Population-Based Incidence Rates of First-Ever Stroke in Central Vietnam

Hirotomo Yamanashi1,2, Mai Quang Ngoc3, Tran Van Huy3, Motoi Suzuki1, Akira Tsujino4, Michiko Toizumi5, Kensuke Takahashi1, Vu Dinh Thiem6, Dang Duc Anh6, Nguyen Thi Hien Anh6, Le Huu Tho7, Takahiro Maeda2,8, Sharon E. Cox9,10, Lay-Myint Yoshida5, Koya Ariyoshi1*

1 Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University Graduate School of Biomedical Sciences, Sakamoto, Nagasaki, Japan, 2 Department of Island and Community Medicine, Nagasaki University Graduate School of Biomedical Sciences, Goto, Nagasaki, Japan, 3 Department of Geriatrics, Khanh Hoa General Hospital, Nha Trang, Khanh Hoa, Vietnam, 4 Department of Neurology and Strokeology, University Graduate School of Biomedical Sciences, Sakamoto, Nagasaki, Japan, 5 Department of Pediatric Infectious Diseases, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan, 6 National Institute of Hygiene and Epidemiology, Hanoi, Vietnam, 7 Khanh Hoa Health Service, Nha Trang, Khanh Hoa, Vietnam, 8 Department of Community Medicine, Nagasaki University Graduate School of Biomedical Sciences, Sakamoto, Nagasaki, Japan, 9 Nagasaki University School of Tropical Medicine and Global Health, Sakamoto, Nagasaki, Japan, 10 London School of Hygiene and Tropical Medicine, London, United Kingdom

* kari@nagasaki-u.ac.jp

Abstract

Introduction

Stroke incidence data with methodologically acceptable design in Southeast Asia countries is limited. This study aimed to determine incidence of age-, sex- and subtype-specific first-ever stroke (FES) in Vietnam.

Methods

We conducted a hospital-based retrospective study, targeting all stroke cases hospitalized at a solo-provider hospital in our study site of Nha Trang from January 2009 to December 2011 with International Classification of Diseases, 10th revision (ICD-10) codes I60-69. We calculated positive predictive values (PPVs) of each ICD-10-coded stroke by conducting a detailed case review of 190 randomly selected admissions with ICD-10 codes of I60-I69. These PPVs were then used to estimate annual incident stroke cases from the computerized database. National census data in 2009 was used as a denominator.

Results

2,693 eligible admissions were recorded during the study period. The crude annual incidence rate of total FES was 90.2 per 100,000 population (95% CI 81.1–100.2). The age-adjusted incidence of FES was 115.7 (95% CI 95.9–139.1) when adjusted to the WHO world populations. Importantly, age-adjusted intracerebral hemorrhage was as much as one third of total FES: 36.9 (95% CI 26.1–51.0).
Conclusions
We found a considerable proportion of FES in Vietnam to be attributable to intracerebral hemorrhage, which is as high or exceeding levels seen in high-income countries. A high prevalence of improperly treated hypertension in Vietnam may underlie the high prevalence of intracerebral hemorrhagic stroke in this population.

Introduction
Incidence and effects of stroke in low- and middle-income countries
Stroke is the second leading cause of death and third leading cause of loss of disability adjusted life years (DALYs) globally and is estimated to be rapidly increasing in low- and middle-income countries (LMICs) [1–4]. So far, published stroke incidence data with methodologically reliable design is limited in LMICs. The recent studies in LMICs showed relatively higher age-adjusted first-ever stroke (FES) incidence per 100,000 person-years compared to high-income countries; 108.2 in Chile, 116.1 in Georgia, 137 in Brazil, and 135 in India in LMICs versus 97 in Italy, 102.8 in Barbados, 73 in UK, 102.9 in New Zealand [5–13].

International comparison of stroke incidence
Comparing stroke incidence in different parts of the world is complex and standardized methods are needed [14]. The WHO MONICA study was a landmark study, comparing stroke incidence from participating centers in Europe, Russia, and China [15]. However, this study had several limitations: a) no center included participants over 75 years old; b) it was not designed to investigate incidence by different pathological types; and c) it was not prospective in design. Feigin et al., proposed criteria for an ideal study of stroke incidence, which included definitions of FES and recurrent stroke, complete population-based case ascertainment and a prospective study design [16]. Because standard definition of stroke requires imaging test such as brain CT scan or MRI, which are not readily available in LMICs, information of pathological type-specific stroke incidence has mostly been confined to high-income countries [17].

Stroke studies in Southeast Asia
Stroke is ranked as the number one cause of loss of DALYs in Southeast Asia [1]. However, no study from Southeast Asia has reported stroke incidence which meets Feigin’s standard definitions and methods criteria [16]. Thus reliable data of population-based FES incidence remains unavailable in Southeast Asia.

Study objectives
We conducted the present study with the objective of estimating the population-based incidence of age-, sex- and subtype-specific FES in Vietnam by utilizing our previously established, large-scale, community-based field site in Nha Trang city, central Vietnam.

