) and lacunar infarction (33%). Total anterior circulation infarctions had the highest severity and 30-day case-fatality rate, in which a third (30·8%) had died at 30 days.

The crude incidence of first-ever transient ischaemic attack was 7·2 (95% CI 5·2–9·9) per 100 000; being 5·5 (3·9–7·5) when age-adjusted to the world population and 11·5 (8·2–15·7) per 100 000 when age-adjusted to the European population.

| | Number of cases of number at risk | Incidence rate (95 % CI) |
|---|---|---|
| **Men** | | |
| 0–24 years | 2/87 343 | 2·3 (0·3–8·3) |
| 25–34 years | 5/32 056 | 15·6 (5·0–36·4) |
| 35–44 years | 13/31 788 | 40·9 (21·8–69·9) |
| 45–54 years | 53/34 460 | 153·8 (115·2–201·2) |
| 55–64 years | 92/26 973 | 341·1 (275·0–418·3) |
| 65–74 years | 128/17 055 | 750·5 (626·1–892·4) |
| 75–84 years | 108/8437 | 1280·1 (1050·0–1545·5) |
| ≥85 years | 46/2517 | 1827·6 (1337·9–2437·8) |
| All | 447/240 629 | 185·8 (168·9–203·8) |
| Age-adjusted (Chile*) | .. | 181·9 (165·3–199·6) |
| Age-adjusted (world†) | .. | 136·1 (123·6–149·4) |
| Age-adjusted (Europe‡) | .. | 280·2 (253·8–308·5) |
| **Women** | | |
| 0–24 years | 3/84 588 | 3·5 (0·0–10·4) |
| 25–34 years | 4/34 643 | 11·5 (3·1–29·6) |
| 35–44 years | 16/34 453 | 46·4 (26·5–75·4) |
| 45–54 years | 41/35 978 | 114·0 (81·8–154·6) |
| 55–64 years | 60/28 372 | 211·5 (161·4–272·2) |
| 65–74 years | 108/18 928 | 570·6 (468·0–688·9) |
| 75–84 years | 129/11 462 | 1125·5 (939·6–1337·3) |
| ≥85 years | 82/4411 | 1859·0 (1478·5–2307·5) |
| All | 443/252 835 | 175·2 (159·3–192·3) |
| Age-adjusted (Chile*) | .. | 146·8 (133·3–161·2) |
| Age-adjusted (world†) | .. | 108·7 (98·4–119·7) |
| Age-adjusted (Europe‡) | .. | 230·8 (209·7–253·6) |
| **Total population** | | |
| 0–24 years | 5/171 931 | 2·9 (0·0–5·5) |
| 25–34 years | 9/66 699 | 13·5 (4·7–22·3) |
| 35–44 years | 29/66 241 | 43·8 (27·8–58·7) |
| 45–54 years | 94/70 438 | 133·5 (106·5–160·4) |
| 55–64 years | 152/55 345 | 274·6 (231·0–318·3) |
| 65–74 years | 236/35 983 | 655·9 (572·2–739·5) |
| 75–84 years | 237/19 899 | 1191·0 (1039·4–1342·6) |
| ≥85 years | 128/6928 | 1847·6 (1527·5–2167·7) |
| All | 890/493 464 | 180·4 (168·7–192·6) |
| Age-adjusted (Chile*) | .. | 163·4 (152·9–174·6) |
| Age-adjusted (world†) | .. | 121·7 (113·7–130·1) |
| Age-adjusted (Europe‡) | .. | 254·1 (237·4–271·7) |

Data are n/N or incidence rate (95% CI). *Total population of Chile according to 2017 census. †WHO world population. ‡Segis' European population.

***Table 1:*** **Age-specific and sex-specific incidence rates per 100 000 population of first-ever stroke**

| | Ischaemic stroke | Intracerebral haemorrhage | Subarachnoid haemorrhage | Undetermined |
|---|---|---|---|---|
| **Men** | | | | |
| 0–24 years | 0, 0·0 (0·0–4·2) | 2, 2·3 (0·3–8·3) | 0, 0·0 (0·0–4·2) | 0, 0·0 (0·0–4·2) |
| 25–34 years | 2, 6·2 (0·7–22·5) | 2, 6·2 (0·7–22·5) | 1, 3·1 (0·0–17·4) | 0, 0·0 (0·0–11·4) |
| 35–44 years | 9, 28·3 (12·9–53·7) | 1, 3·1 (0·0–17·5) | 2, 6·3 (0·7–22·7) | 1, 3·1 (0·0–17·5) |
| 45–54 years | 34, 98·7 (68·3–137·9) | 12, 34·8 (18·0–60·8) | 4, 11·6 (3·1–29·7) | 2, 5·8 (0·7–21·0) |
| 55–64 years | 69, 255·8 (199·0–323·8) | 16, 59·3 (33·9–96·3) | 2, 7·4 (0·8–26·8) | 5, 18·5 (6·0–43·3) |
| 65–74 years | 102, 598·1 (487·6–726·0) | 15, 88·0 (49·2–145·1) | 1, 5·9 (0·1–32·6) | 10, 58·6 (28·1–107·8) |
| 75–84 years | 90, 1066·7 (857·7–1311·2) | 4, 47·4 (12·8–121·4) | 2, 23·7 (2·7–85·6) | 12, 142·2 (73·4–248·5) |
| ≥85 years | 30, 1191·9 (804·0–1701·6) | 4, 158·9 (42·8–406·9) | 0, 0·0 (0·0–145·7) | 12, 476·8 (246·1–832·9) |
| All | 336, 139·6 (125·1–155·4) | 56, 23·3 (17·6–30·2) | 12, 5·0 (2·6–8·7) | 42, 17·5 (12·6–23·6) |
| Age-adjusted (Chile*) | 136·0 (121·8–151·4) | 22·6 (17·0–29·4) | 4·9 (2·5–8·5) | 18·0 (13·0–24·4) |
| Age-adjusted (world†) | 101·5 (90·9–113·0) | 17·9 (13·5–23·4) | 4·2 (2·1–7·3) | 12·1 (8·7–16·4) |
| Age-adjusted (Europe‡) | 212·5 (189·6–237·3) | 30·4 (22·6–39·9) | 6·0 (3·0–10·6) | 30·9 (22·0–42·1) |
| **Women** | | | | |
| 0–24 years | 0, 0·0 (0·0–4·3) | 1, 1·2 (0·0–6·6) | 0, 0·0 (0·0–4·3) | 0, 0·0 (0·0–4·3) |
| 25–34 years | 2, 5·8 (0·6–20·8) | 0, 0·0 (0·0–10·6) | 2, 5·8 (0·6–20·8) | 0, 0·0 (0·0–10·6) |
| 35–44 years | 11, 31·9 (15·9–57·1) | 2, 5·8 (0·7–21·0) | 3, 8·7 (1·8–25·4) | 0, 0·0 (0·0–10·6) |
| 45–54 years | 27, 75·0 (49·4–109·2) | 7, 19·5 (7·8–40·1) | 6, 16·7 (6·1–36·3) | 1, 2·8 (0·0–15·5) |
| 55–64 years | 36, 126·9 (88·9–175·7) | 7, 24·7 (9·8–50·8) | 7, 24·7 (9·9–50·8) | 9, 31·7 (14·5–60·2) |
| 65–74 years | 80, 422·7 (335·1–526·0) | 13, 68·7 (36·5–117·5) | 8, 42·3 (18·2–83·3) | 7, 37·0 (14·8–76·2) |
| 75–84 years | 98, 855·0 (694·1–1042·0) | 14, 122·1 (66·7–204·9) | 6, 52·3 (19·1–113·9) | 11, 96·0 (47·8–171·7) |
| ≥85 years | 49, 1110·9 (821·7–1468·7) | 11, 249·4 (124·3–446·2) | 3, 68·0 (13·7–198·7) | 19, 430·7 (259·2–672·7) |
| All | 303, 119·8 (106·7–134·1) | 55, 21·8 (16·4–28·3) | 35, 13·8 (9·6–19·3) | 47, 18·6 (13·7–24·7) |
| Age-adjusted (Chile*) | 99·8 (88·8–111·8) | 18·3 (13·7–23·8) | 12·4 (8·6–17·3) | 15·0 (11·0–20·0) |
| Age-adjusted (world†) | 73·9 (65·5–83·0) | 13·6 (10·1–17·9) | 9·9 (6·8–13·9) | 9·9 (7·2–13·3) |
| Age-adjusted (Europe‡) | 159·3 (141·7–178·4) | 28·3 (21·3–37·0) | 16·9 (11·7–23·6) | 25·2 (18·5–33·6) |
| **Total population** | | | | |
| 0–24 years | 0, 0·0 (0·0–2·1) | 3, 1·7 (0·4–5·1) | 0, 0·0 (0·0–2·1) | 0, 0·0 (0·0–2·1) |
| 25–34 years | 4, 6·0 (1·6–15·4) | 2, 3·0 (0·3–10·8) | 3, 4·5 (0·9–13·1) | 0, 0·0 (0·0–5·5) |
| 35–44 years | 20, 30·2 (18·4–46·6) | 3, 4·5 (0·9–13·2) | 5, 7·5 (2·4–17·6) | 1, 1·5 (0·0–8·4) |
| 45–54 years | 61, 86·6 (66·2–111·2) | 19, 27·0 (16·2–42·1) | 10, 14·2 (6·8–26·1) | 3, 4·3 (0·9–12·4) |
| 55–64 years | 105, 189·7 (155·2–229·7) | 23, 41·6 (26·3–62·4) | 9, 16·3 (7·4–30·9) | 14, 25·3 (13·8–42·4) |
| 65–74 years | 182, 505·8 (435·0–584·9) | 28, 77·8 (51·7–112·5) | 9, 25·0 (11·4–47·5) | 17, 47·2 (27·5–75·6) |
| 75–84 years | 188, 944·8 (814·5–1089·9) | 18, 90·5 (53·6–143·0) | 8, 40·2 (17·3–79·2) | 23, 115·6 (73·2–173·4) |
| ≥85 years | 79, 1140·3 (902·8–1421·2) | 15, 216·5 (121·1–357·1) | 3, 43·3 (8·7–126·5) | 31, 447·5 (304·0–635·2) |
| All | 639, 129·5 (111·8–112·0) | 111, 22·5 (18·5–27·1) | 47, 9·5 (7·0–12·7) | 89, 18·0 (14·5–22·2) |
| Age-adjusted (Chile*) | 116·7 (107·8–126·2) | 20·7 (17·0–24·9) | 8·9 (6·6–11·9) | 16·3 (13·1–20·1) |
| Age-adjusted (world†) | 86·8 (80·1–94·0) | 15·9 (13·0–19·3) | 7·2 (5·3–9·7) | 10·9 (8·7–13·4) |
| Age-adjusted (Europe‡) | 183·8 (169·6–198·9) | 29·9 (24·5–36·2) | 12·0 (8·7–16·0) | 27·6 (22·1–34·1) |

Data are n, incidence rate (95% CI). Four cases with the diagnosis of cerebral venous sinus thrombosis are not included in the table. *Total population of Chile according to 2017 census. †WHO world population. ‡Segis' European population.