Methods
Study location
The current study was conducted in Nha Trang, the capital city of Khanh Hoa Province in South-central Vietnam. The city comprises 19 urban and 8 suburban communes, with a total population of 392,279 in 2009. The Khanh Hoa General Hospital (KHGH) is located in the
center of Nha Trang and provides primary to tertiary care for residents. The hospital has an 800-bed capacity, being equipped with two CT scanners and one MRI scanner. KHGH served as the sole provider of hospital acute admission care in the city at the time of study. All admissions in KHGH were recorded in a computerized database with International Classification of Diseases, 10th revision (ICD-10) coding along with age, gender, date of admission, discharge status, and address codes.

Study design

We conducted a hospital-based retrospective study, targeting all stroke cases hospitalized at KHGH from January 2009 through to December 2011 (36 months). Eligible cases were identified from the hospital admission database, based on the criteria of ICD-10 code of I60-69 and residing in Nha Trang. To verify the diagnosis of subtype specific FES, 190 medical charts meeting the ICD-10 code criteria were randomly selected and reviewed by a study clinician and an independent neurologist. A standardized form was used to collect demographic information, history of stroke, external injury, hypertension, diabetes mellitus, neurological signs, stroke subtype diagnosis, performing time and remarks of brain CT/ MRI, and status at discharge.

Stroke was defined according to the WHO clinical definition, as a focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death), and of presumed vascular origin [18]. Transient ischemic attack (TIA) was excluded. A stroke case was further classified into one of four subtypes: 1. Ischemic stroke (cases of stroke for which brain CT undertaken on or before the discharge date, showed an area of low attenuation in a region compatible with the clinical picture or for which CT was normal but fulfilled the WHO criteria): 2. Intracerebral hemorrhage (brain CT showed an area of high attenuation in a region compatible with clinical signs and symptoms): 3. Subarachnoid hemorrhage (acute onset of severe headache, sometimes associated with loss of consciousness, seizures, or focal neurological signs not associated with trauma, and a brain CT scan showing subarachnoid or cisternal high attenuation): 4. Undetermined stroke (histories and signs were compatible with stroke but brain CT findings were not available). FES was distinguished from recurrent stroke by no history of previous stroke on medical charts. A case with only a history of TIA was regarded as FES.

Estimation procedure of first-ever stroke incidence rates

Population-based incidence rates of age- and subtype-specific FES were estimated as follows. Firstly, we calculated positive predictive values (PPVs) of true FES subtype for each ICD-10-coded stroke (I60-69) as a similar approach was applied in previous studies [19–21] and our preceding medical chart review revealed that the discharge diagnosis included some ineligible recurrent strokes and a number of miscoding diagnoses, varying by ICD-10-code. In the current study, PPV was defined as the proportion of confirmed cases of FES subtypes by the study clinician and neurologist where the denominator was the total number of reviewed cases with each of ICD-10-coded stroke (I60-69). We also calculated PPVs of targeted FES subtype for miscoded cases to take the miscoding cases into account.

Secondly, we estimated the annual number of age-, sex-specific FES cases admitted to KHGH. Out of all the discharge summaries in KHGH, which were assigned to an ICD-10 diagnosis, we counted all ICD-10-coded stroke cases during the three year study period and multiplied the number of cases for each ICD-10-code by the PPV of each ICD-10-code for the targeted FES subtype. The annual number of each FES subtype was estimated by summing up
all targeted FES subtypes, including miscoded cases classified elsewhere; then divided by three 
to obtain the annual incidence.

Thirdly, based on the assumption that all FES cases in Nha Trang city were admitted to 
KHGH, the age-, sex- and subtype-specific FES incidence rates were calculated by dividing the 
estimated annual incidence by the number of the relevant population in the city in a certain 
age group. To compare our estimated incidence with other countries, direct age standardiza-
tions were performed using two standard populations: the Vietnamese population in 2009 
according to the national census [22], and the WHO standard population [23]. The 95% confi-
dence intervals (CI) for the incidence rates were calculated using Poisson regression. Charac-
teristics of first-ever ischemic stroke and intracerebral hemorrhage cases confirmed in medical 
chart review were compared using chi-square tests for categorical variables and Student’s t-
tests for continuous variables. STATA 14.0 was used for all statistical analyses. The Institu-
tional Review Board of the National Institute of Hygiene and Epidemiology, Hanoi, Vietnam, 
and of the Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan approved this 
study (130606111). We did not obtain informed consent because the data was analyzed 
anonymously.