*Table 2:* **Incidence rates per 100 000 of first-ever pathological stroke type by age and sex**

The distribution of vascular risk factors and premorbid medication use in patients with first-ever stroke overall and by pathological subtype is shown in the appendix (p 8). Hypertension was the leading risk factor followed by diabetes, hypercholesterolaemia, and cardiopathies. Patients with ischaemic stroke had a higher prevalence of hypercholesterolaemia and cardiopathies, especially atrial fibrillation, which was present in 83 (13·5% [95% CI 11·0–16·4]) of 615 cases. Patients with intracerebral haemorrhage were more likely to be heavy drinkers and those with subarachnoid haemorrhage to be smokers, although these two risk factors are probably under-reported as is usually the case. The frequency of previous primary preventive medication use for vascular risk factors was low in this high-risk population. Antihypertensive and antiplatelet medications were the most frequently used, but less than a third of patients were taking them. Oral anticoagulation was only being used by

| | All strokes | Ischaemic stroke | Intracerebral haemorrhage | Subarachnoid haemorrhage | Undetermined |
|---|---|---|---|---|---|
| Sex | | | | | |
| Men | 110, 24·6% (20·7–28·9) | 43, 12·8% (9·6–16·8) | 37, 66·1% (52·8–77·2) | 5, 41·7% (18·4–69·3) | 25, 59·5% (44·2–73·2) |
| Women | 109, 24·7% (20·8–29·1) | 32, 10·6% (7·6–14·6) | 24, 43·6% (31·2–56·9) | 18, 51·4% (35·3–67·3) | 35, 74·5% (60·2–84·9) |
| Age, years | | | | | |
| 0–44 | 7, 17·1% (7·7–3·3) | 3, 12·5% (4·1–32·4) | 3, 37·5% (12·5–71·6) | 1, 12·5% (1·7–53·8) | 0 |
| 45–64 | 44, 18·0% (13–5–23–6) | 13, 7·8% (4·6–13·0) | 19, 45·2% (31·0–60·3) | 7, 36·8% (18·6–59·7) | 5, 29·4% (12·8–54·2) |
| 65–84 | 113, 23·9% (20·2–28–0) | 44, 11·9% (9·0–15·6) | 29, 63·0% (48·4–75·7) | 12, 70·6% (45·8–87·2) | 28, 70·0% (54·2–82·1) |
| ≥85 | 55, 42·9% (34·7–52·0) | 15, 19·0% (11·8–29·2) | 10, 66·7% (40·6–85·4) | 3, 100·0% | 27, 87·1% (70·2–95·1) |
| Total | 219, 24·6% (21·9–27·6) | 75, 11·7% (9·5–14·5) | 61, 55·0% (45·6–64·0) | 23, 48·9% (35·1–63·0) | 60, 67·4% (57·0–79·3) |

Data are number of deaths within 30 days, case-fatality rate (95% CI). Four cases with the diagnosis of cerebral venous sinus thrombosis are not included in the table.

***Table 3:*** **30-day case-fatality rates of first-ever stroke by sex, age group, and pathological subtypes**

| | mRS score 0–2 | mRS score 3–5 | mRS score 6 |
|---|---|---|---|
| Sex | | | |
| Men | 174/447 (39%); 34·5–43·5 | 64/447 (14%); 11·4–17·9 | 137/447 (31%); 26·5–35·1 |
| Women | 167/443 (38%); 33·3–42·3 | 101/443 (23%); 19·1–26·9 | 130/443 (29%); 25·3–33·8 |
| Age, years | | | |
| 0–44 | 29/43 (67%); 52·2–79·7 | 1/43 (2%); 0·3–14·8 | 7/43 (16%); 8·0–30·4 |
| 45–64 | 121/246 (49%); 43·0–55·4 | 36/246 (15%); 10·7–19·6 | 53/246 (22%); 16·8–27·1 |
| 65–84 | 176/473 (37%); 33·0–41·7 | 96/473 (20%); 16·9–24·2 | 139/473 (29%); 25·4–33·7 |
| ≥85 | 15/128 (12%); 7·2–18·5 | 32/128 (25%); 18·3–33·2 | 68/128 (53%); 44·5–61·6 |
| Pathological subtype* | | | |
| Ischaemic stroke | 282/639 (44%); 40·2–48·0 | 140/639 (22%); 18·8–25·4 | 94/639 (15%); 12·1–17·8 |
| Intracerebral haemorrhage | 26/111 (23%); 16·5–32·2 | 14/111 (13%); 7·6–20·2 | 66/111 (59%); 50·1–68·2 |
| Subarachnoid haemorrhage | 16/47 (34%); 32·2–65·1 | 4/47 (9%); 2·8–21·3 | 13/47 (28%); 16·1–42·9 |
| Undetermined | 16/89 (18%); 10·9–27·9 | 4/89 (4%); 3·2–20·6 | 24/89 (27%); 18·4–37·6 |
| Ischaemic stroke clinical subtype | | | |
| Total anterior circulation infarction | 7/91 (8%); 3·7–15·3 | 22/91 (24%); 16·5–34·0 | 49/91 (54%); 43·6–63·8 |
| Partial anterior circulation infarction | 106/230(46%); 39·7–52·6 | 67/230 (29%); 23·6–35·3 | 20/230 (9%); 5·7–13·1 |
| Lacunar infarction | 133/214 (62%); 55·5–68·4 | 37/214 (17%); 12·8–23·0 | 6/214 (3%); 1·3–6·1 |
| Posterior circulation infarction | 36/80 (45%); 34·5–56·0 | 13/80 (16%); 9·7–26·0 | 16/80 (20%); 12·6–30·2 |
| Undetermined | .. | .. | 24/24 (100%) |
| Total† | 341/890 (38%); 35·2–41·6 | 165/890 (19%); 16·1–21·2 | 267/890 (30%); 27·1–33·1 |

Data are n/N (%); 95% CI. mRS=modified Rankin Scale. 0=no symptoms at all. 1=no significant disability despite symptoms; able to carry out all usual duties and activities. 2=slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance. 3=moderate disability; requiring some help, but able to walk without assistance. 4=moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance. 5=severe disability; bedridden, incontinent, and requiring constant nursing care and attention. 6=dead. *Four cases with the diagnosis of cerebral venous sinus thrombosis are not included in the table. †Total includes 117 patients alive but lost to follow-up, which are not in the table, but described in the appendix (p 29).

***Table 4:*** **Prognosis at 6 months of first-ever stroke by sex, age group, and pathological and clinical subtype**

22 (35%) of 63 patients with known previous atrial fibrillation (appendix p 8).

Telephone follow-ups were completed for 769 (86%) of 890 patients with first-ever strokes at 6 months and 747 (84%) at 1 year. All those not followed up were considered to be alive at the time of the call as death certificates were checked concomitantly. The main reasons for loss to follow up were wrong telephone number or no answer to three calls. Patients not followed up were similar to those followed up, only differing significantly at 6 months in that those who were lost to follow-up were more likely to be men (appendix pp 29–30).

At 6 months after first-ever incident stroke, 19% (16·1–21·2) were dependent (modified Rankin Scale score 3–5) and 30% (27·1–33·1) had died (table 4). No significant differences were seen by sex, but the risk of death or dependency increased significantly with age. Patients with total anterior circulation infarctions had the worst overall prognosis, with 93·8% of patients having died or

become disabled at 6 months (modified Rankin Scale score 3–6), followed by patients with intracerebral haemorrhage of whom 66·4% had died or become disabled at 6 months (table 4). At 1 year, the probability of death increased slightly for all ages, both sexes, and all pathological and clinical subtypes (appendix p 9).

The causes of death at 30 days, 6 months, and 12 months are shown in the appendix (p 10). Most deaths (75%) occurred during the first month, of which 83% were considered to be due to direct neurological complications of stroke. At 6 months and 12 months, most were due to complications of immobility (ie, sequelae of cerebrovascular disease, pneumonia, infections, and respiratory diseases) followed by cardiovascular deaths (appendix p 10).

Patient-reported outcomes according to the EuroQoL Group 5-Dimension Self-Report Questionnaire at 6 months and 12 months are shown in the appendix (pp 11–14). At 6 months, the overall health utility score was low, and lower in women than men, decreasing significantly with age. It was also lower in patients who had intracerebral haemorrhages and total anterior circulation infarctions. The highest prevalence of problems was for the dimension of pain or discomfort (66·4% [95% CI 62·2–70·4]). The same pattern was observed at 12 months of follow-up, with a mean increase in total utility from 0·46 (SD 0·41) to 0·54 (0·42; appendix pp 13–14).

## Discussion

In this study, we report that the incidence rate of first-ever stroke was higher in Ñuble than our previous finding in Iquique,[10] and those of recent population-based incidence studies in Latin America in Tandil, Argentina[18] and Matao, Brazil,[19] being similar to those studies with intermediate incidences.[20] The incidence rate of 163·4 (95% CI 152·9–174·6) was also higher than the GBD age-adjusted incidence rate of 108·0 (100·4–116·0) for Chile in 2017.[21] Possible explanations for our findings are that we assessed an older population (mean age 69·0 years [SD 14·1] *vs* 64·4 [16·1] years in Iquique), with a higher proportion of the population being aged 65 years or older in Ñuble compared with Iquique. When age-adjusted to the WHO standard population, the incidence rate remained higher than that of Iquique, albeit with crossing CIs (Iquique 89·6 [95% CI 87·2–114·1] *vs* Ñuble 121·7 [113·7–130·1]). The Ñuble population had a higher prevalence of vascular risk factors, particularly obesity and sedentarism; rurality and poverty; indoor air pollution associated with use of domestic solid fuels (wood); and lower consumption of healthy foods than that of Chile.[6,20]

The frequency and incidence of pathological subtypes showed an increased risk of ischaemic stroke and a lower risk of intracerebral haemorrhage than our previous findings for Iquique.[10] The rates for every subtype are very similar to those reported in Joinville (Brazil)[22] and higher in the case of ischaemic stroke than those reported in Tandil (Argentina).[18] The frequency is similar to previous reports in older populations, with prolonged exposure to atherogenic risk factors and more cases of cardiac disease (especially atrial fibrillation), better control of hypertension, and lower alcohol consumption.[21,23] The age-adjusted global incidence of ischaemic stroke was higher (86·8 [95% CI 80·1–94·0]) than the GBD estimate of 61·1 (54·3–69·0) in 2017 for Chile. Contrarily, the age-adjusted global incidence of intracerebral haemorrhage (15·9 [95% CI 13·0–19·3]) was lower than the GBD estimate of 29·6 (27·1–32·3); the same was the case for subarachnoid haemorrhage (7·2 [5·3–9·7] *vs* 17·3 [15·4–19·4]).[24] These differences probably arise from this study being population-based and thus capturing all strokes, particularly milder ones with a lower probability of death than haemorrhagic strokes. The incidence of intracerebral haemorrhage has been shown to be declining in high-income countries and increasing in low-income and middle-income countries.[25] The latter could be associated with a higher risk of non-lobar bleeding in populations with uncontrolled hypertension and alcohol use, particularly younger men.[26] The incidence of subarachnoid haemorrhage was similar to our previous findings in Iquique and the Aconcagua Valley and in the lower range of the global incidence of subarachnoid haemorrhage, which seems to be declining in parallel with hypertension and smoking.[27,28]

Unexpectedly, the overall 30-day case-fatality rate was similar to our previous finding and within the range reported in many community stroke studies.[19,20,29] The rates in Ñuble were slightly higher (24·6%) than the 18·1% (95% CI 17·7–18·4) in 51 130 patients with stroke (as classified by ICD-10) discharged from 272 Chilean hospitals between 2003 and 2007.[5] The 30-day mortality risk was lower in those with ischaemic stroke than in patients with intracerebral haemorrhage and undetermined stroke type, which is consistent with previous population-based incidence studies and GBD, showing that the number of disability-adjusted life-years due to haemorrhagic stroke is higher than those due to ischaemic stroke.[2] Undetermined stroke types had the highest case-fatality rates, a typical finding in patients too ill to have a CT scan and therefore a diagnosis of pathological subtype.