Results

Medical chart review

Medical chart review revealed 75 FES and 19 recurrent stroke cases among the randomly 
selected 190 case charts with ICD-10 coding of I60-69. Of the FES cases, 38 (50.7%) and 25 
(33.3%) cases were ischemic stroke and intracerebral hemorrhage, respectively. There were 2 
(2.7%) cases of subarachnoid hemorrhage. 65 (87%) cases had CT/MRI results but 10 cases 
(13.3%) were categorized as undetermined subtype due to lack of brain CT/MRI findings. The 
remaining non-stroke cases were ascertained to be due to the following diseases: headache 
(n = 51), TIA (n = 12), dizziness (n = 10), subdural hematoma (n = 3), pneumonia (n = 3), 
brain tumor (n = 2), cardiopulmonary arrest (n = 1), epilepsy (n = 1), hypoglycemia (n = 1), 
alcohol poisoning (n = 1), hypertension (n = 1), syncope (n = 1), traffic accident (n = 1), and 
undiagnosed (n = 8).

Characteristics of the subtype specific FES cases are summarized in Table 1. The mean age 
of intracerebral hemorrhage was younger than ischemic stroke, though the difference was not 
statistically significant (p = 0.141). Nearly 90% of total FES cases and 100% of hemorrhagic 
stroke cases were directly admitted rather than referred via clinics. The majority of FES cases 
had past history of hypertension, diabetes mellitus or dyslipidemia, though one third of intra-
cerebral hemorrhage cases were not diagnosed with hypertension prior to this admission. Sur-
vival status at discharge was available in all FES cases. Of those, 3 patients died in hospital and 
10 (76.9%) patients were discharged in grave condition to die at home, resulting in case fatality 
rate of 17.3 (95% CI 9.2–29.6). The case fatality rate was significantly higher among the 25 
intracerebral hemorrhage cases than 38 ischemic stroke cases (p<0.001).

Positive Predictive Values of ICD-10-coded stroke

The PPV of each ICD-10-coded stroke subtype was calculated (Table 2). True cerebral hemor-
rhage cases were recorded mainly as I61 but also some cases were recorded as I63, I64 and I67. 
Therefore to take the miscoding cases into account, for example, we calculated PPVs of first-
ever intracerebral hemorrhage not only over I61-coded stroke (PPV 0.633) but also over mis-
coded stroke, which were coded as I63 (PPV 0.022), I64 (0.071) and I67 (0.030). True ischemic 
stroke cases were recorded as I63 (PPV 0.609) and also miscoded as I64 (0.214) and I61 
(0.033). True undetermined stroke cases were recorded as I64 (PPV 0.143) and I63 (0.087).
The reviewed 190 cases contained two confirmed subarachnoid hemorrhage cases but these were recorded as I61 (PPV 0.033) and I64 (0.024) but not as I60. Thus 0.633, PPV of I61 was assigned to the PPV of I60 since other published studies showed PPVs were similar between I60 and I61 [20, 21].

Estimated annual number of first-ever stroke cases

According to the ICD-10-code database, a total of 4,344 stroke cases were admitted to KHGH during the 3 years of study period. Among them, 2,693 (62%) were residents of Nha Trang thus eligible for the current analysis. The age-, sex- and subtype-specific distribution of ICD-10-coded stroke cases admitted to KHGH are shown in S1 Table. 1,287 (47.8%) were males and the mean age was 60.1 (Standard Deviation, SD 18.0) years. Discharge status was missing in one case. In total 258 (9.5%) died or were discharged in critical condition but this ranged from 0% to 34.4% depending on ICD-10 code: 0/7 (0%) in subarachnoid hemorrhage (ICD-10-I60), 148/430 (34.4%) Intracerebral hemorrhage (ICD-10-I61), 50/702 (7.1%) ischemic stroke (ICD-10-I63), 57/503 (11.3%) undetermined (ICD-10-I64), and 1/887 (0.1%) other cerebral vascular diseases (ICD-10-I67). Mean duration of admission among those who survived was 9.9 days (SD 9.6) in all cases, ranging from 0 to 116 days: 11.3 (SD 13.7) for ICD-10-I60, 11.5 (SD 11.0) for ICD-10-I61, 11.5 (SD 10.1) for ICD-10-I63, 10.4 (SD 9.8) for ICD-10-I64, and 7.6 (SD 8.2) for ICD-10-I67.

Estimated number of annual FES cases for each subtype were calculated by multiplying the total number of age-, sex- and subtype-specific ICD-10-coded cases by the PPV then divided by three years (S2 Table). For example, the total number of intracerebral hemorrhage cases for three years was estimated as the sum of I61-coded stroke cases multiplied by the PPV of I61 to predict intracerebral hemorrhage, the number of I63-coded stroke cases multiplied by PPV of I63 to predict intracerebral hemorrhage (miscoding no.1), the number of I64-coded stroke cases multiplied by PPV of I64 to predict intracerebral hemorrhage (miscoding no.2), and the number of I67-coded stroke cases multiplied by PPV of I67 to predict intracerebral hemorrhage (miscoding no.3).
Table 2. Results of medical chart review and positive predictive values. FES indicates first-ever stroke.