Although higher than our previous finding in Iquique,[10] the incidence of first-ever transient ischaemic attack was low, similar to the rates reported in Joinville using analogous methods and lower than those found in Tandil.[18,30] These findings provide support for the hypothesis that the incidence of transient ischaemic attack is lower in Latin American regions with predominantly people of mixed heritage than in white people. It is also possible that because we used the new definition of transient ischaemic attack, more patients with transient symptoms but with ischaemic lesions

in CT scans were classified as having infarctions and not transient ischaemic attacks. It has been proposed that this new tissue-based definition reduces the estimated incidence of transient ischaemic attack by 33% (95% CI 19–44) and increases estimates of incident stroke by 7% (4–10).[31] We cannot rule out the possibility of under-ascertainment as patients might have presented less to the emergency services or could have been misclassified.

The distribution of ischaemic stroke clinical syndromic subtypes is also different from our previous finding[10] and the most recent study in Matao (Brazil), with fewer lacunar infarctions and more partial anterior circulation infarctions.[19] Our findings are again similar to those in Joinville and the INTERSTROKE study, reporting similar rates of lacunar infarction and partial anterior circulation infarction.[29,32] This finding could reflect an increasing burden associated with cardioembolic causes and older age in this population, as described in Adelaide, Australia.[33]

The prevalence of risk factors is similar to the findings from previous population-based stroke studies, which, albeit with some variations, seem independent of income or ethnicity and are similar to the results of the INTERSTROKE study (which included 1471 cases from South America overall, with 208 from Chile) and also similar to the estimates of the systematic analysis of stroke risk factors from the GBD study.[32,34] Hypertension was the most prevalent risk factor in total strokes and first-ever strokes, as well as by pathological subtype. These findings are in line with those of the INTERSTROKE study, which estimated a population attributable risk (PAR) for hypertension in stroke in Latin America of 46·3% (95% CI 34·8–58·2) and of the GBD study, which estimated a PAR of 34·6% (30·4–39·1).[32,35] The prevalence of diabetes was higher in the current study than in Iquique, and closer to that of high-income countries, and although its PAR has been estimated to be from only 5·0% for stroke in Latin America (GBD study) and 5·6% for South America (INTERSTROKE study), it could be associated with an increasing prevalence of obesity. The prevalence of hypercholesterolaemia was also higher in this study than in Iquique and similar to that found in Joinville, and could indicate an increasing PAR with increasing income per capita as suggested by GBD.[29,35] This finding of higher hypercholesterolaemia could be associated with the higher incidence of ischaemic stroke in Ñuble than in Iquique. Unfortunately, we did not collect data for body-mass index, waist-to-hip ratios, diet patterns, or physical activity, which have PARs for stroke estimated at 20·9–37·5%, 37·3–44·9%, and 40%, respectively, and which could also be driving the increase in ischaemic stroke incidence in this population.[32,35,36] To our surprise, even though this population was older, the prevalence of premorbid atrial fibrillation in patients with ischaemic stroke was similar to our previous finding,[10] and slightly lower than the pooled estimates of incidence studies reporting a frequency of 18·6% (95% CI 16·8–20·3). This finding is probably related to low detection capacity, low community awareness, and the absence of specific health system surveillance of atrial fibrillation, there being no national guidelines yet for the condition in Chile. Even though oral vitamin K antagonists are funded and available in the public health sector, the prevalence of oral anticoagulation use in patients with atrial fibrillation is low, similar to the studies showing a pooled estimate of only 31·6% (95% CI 18·2–44·9), denoting the extent of the treatment gap in the prevention of cardio-embolism, especially ischaemic embolic stroke and in agreement with substantial worldwide under-treatment.[37] Observational studies in Latin America have suggested that the physician's choice is the main reason for not using anticoagulation in patients at moderate to high risk with atrial fibrillation.[38] Other barriers to their use in underserved populations include the cost of travelling to the anticoagulation clinics and very little access of the public health sector to direct oral anticoagulation agents, even though shown to be cost-effective.[39]

The prognosis at 6 months in our study was slightly worse than previous findings in Iquique and Joinville, but non-significantly.[10,29] This result is probably associated mostly with this population being older. We did not find an increased risk of death in women at 1 year as reported in a pooled analysis of individual patient data from 13 population-based stroke incidence studies,[40] although our results are unadjusted by age, stroke severity, pre-stroke function, and the presence of atrial fibrillation, which contribute to greater mortality after a stroke in women.[40]

The causes of death after stroke in our study showed a lower frequency adjudicated to pneumonia in the first month than our previous finding in the PISCIS study.[10] This difference can be explained by the methods used. In the PISCIS study, the field investigator neurologist reviewed all cases and assigned the primary cause of death. In the ÑANDU project, we classified them according to the entries in the death certificates. It has been shown previously that even experts rely on the length of the period between stroke and death, as well as type and severity. Therefore, early after a severe stroke, if the patient dies of pneumonia they will most probably be classified as dying from stroke, while if a patient who is bedridden with dysphagia dies of a chest infection 4 months after stroke, the classification most probably would be aspirational pneumonia.[41] Nevertheless, our findings continue to support the notion that, at a population level, to decrease stroke deaths, efforts should be primarily aimed at decreasing the occurrence of first-ever severe stroke, treating the stroke aggressively, and preventing complications of immobility and recurrences. 3·4% of all deaths were considered to be due to cancer in this study, either known previously or diagnosed after stroke, a finding that has been increasingly described.[42]

Very few population-based studies have previously provided unbiased estimates of health-related quality of life in those who survive a stroke. Our findings agree with previous population-based studies in Auckland, New Zealand (6-year follow-up), Melbourne, Australia (2-year follow-up), and Oxford, UK (5-year follow-up), showing lower utility scores in women, with increasing age, and with increasing stroke severity.[43–45] Multicentre hospital studies also provide good estimates of health-related quality of life after stroke. In the AVAIL registry in the USA, women were also found to have a significantly lower quality of life than men at 12 months after adjustments for sociodemographic and clinical stroke-related variables—particularly in the dimensions of mobility, pain and discomfort, and anxiety and depression.[46] In China, a prospective study of health-related quality of life in survivors of acute stroke at 12 months in 62 hospitals reported that the strongest predictors of quality of life were level of disability at hospital discharge and income.[47] In Brazil, in a study in a network of rehabilitation hospitals, motor impairment, disability, and mood disturbances were the independent predictors of health-related quality of life in survivors of stroke.[48]

This is the third community stroke incidence study in Chile to our knowledge and the second to include all pathological subtypes, being one of the few in Latin America. Since the PISCIS study[10] from 2000 to 2002, much has changed in the country. According to the World Bank, from 2000 to 2017, life expectancy in Chile increased from 76·3 years to 79·9 years, with 11·4% being 65 years or older; gross national income per capita increased from US$5·060 to $13·290; poverty decreased from 36·0% to 8·6%; and the Gini index decreased from 52·8 to 44·4.[49] In this sociodemographic context, the burden of vascular diseases in Chile, including stroke, fell from second to third place behind neoplasm and musculoskeletal disorders, but the prevalence of vascular risk factors increased.[50] Health care for stroke has also changed substantially, including the incorporation of ischaemic stroke and subarachnoid haemorrhage in the minimum standards of care law and the addition of a lowering of stroke case-fatality rates as a specific aim in the national health 2010–20 plan.[35,51]

This study shows that the main driver behind the increased burden of stroke in this particularly high-risk population in Chile is a high incidence of first-ever stroke, particularly ischaemic stroke. This high burden is also explained by the poor prognosis and quality of life after first-ever intracerebral haemorrhage and total anterior circulation infarctions (or severe ischaemic strokes). Although investigated in an older, poorer, more rural population and separated by more than 2000 km, it is concerning to find that the incidence was higher than our previous study done 20 years before, particularly because many populations in Chile are similar to this one. Even though comparing populations is not easy, indices such as the human development index are widely used for this purpose. Ñuble has a human development index of 0·808, which is lower than the national figure of 0·847 and sixth among 16 regions of Chile.[52] Furthermore, the Ñuble region is one of the six regions in Chile in which 20% or more of the population is classified as poor according to the multidimensional poverty index. In this respect, Ñuble is similar to many underserved populations in Latin America, and other regions in the world.

It is unlikely that we missed cases, as hospital admission for stroke is mandated by law in Chile and we ensured prospective checking of all possible hospital admissions and discharges during the study period in all hospitals in the region. We also included national administrative data for every hospital, not only in the region but nationwide, which includes the patient's home address. It is also unlikely that we missed non-hospitalised deaths in the community as we continuously reviewed national death certificates and checked that all diagnoses were included. Some patients with stroke who were not admitted to hospital and did not die, who remained in the community could have been missed if the suspicion of stroke symptoms was low, but we minimised this factor through permanent awareness and information campaigns both to the public and the local health workers, which contributed to making this project very visible to the community throughout the study. We used all the strategies for case ascertainment proposed for ideal community stroke studies and thus are confident in our estimation of incidence rates.[8]

These unbiased epidemiological data should help in increasing the public health efforts with novel policies aimed particularly at the prevention of first-ever incident strokes.[53] Efforts should be aimed both at primordial and primary prevention, incorporating different approaches and new strategies, some of which have been outlined and summarised.[36,54,55]

#### Contributors

PML, LH, and AMM were responsible for the literature search, planning, writing of the protocol, and conduction of the project. AMM, CG, and DSM were responsible for the identification of cases, the information campaign, social media, obtaining informed consent, clinical record review, and completion of the database. BP was responsible for dysphagia evaluation and management protocol education, ethics committee liaison, project coordination, and management. AV, EL, and AR identified cases, participated in the educational programmes, and reviewed clinical records. VVO, JA, AMB, PMV, and VD adjudicated most of the cases. AH and CS adjudicated difficult cases and stroke mimics. PML adjudicated stroke severity. PML, CV, and LH were responsible for the database organisation, administration, and analysis of data. PML wrote the first draft of the manuscript, which all authors approved. All authors accessed the data and three authors (PML, LH, and CV) verified the data.

#### Declaration of interests

PML reports grants from ANID-FONIS and Clínica Alemana de Santiago; and non-financial support from Boehringer Ingelheim and Bristol Myers Squibb during the conduct of the study; grants from The George Institute for Global Health; and personal fees from AstraZeneca and Bayer, outside the submitted work. LH reports grants from ANID-FONIS, during the conduct of the study; and grants from Boehringer Ingelheim, outside the submitted work. AMM, CV, CG, BP,

and DSM report grants from ANID-FONIS, during the conduct of the study. VVO reports grants from Clinica Alemana de Santiago, during the conduct of the study; and grants from Boehringer Ingelheim and ANID-FONDECYT, outside the submitted work. PMV reports grants from ANID-FONDECYT and The George Institute for Global Health, outside the submitted work. AMB reports research support from Clínica Alemana de Santiago, outside the submitted work. All other authors declare no competing interests.

#### Data sharing

Individual participant data that underlie the results reported in this Article, after de-identification (text, tables, figures, and appendices) will be available (including data dictionaries in Spanish) immediately following publication indefinitely, to anyone who wishes to access the data, for any purpose. Individuals who would like to access the data should contact the corresponding author.

#### Acknowledgments

This study was funded by a grant from the National Agency for Research and Development and the Technology-Health Research Fund (ANID-FONIS SA14ID0113) and with unrestricted grants from Clínica Alemana de Santiago, Boehringer Ingelheim, and Bristol Meyers Squibb. The study also received research support from The Herminda Martin Clinical Hospital of Chillán, Universidad Mayor, and Universidad de Concepción. We thank the hospital authorities, local health service authorities, and regional health secretary authorities for their continuing and unconditional support of the ÑANDU project. We also thank Clínica Alemana de Santiago, the Herminda Martin Hospital of Chillán, Boehringer Ingelheim, and Bristol Myers Squibb for their unconditional support of this investigation.