| ICD-10 code | Total | I60 (Subarachnoid hemorrhage) | I61 (Intracerebral hemorrhage) | I62 (Other nontraumatic intracranial hemorrhage: subdural hemorrhage etc.) | I63 (Cerebral infarction; ischemic stroke) | I64 (Stroke, not specified as hemorrhage or infarction: undetermined stroke) | I65 (Oclusion and stenosis of precerebral arteries) | I66 (Oclusion and stenosis of cerebral arteries) | I67 (Other cerebrovascular diseases: cerebral aneurysm etc.) | I68 (Cerebral amyloid angiopathy) | I69 (Sequelae of cerebrovascular disease) |
|-------------|-------|-----------------------------|-------------------------------|--------------------------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------|
| Reviewed cases (N) | 190   | 0                           | 30                           | 1                                                                            | 46                                    | 42                                                                                                                                  | 1                                                                       | 1                                                                                      | 66                                                                                               | 3                                                                                     | 0                                                                                     |
| Confirmed diagnosis |       |                             |                               |                                                                              |                                        |                                                                                                                                       |                                                                          |                                                                                         |                                                                                                   |                                                                                          |                                                                                           |
| Ischemic stroke     | 38    | 0                           | 1                            | 0                                                                            | 28                                    | 9                                                                     | 0                                                                       | 0                                                                                      | 0                                                                                               | 0                                                                                     | 0                                                                                     |
| Intracerebral hemorrhage | 25   | 0                           | 19                           | 0                                                                            | 1                                     | 3                                                                     | 0                                                                       | 2                                                                                      | 0                                                                                               | 0                                                                                     | 0                                                                                     |
| Subarachnoid hemorrhage | 2    | 0                           | 1                            | 0                                                                            | 1                                     | 1                                                                     | 0                                                                       | 0                                                                                      | 0                                                                                               | 0                                                                                     | 0                                                                                     |
| Undetermined stroke | 10    | 0                           | 0                            | 0                                                                            | 4                                     | 6                                                                     | 0                                                                       | 0                                                                                      | 0                                                                                               | 0                                                                                     | 0                                                                                     |
| Positive Predictive Values |     |                              |                               |                                                                              |                                        |                                                                                                                                       |                                                                          |                                                                                         |                                                                                                   |                                                                                          |                                                                                           |
| Ischemic stroke     | -     | 0.033                       | -                            | 0.609                                                                       | 0.214                                  | -                                                                     | -                                                                       | -                                                                                      | -                                                                                               | -                                                                                     | -                                                                                     |
| Intracerebral hemorrhage | -    | 0.633                       | -                            | 0.022                                                                       | 0.071                                  | -                                                                     | -                                                                       | 0.030                                                                                       | -                                                                                               | -                                                                                     | -                                                                                     |
| Subarachnoid hemorrhage | 0.633* | 0.033                       | -                            | -                                                                           | 0.024                                  | -                                                                     | -                                                                       | -                                                                                      | -                                                                                               | -                                                                                     | -                                                                                     |
| Undetermined stroke | -     | -                           | -                            | 0.087                                                                       | 0.143                                  | -                                                                     | -                                                                       | -                                                                                      | -                                                                                               | -                                                                                     | -                                                                                     |

* The PPV of I61 (0.633) was assigned.

doi:10.1371/journal.pone.0160665.t002
hemorrhage (misdoding no.3). Similarly, to estimate total number of ischemic stroke cases, the numbers of cases categorized as I61, I63 and I64 were multiplied by each codes PPVs for ischemic stroke and summed; to estimate total number of undetermined stroke cases, the numbers of cases categorized as I63 and I64 were multiplied by each codes PPVs for undetermined stroke and summed. For estimation of the total number of subarachnoid hemorrhages, the numbers of cases categorized as I60, I61 (misdoded cases) and I64 (misdoded cases) were multiplied by each PPVs and summed.

Stroke incidence rates

The crude annual incidence rate of total FES was 90.2 per 100,000 population (95% CI 81.1–100.2) (Table 3). When adjusted to the WHO world populations or Vietnamese population of 2009, the age-adjusted incidence of FES was 115.7 (95% CI 95.9–139.1) and 95.7 (77.8–117.2), respectively. The total stroke incidence increased with age with the peak of 1055.7 in people aged 85 years or over. This increasing tendency with age was not seen in intracerebral hemorrhage incidence in men between aged 75–84 and aged 85 years or over, as well as ischemic stroke in women and total FES. Crude incidence in the oldest age group women (aged ≥85 yrs) exceeded that of men.

Ischemic stroke was the most common subtype but it is noteworthy that intracerebral hemorrhage constituted as much as one third of total stroke in this population. When the subtype-specific FES incidence rates were calculated, the crude incidence of ischemic stroke was only 1.57 fold greater than hemorrhagic: 46.7 (95% CI 40.1–53.9) vs 29.8 (95% CI 24.7–35.8), respectively. The incidence of FES was higher in men than in women regardless of pathological type. However total number of women admitted to KHGH with ICD-10-coded stroke was higher than men. This discrepancy was mainly attributed to the considerably higher number of women admitted with ICD-10-I67 (S1 Table). Subarachnoid hemorrhage was the least common in FES contributing only 2.9% to the incidence rate. The fatality rate of subarachnoid hemorrhage was quite low in both chart review and ICD-10-coded stroke cases (I60).