#### References

1 GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392:** 1859–922.

2 Johnson CO, Nguyen M, Roth GA, et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; **18:** 439–58.

3 Margozzini Maira P, Passi Solar A. Encuesta Nacional de Salud, ENS 2016–2017: un aporte a la planificación sanitaria y políticas públicas en Chile. ARS Med; Santiago En Línea, 2018: 30–34.

4 Icaza MG, Núñez ML. Atlas de mortalidad por enfermedades cerebrovasculares. 2006. http://pifrecv.utalca.cl/docs/Atlas_de_Mortalidad_por_Enfermedades_Cardiovasculares.pdf (accessed July 13, 2020).

5 Hoffmeister L, Lavados PM, Murta-Nascimento C, Araujo M, Olavarría VV, Castells X. Short- and long-term survival after stroke in hospitalized patients in Chile: a nationwide 5-year study. *J Stroke Cerebrovasc Dis* 2013; **22:** e463–69.

6 Lavados PM, Díaz V, Jadue L, Olavarría VV, Cárcamo DA, Delgado I. Socioeconomic and cardiovascular variables explaining regional variations in stroke mortality in Chile: an ecological study. *Neuroepidemiology* 2011; **37:** 45–51.

7 Hoffmeister L, Lavados PM, Comas M, Vidal C, Cabello R, Castells X. Performance measures for in-hospital care of acute ischemic stroke in public hospitals in Chile. *BMC Neurol* 2013; **13:** 23.

8 Feigin V, Norrving B, Sudlow CLM, Sacco RL. Updated criteria for population-based stroke and transient ischemic attack incidence studies for the 21st century. *Stroke* 2018; **49:** 2248–55.

9 Thrift AG, Thayabaranathan T, Howard G, et al. Global stroke statistics. *Int J Stroke* 2017; **12:** 13–32.

10 Lavados PM, Sacks C, Prina L, et al. Incidence, 30-day case-fatality rate, and prognosis of stroke in Iquique, Chile: a 2-year community-based prospective study (PISCIS project). *Lancet* 2005; **365:** 2206–15.

11 WHO. STEPwise approach to stroke surveillance. World Health Organization. 2020. http://www.who.int/chp/steps/stroke/en/ (accessed July 13, 2020).

12 Instituto Nacional de Estadísticas. Resultados Censo 2017. Web Diseminación Censo. 2017. http://resultados.censo2017.cl/ (accessed June 4, 2019).

13 Encuesta CASEN. Observatorio Social. 2017. http://observatorio.ministeriodesarrollosocial.gob.cl (accessed July 13, 2020).

14 Williams LS, Yilmaz EY, Lopez-Yunez AM. Retrospective assessment of initial stroke severity with the NIH Stroke Scale. *Stroke* 2000; **31:** 858–62.

15 Lindsell CJ, Alwell K, Moomaw CJ, et al. Validity of a retrospective National Institutes of Health Stroke Scale scoring methodology in patients with severe stroke. *J Stroke Cerebrovasc Dis* 2005; **14:** 281–83.

16 Breslow NE, Day NE. Statistical methods in cancer research. Volume II—the design and analysis of cohort studies. Lyon: IARC Scientific Publications, 1987.

17 Bennett DA, Brayne C, Feigin VL, et al. Explanation and elaboration of the standards of reporting of neurological disorders checklist: a guideline for the reporting of incidence and prevalence studies in euroepidemiology. *Neuroepidemiology* 2015; **45:** 113–37.

18 Bahit MC, Coppola ML, Riccio PM, et al. First-ever stroke and transient ischemic attack incidence and 30-day case-fatality rates in a population-based study in Argentina. *Stroke* 2016; **47:** 1640–42.

19 Minelli C, Cabral NL, Ujikawa LT, et al. Trends in the incidence and mortality of stroke in Matão, Brazil: the Matão Preventing Stroke (MAPS) study. *Neuroepidemiology* 2020; **54:** 75–82.

20 Kim J, Thayabaranathan T, Donnan GA, et al. Global stroke statistics 2019. *Int J Stroke* 2020; **15:** 819–38.

21 Krishnamurthi RV, Ikeda T, Feigin VL. Global, regional and country-specific burden of ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage: a systematic analysis of the Global Burden of Disease Study 2017. *Neuroepidemiology* 2020; **54** (suppl 2)**:** 171–79.

22 Cabral NL, Gonçalves ARR, Longo AL, et al. Trends in stroke incidence, mortality and case fatality rates in Joinville, Brazil: 1995–2006. *J Neurol Neurosurg Psychiatry* 2009; **80:** 749–54.

23 Feigin VL, Lawes CMM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009; **8:** 355–69.

24 Supplementary material for Krishnamurthi RV, Ikeda T, Feigin VL. Global, regional and country-specific burden of ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage: a systematic analysis of the Global Burden of Disease Study 2017. Karger Publishers. 2020. https://karger.figshare.com/articles/Supplementary_Material_for_Global_Regional_and_Country-Specific_Burden_of_Ischaemic_Stroke_Intracerebral_Haemorrhage_and_Subarachnoid_Haemorrhage_A_Systematic_Analysis_of_the_Global_Burden_of_Disease_Study_2017/11876493 (accessed May 30, 2020).

25 Krishnamurthi RV, Moran AE, Forouzanfar MH, et al. The global burden of hemorrhagic stroke: a summary of findings from the GBD 2010 study. *Glob Heart* 2014; **9:** 101–06.