Discussion

This is the first population-based study in southeast Asia, documenting age-, sex- and subtype-specific stroke incidence rates. We found a considerable proportion of FES in central Vietnam to be attributable to intracerebral hemorrhage and age-adjusted incidence rate of intracerebral hemorrhage at 36.9 is the highest reported since 2000, including other LMICs (Table 4) [5–13]. It is plausible that this observation may be due to substantial numbers of hypertensive patients not being either diagnosed, treated or suboptimaly treated in Vietnam.

It has been reported that the incidence of hemorrhagic stroke is more strongly associated with blood pressure than ischemic stroke [24, 25]. A similar situation existed in Japan about 50 years ago where the incidence and mortality of intracerebral hemorrhage was very high particularly among men with untreated or sub-treated hypertension [26]. A previous community-based studies in Vietnam in 2002–2008 reported only 17.4–48.4% of hypertensive patients were aware of their blood pressure status, and only 29.6–36.7% of the hypertension patients who were aware of their condition, were under treatment with anti-hypertensive drugs [27, 28]. National representative verbal autopsy survey in 2006–2007 in Vietnam found that cerebrovascular diseases and hypertensive diseases were ranked within top three in both sexes [29]. Following a lesson learned in Japan that the incidence of intracerebral hemorrhage in Japanese men steeply declined from 1961 to 2002 along with the dissemination of antihypertensive drug use from 2.0% to 17.5% in the study population [26], community-based blood pressure screening and treatment dissemination should be urgently implemented in Vietnam.
### Table 3. Age-specific and sex-adjusted incidence rates per 100,000 of first-ever stroke, all and by pathological subtype.

| Age group, years | Male | Incidence rate (95% CI) | Female | Incidence rate (95% CI) |
|------------------|------|-------------------------|--------|-------------------------|
| <15              |      |                         |        |                         |
| 15–24            |      |                         |        |                         |
| 25–34            |      |                         |        |                         |
| 35–44            |      |                         |        |                         |
| 45–54            |      |                         |        |                         |
| 55–64            |      |                         |        |                         |
| 65–74            |      |                         |        |                         |
| 75–84            |      |                         |        |                         |
| 85+              |      |                         |        |                         |

| Stroke subtype   | Total stroke population (N) | Estimated number of cases (95% CI) | Total stroke population (N) | Estimated number of cases (95% CI) |
|------------------|-----------------------------|----------------------------------|-----------------------------|----------------------------------|
| Ischemic stroke  | 49,049                      | 0.1 (2.0-1.3-1.6)                | 49,049                      | 0.1 (2.0-1.3-1.6)                |
| Intracerebral hemorrhage | 35,256                 | 0.3 (2.0-1.3-1.6)                | 35,256                 | 0.3 (2.0-1.3-1.6)                |
| Subarachnoid hemorrhage | 31,764                 | 0.5 (2.0-1.3-1.6)                | 31,764                 | 0.5 (2.0-1.3-1.6)                |
| Undetermined stroke subtype | 37,049               | 0.2 (2.0-1.3-1.6)                | 37,049               | 0.2 (2.0-1.3-1.6)                |

(Continued)
**Table 3. (Continued)**

| Total population (N) | Ischemic stroke | Intracerebral hemorrhage | Subarachnoid hemorrhage | Undetermined stroke subtype | Total stroke |
|----------------------|-----------------|--------------------------|-------------------------|----------------------------|--------------|
|                      | Estimated number of cases | Incidence rate (95% CI) | Estimated number of cases | Incidence rate (95% CI) | Estimated number of cases | Incidence rate (95% CI) | Estimated number of cases | Incidence rate (95% CI) | Estimated number of cases | Incidence rate (95% CI) |
| ≥85                  | 2,084           | 12.2                     | 575.8 (297.5–1005.8)   | 6.0                        | 287.9 (105.7–626.7)   | 0.6                        | 48.0 (1.2–267.4)   | 3.5                        | 191.9 (52.3–491.4)   | 22.3                      | 1055.7 (661.6–1598.3) |
| Total                | 3,92,279        | 183.1                    | 46.7 (40.1–53.9)       | 116.8                      | 29.8 (24.7–35.8)      | 10.2                      | 2.6 (1.2–4.7)       | 44.3                      | 11.2 (8.2–15.1)       | 354.5                      | 90.2 (81.1–100.2)     |

Age-adjusted by Vietnam *

|                      | Estimated number of cases | Incidence rate (95% CI) | Estimated number of cases | Incidence rate (95% CI) | Estimated number of cases | Incidence rate (95% CI) | Estimated number of cases | Incidence rate (95% CI) |
|----------------------|--------------------------|-------------------------|--------------------------|-------------------------|--------------------------|-------------------------|--------------------------|-------------------------|
| ≥85                  | 49.6 (37.1–65.9)         | 31.1 (21.1–44)          | 2.7 (0.6–8.8)            | 12.1 (6.2–21)           | 95.7 (77.8–117.2)       |                          |                          |                          |
| Total                | 60.7 (46.7–78.4)         | 36.9 (26.1–51)          | 3.2 (0.6–8.8)            | 14.6 (8.4–24.7)         | 115.7 (95.9–139.1)      |                          |                          |                          |

*2009 Vietnam national census.

**WHO world standard.

doi:10.1371/journal.pone.0160665.t003
Table 4. Age-adjusted stroke incidence and proportion of pathological type, by high-income or low- and middle-income countries. NR = not reported. The direct age standardizations were performed using WHO world standard populations.

| Study site                  | Study duration (year) | Age-adjusted incidence of first-ever stroke per year/100,000 population (95% CI) | Age-adjusted incidence of ischemic stroke per year/100,000 population (95% CI) | Age-adjusted incidence of intracerebral hemorrhage per year/100,000 population (95% CI) | Age-adjusted incidence of subarachnoid hemorrhage per year/100,000 population (95% CI) | Age-adjusted incidence of undetermined stroke per year/100,000 population (95% CI) |
|-----------------------------|-----------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| **High-income countries**   |                       |                                                                                 |                                                                                 |                                                                                 |                                                                                 |                                                                                 |
| Valley d’Aosta, Italy(5)    | 2004–2005             | 97 (80–114)                                                                     | 75 (60–90)                                                                       | 10 (5–15)                                                                       | 5 (1–9)                                                                         | 8 (3–13)                                                                       |
| Barbados, Barbados (6)      | 2001–2002             | 102.8 (84.1–124.9)†                                                              | 88.3 (70.6–108.4)†                                                               | 13.3 (6.9–22.2)†                                                               | 2.8 (0.6–8.8)†                                                                  | 3.6 (1.1–10.2)†                                                              |
| Oxfordshire, UK(7)          | 2002–2004             | 73 (64–83)                                                                       | NR                                                                              | NR                                                                              | NR                                                                              | NR                                                                              |
| Auckland, New Zealand(8,9)  | 2002–2003             | 102.9 (84.1–124.9)†                                                              | 75.2 (59–94)                                                                     | 13.2 (6.9–22.2)¶                                                               | 6.9 (2.8–14.4)¶                                                               | 7.6 (3.5–15.8)¶                                                             |
| **Low- and middle-income countries** |                       |                                                                                 |                                                                                 |                                                                                 |                                                                                 |                                                                                 |
| Iquique, Chile(10)          | 2000–2002             | 108.2 (95.8–120.6)                                                              | 63.9 (49.3–81.7)¶                                                               | 22.2 (13.8–33.3)¶                                                             | NR                                                                              | NR                                                                              |
| Tbilisi, Georgia(11)        | 2000–2003             | 116.1 (95.9–139.1)†                                                             | 60.3 (45.8–77.2)†                                                               | 29.3 (19.4–41.7)†                                                             | 14.1 (7.7–23.5)†                                                              | 12.5 (6.9–22.2)†                                                            |
| Matao, Brazil(12)           | 2003–2004             | 137 (112–166.4)                                                                  | 122.9 (102.2–146.8)†                                                           | 20.0 (13–32.1)†                                                               | NR                                                                              | NR                                                                              |
| Trivandrum, India(13)       | 2005                  | 135 (123–146)                                                                    | 74.8 (66.3–83.2)                                                                | 10.1 (7–13.2)                                                                  | 4.2 (2.2–6.1)                                                                  | NR                                                                              |
| Nha Trang, Vietnam          | 2009–2011             | 115.7 (95.9–139.1)                                                               | 60.7 (46.7–78.4)                                                                | 36.9 (26.1–51)                                                                | 3.2 (0.6–8.8)                                                                  | 3.2 (0.6–8.8)                                                                |

† Calculated by the author, based on the reports.
¶ Calculated by the author, based on the reports. Incidence rate aged <15 assumed zero.

doi:10.1371/journal.pone.0160665.t004
Projection of stroke patients in Vietnam in 2010 and 2030

We predict a dramatic increase in the number of stroke cases as the Vietnamese population ages. Life expectancy at birth increased rapidly from 6.1 to 8.4 years for men, and from 7.3 to 8.9 years in women for two decades in Vietnam, Lao, and Cambodia [30]. According to national census 2009, the population pyramid of Vietnam was bell-shaped, which is compatible with that of our study population in Nha Trang [22]. Six percent of the Vietnamese population is older than 65 years old in 2009. We estimated the total number of FES patients in Vietnam in 2010 and 2030, assuming that age- and sex-specific stroke incidence rates do not vary across the country or over time and using the Vietnamese population in 2010 and predicted population in 2030 [22]. The total number of male and female patients in each age group was calculated by multiplying the predicted age- and sex-specific population by the age- and sex-specific crude incidence rates of our current study. We found the total number of FES cases in Vietnam will increase 1.85 fold (83,546 in 2010 to 154,777 in 2030) by the year 2030.