26 Lavados PM, Sacks C, Prina L, et al. Incidence of lobar and non-lobar spontaneous intracerebral haemorrhage in a predominantly Hispanic-Mestizo population—the PISCIS stroke project: a community-based prospective study in Iquique, Chile. *Neuroepidemiology* 2010; **34:** 214–21.

27 Alvarez G, Cox P, Pairoa M, García M, Delgado I, Lavados PM. Incidence of subarachnoid haemorrhage in the Aconcagua Valley, Chile: a community-based, prospective surveillance project. *J Neurol Neurosurg Psychiatry* 2010; **81:** 778–82.

28 Etminan N, Chang H-S, Hackenberg K, et al. Worldwide incidence of aneurysmal subarachnoid hemorrhage according to region, time period, blood pressure, and smoking prevalence in the population: a systematic review and meta-analysis. *JAMA Neurol* 2019; **76:** 588–97.

29 Cabral NL, Gonçalves ARR, Longo AL, et al. Incidence of stroke subtypes, prognosis and prevalence of risk factors in Joinville, Brazil: a 2 year community based study. *J Neurol Neurosurg Psychiatry* 2009; **80:** 755–61.

30 Fonseca PG, Weiss PAK, Harger R, et al. Transient ischemic attack incidence in Joinville, Brazil, 2010: a population-based study. *Stroke* 2012; **43:** 1159–62.

31 Ovbiagele B, Kidwell CS, Saver JL. Epidemiological impact in the United States of a tissue-based definition of transient ischemic attack. *Stroke* 2003; **34:** 919–24.

32 O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016; **388:** 761–75.

33 Leyden JM, Kleinig TJ, Newbury J, et al. Adelaide stroke incidence study: declining stroke rates but many preventable cardioembolic strokes. *Stroke* 2013; **44:** 1226–31.

34 Feigin VL, Roth GA, Naghavi M, et al. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol* 2016; **15:** 913–24.

35 Ouriques Martins SC, Sacks C, Hacke W, et al. Priorities to reduce the burden of stroke in Latin American countries. *Lancet Neurol* 2019; **18:** 674–83.

36 Pandian JD, Gall SL, Kate MP, et al. Prevention of stroke: a global perspective. *Lancet* 2018; **392:** 1269–78.

37 Yiin GSC, Li L, Bejot Y, Rothwell PM. Time trends in atrial fibrillation-associated stroke and premorbid anticoagulation. *Stroke* 2018; published online Nov 29. https://doi. org/10.1161/STROKEAHA.118.022249.

38 Jerjes-Sanchez C, Corbalan R, Barretto ACP, et al. Stroke prevention in patients from Latin American countries with non-valvular atrial fibrillation: insights from the GARFIELD-AF registry. *Clin Cardiol* 2019; **42:** 553–60.

39 Lanas F, Castro C, Vallejos C, et al. Latin American Clinical Epidemiology Network Series - Paper 2: Apixaban was cost-effective vs. acenocoumarol in patients with nonvalvular atrial fibrillation with moderate to severe risk of embolism in Chile. *J Clin Epidemiol* 2017; **86:** 75–83.

40 Phan HT, Blizzard CL, Reeves MJ, et al. Sex differences in long-term mortality after stroke in the INSTRUCT (INternational STRoke oUtComes sTudy): a meta-analysis of individual participant data. *Circ Cardiovasc Qual Outcomes* 2017; **10:** e003436.

41 Halkes PHA, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Classification of cause of death after stroke in clinical research. *Stroke* 2006; **37:** 1521–24.

42 Dardiotis E, Aloizou A-M, Markoula S, et al. Cancer-associated stroke: pathophysiology, detection and management. *Int J Oncol* 2019; **54:** 779–96.

43 Hackett ML, Duncan JR, Anderson CS, Broad JB, Bonita R. Health-related quality of life among long-term survivors of stroke: results from the Auckland Stroke Study, 1991–1992. *Stroke* 2000; **31:** 440–47.

44 Sturm JW, Donnan GA, Dewey HM, et al. Quality of life after stroke: the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 2004; **35:** 2340–45.

45 Luengo-Fernandez R, Gray AM, Bull L, Welch S, Cuthbertson F, Rothwell PM. Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. *Neurology* 2013; **81:** 1588–95.

46 Bushnell CD, Reeves MJ, Zhao X, et al. Sex differences in quality of life after ischemic stroke. *Neurology* 2014; **82:** 922–31.

47 Delcourt C, Hackett M, Wu Y, et al. Determinants of quality of life after stroke in China: the ChinaQUEST (QUality Evaluation of Stroke care and Treatment) study. *Stroke* 2011; **42:** 433–38.

48 Carod-Artal FJ, Trizotto DS, Coral LF, Moreira CM. Determinants of quality of life in Brazilian stroke survivors. *J Neurol Sci* 2009; **284:** 63–68.

49 The World Bank. Data. Chile. 2020. https://data.worldbank.org/country/chile (accessed April 12, 2020).

50 GBD Compare. IHME Viz Hub. 2020. http://vizhub.healthdata.org/gbd-compare (accessed April 12, 2020).

51 Lavados PM, Salinas R, Maturana R. Government programs for treating stroke in Chile. *Int J Stroke* 2007; **2:** 51–52.

52 Sub-national HDI. Global Data Lab. 2020. https://globaldatalab.org/shdi/shdi/ (accessed Sept 7, 2020).

53 Feigin VL, Norrving B, George MG, Foltz JL, Roth GA, Mensah GA. Prevention of stroke: a strategic global imperative. *Nat Rev Neurol* 2016; **12:** 501–12.

54 Feigin VL. Anthology of stroke epidemiology in the 20th and 21st centuries: assessing the past, the present, and envisioning the future. *Int J Stroke* 2019; **14:** 223–37.

55 Brainin M, Feigin VL, Norrving B, Martins SCO, Hankey GJ, Hachinski V. Global prevention of stroke and dementia: the WSO Declaration. *Lancet Neurol* 2020; **19:** 487–88.