Limitations

Potential limitations of this study include the possible underestimation of the true FES incidence due to ascertainment from a single hospital (and not including private clinics) and limited to those with hospital ICD-10-coded stroke which could result in missed cases. However, in this study setting, there was no other hospital with admission facility for stroke patients, and also we assumed that economic barriers to hospital admission was low in Vietnam, because it used to be a socialist country and the majority of residents hold health insurance [31]. On the other hand, observed low fatality rate of patients with subarachnoid hemorrhage may indicate that our study missed some pre-hospital death cases. Furthermore our study design was retrospective. Nevertheless, these limitations don’t alter our conclusion of a high age-adjusted FES and intracerebral hemorrhage incidence in comparison with other countries. Finally, our study doesn’t consider possible changes of denominator during the study period of 2009–2011 due to a single population census in 2009.

Conclusions

The age-adjusted incidence rate of FES in central Vietnam is compatible with previous reports showing stroke incidence rates in LMICs as high or exceeding levels seen in high-income countries. Our findings also highlight the relatively high proportion of intracerebral hemorrhage, which is important to consider screening and preventive strategies in Vietnam.

Supporting Information

S1 Table. Total number of age-, sex-specific ICD-10-coded stroke cases admitted to Khanh Hoa General Hospital who were residing in Nha Trang.
(PDF)

S2 Table. Estimated annual number of age-, sex-specific true first-ever stroke cases admitted to Khanh Hoa General Hospital by stroke subtypes.
(PDF)
Acknowledgments
This study was a collaborative research effort between Nagasaki University (Japan), National Institute of Hygiene and Epidemiology (Vietnam), Khanh Hoa Provincial Public Health Service (Vietnam), and KHGH (Vietnam). We thank those who cooperated in this study in both Vietnam and Japan.

Author Contributions
Conceptualization: HY MS AT KT LY KA.
Formal analysis: HY MS AT KT SC LY KA.
Funding acquisition: LY KA.
Investigation: HY MN TH MS AT MT KT VT DA NA LT SC LY KA.
Methodology: HY MS AT KT TM LY KA.
Project administration: DA LY KA.
Resources: HY MN TH MS AT MT KT VT DA NA LT SC LY KA.
Visualization: HY MN TH MS AT MT KT VT DA NA LT TM SC LY KA.
Writing - original draft: HY MS LY KA.
Writing - review & editing: HY MN TH MS AT MT KT VT DA NA LT TM SC LY KA.

References
1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380:2095–2128. doi: 10.1016/S0140-6736(12)61728-0 PMID: 23245604
2. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380:2197–2223. doi: 10.1016/S0140-6736(12)61689-4 PMID: 23245608
3. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health. 2013; 1:e259–281. doi: 10.1016/S2214-109X(13)70089-5 PMID: 25104492
4. Feigin VL, Lawes CM, 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; 8:355–369. doi: 10.1016/S1474-4422(09)70025-0 PMID: 19233729
5. Corso G, Bottacchi E, Giardini G, De la Pierre F, Meloni T, Pesenti Campagnoni M, et al. Community-based study of stroke incidence in the Valley of Aosta, Italy. CARe-cerebrovascular Aosta Registry: years 2004–2005. Neuroepidemiology. 2009; 32:186–195. doi: 10.1159/000195688 PMID: 19169040
6. Corbin DO, Poddar V, Hennis A, Gaskin A, Rambarat C, Wolfe CD, et al. Incidence and case fatality rates of first-ever stroke in a black caribbean population: the Barbados Register of Strokes. Stroke. 2004; 35:1254–1258. PMID: 15087558
7. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet. 2004; 363:1925–1233. PMID: 15194281
8. Feigin V, Carter K, Hackett M, Barber PA, McNaughton H, Dyall L, et al. Ethnic disparities in incidence of stroke subtypes: Auckland Regional Community Stroke Study, 2002–2003. Lancet Neurol. 2006; 5:130–139. PMID: 16426989
9. Anderson CS, Carter KN, Hackett ML, Feigin V, Barber PA, Broad JB, et al. Trends in stroke incidence in Auckland, New Zealand, during 1981 to 2003. Stroke. 2005; 36:2087–2093. PMID: 16151034
10. Lavados PM, Sacks C, Prina L, Escobar A, Tossi C, Araya F, 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; 365:2206–2215. PMID: 15979299

11. Tsiskaridze A, Djibuti M, van Melle G, Lomidze G, Apridonidze S, Gauarashvili I, et al. Stroke incidence and 30-day case-fatality in a suburb of Tbilisi: results of the first prospective population-based study in Georgia. Stroke. 2004; 35:2523–2528. PMID: 15472096

12. Minelli C, Fen LF, Minelli DP. Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matão, Brazil: a population-based prospective study. Stroke. 2007; 38:2906–2911. PMID: 17916767

13. Sridharan SE, Unnikrishnan JP, Sukumaran S, Sylaja PN, Nayak SD, Sarma PS, et al. Incidence, types, risk factors, and outcome of stroke in a developing country: the Trivandrum Stroke Registry. Stroke. 2009; 40:1212–1218. doi: 10.1161/STROKEAHA.108.531293 PMID: 19228849

14. Sudlow CL, Warlow C. Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International Stroke Incidence Collaboration. Stroke. 1997; 28:491–499. PMID: 9056601

15. Thorvaldsen P, Kuulasmaa K, Rajakangas AM, Rastenyte D, Sarti C, Wilhelmsen L. Stroke Trends in 187 countries, 1990–2010: a systematic analysis for the Global Burden Disease Study 2010. Lancet. 2012; 380:2144–2162. doi: 10.1016/S0140-6736(12)61699-9 PMID: 23046606

16. Zia E, Hedblad B, Pessah-Rasmussen H, Berglund G, Janzon L, Engstrom G. Blood pressure in relation to the incidence of cerebral infarction and intracerebral hemorrhage. Hypertensive hemorrhage: debated nomenclature is still relevant. Stroke. 2007; 38:2681–2685. PMID: 17761929

17. Minelli C, Fen LF, Minelli DP. Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matão, Brazil: a population-based prospective study. Stroke. 2007; 38:2906–2911. PMID: 17916767

18. Hatano S. Experience from a multicentre stroke register: a preliminary report. Bull World Health Organ. 1976; 54:541–553. PMID: 1088404

19. Spolaore P, Brocco S, Fedeli U, et al. Measuring accuracy of discharge diagnoses for a region-wide surveillance of hospitalized strokes. Stroke. 2005; 36(5):1031–4. PMID: 15790948

20. Sedova P, Brown RD Jr, Zvolsky M, Kadlecova P, Bryndziar T, Volny O, et al. Validation of Stroke Diagnosis in the National Registry of Hospitalized Patients in the Czech Republic. J Stroke Cerebrovasc Dis. 2015; 24:2032–2038. doi: 10.1016/j.jstrokecerebrovasdis.2015.04.019 PMID: 26139454

21. Kirkman MA, Mahattanakul W, Gregson BA, and Mendelow AD. The accuracy of hospital discharge coding for hemorrhagic stroke. Acta Neurol Belg. 2009; 109:114–119. PMID: 19681442

22. The 2009 Population and Housing Census: major findings. 2010. Available: http://unstats.un.org/unsd/demographic/sources/census/2010_phc/Viet%20Nam/Vietnam-Findings.pdf.

23. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age Standardization of Rates: A New WHO Standard. Geneva: World Health Organization 2003. Available: http://www.who.int/healthinfo/paper31.pdf.

24. Zia E, Hedblad B, Pessah-Rasmussen H, Berglund G, Janzon L, Engstrom G. Blood pressure in relation to the incidence of cerebral infarction and intracerebral hemorrhage. Hypertensive hemorrhage: debated nomenclature is still relevant. Stroke. 2007; 38:2681–2685. PMID: 17761929

25. Kim HC, Nam CM, Jee SH, Suh I. Comparison of blood pressure-associated risk of intracerebral hemorrhage and subarachnoid hemorrhage: Korea Medical Insurance Corporation study. Hypertension. 2006; 48:393–397. PMID: 16998702

26. Hata J, Ninomiya T, Hirakawa Y, Nagata M, Mukai N, Gotoh S, et al. Secular trends in cardiovascular disease and its risk factors in Japanese: half-century data from the Hisayama Study (1961–2009). Circulation. 2013; 128:1198–1205. doi: 10.1161/CIRCULATIONAHA.113.002424 PMID: 23902756

27. Minelli C, Fen LF, Minelli DP. Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matão, Brazil: a population-based prospective study. Stroke. 2007; 38:2906–2911. PMID: 17916767

28. Son PT, Quang NN, Viet NL, Khai PG, Wall S, Weinehall L, et al. Prevalence, awareness, treatment and control of hypertension in Vietnam: results from a national survey. J Hum Hypertens. 2012; 26:268–280. doi: 10.1111/j.1365-2753.2011.01877.x PMID: 21906775

29. Ngo AD, Rao C, Hoa NP, Adair T, Chuc NT. Mortality patterns in Vietnam, 2006: Findings from a national verbal autopsy survey. BMC Res Notes. 2010; 3:78. doi: 10.1186/1756-0500-3-78 PMID: 20236551

30. Salomon JA, Wang H, Freeman MK, Vos T, Flaxman AD, Lopez AD, et al. Healthy life expectancy for 187 countries, 1990–2010: a systematic analysis for the Global Burden Disease Study 2010. Lancet. 2012; 380:2144–2154. doi: 10.1016/S0140-6736(12)61690-9 PMID: 23246606

31. Do N, Oh J, Lee JS. Moving toward universal coverage of health insurance in Vietnam: barriers, facilitating factors, and lessons from Korea. J Korean Med Sci. 2014; 29:919–925. doi: 10.3346/jkms.2014.29.7.919 PMID: 25046223