Original Article

Factors Predicting Stroke Mortality in Thailand: Thai Epidemiologic Stroke Study

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Objective: To determine the factors predicting stroke mortality in Thailand.

Materials and Methods: The Thai Epidemiologic Stroke (TES) study is a prospective community-based cohort study that recruited participants from the general population from five regions of Thailand. Between 2004 and 2006, 19,620 participants aged 45 to 80 years, free of stroke, took part in the baseline survey. The participants were followed up for mortality over 12 years. Competing risk regression analysis was used to identify the predictors of stroke mortality. Subdistribution hazard ratio (SHR) and 95% confidence intervals were used to illustrate the associations.

Results: During a median follow-up time of 11.1 years (202,803 person-years), 305 participants died of stroke, and 3,176 participants died of non-stroke cause. In multivariate analysis, older age group (70 to 80 years) (SHR 3.37, 95% CI 2.25 to 5.04), geographic region, that was, living in northeastern region (SHR 2.05, 95% CI 1.26 to 3.34), hypertension (SHR 2.05, 95% CI 1.56 to 2.68), current smoker (SHR 1.97, 95% CI 1.33 to 2.91), and men (SHR 1.46, 95% CI 1.01 to 2.10) were significantly associated with a higher risk of stroke mortality. Whereas hypercholesterolemia was significantly associated with a lower risk of stroke death (SHR 0.74, 95% CI 0.57 to 0.96). Marital status, education level, occupation, low personal income, alcohol consumption, body mass index, diabetes mellitus, and snoring were not significantly related to stroke mortality.

Conclusion: Older age, geographic region (northeastern region), hypertension, current smoker, and men were significant predictors of a higher risk of stroke mortality. Clinical preventive focus targeting these groups may reduce the stroke mortality in the Thai population.

Keywords: Thailand, Stroke, Mortality, Risk factor

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Globally, stroke is the second most common cause of death after ischemic heart disease[1,2]. Furthermore, its impact is likely to increase in the future due to ongoing demographic changes, including aging of the population and health transitions observed in developing countries[1]. During the past several decades, the burden of stroke in the world has shifted from developed to developing countries[2]. Nowadays, 87% of all stroke-related deaths and 89% of the total disability-adjusted life years (DALYs) lost because of stroke occur in developing countries[2]. Although attempts should be made to improve acute stroke care services in developing countries, data from the developed countries suggests that a strong emphasis on prevention would be needed to reduce the burden of stroke[3]. Despite a significant and increasing amount of research on stroke risk factors[3,4], good quality data on stroke risk factors in developing countries including Thailand are lacking[3,5,6].

In Thailand, stroke is the first leading cause of death in both sexes[7,8]. It carries the first rank for disease burden in Thailand measured by DALYs lost in female and the third in male[9]. With stroke being a major public health problem, more information on stroke epidemiology in Thailand is urgently needed to facilitate future healthcare planning. To reduce stroke mortality, it is essential to identify the factors

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predicting stroke mortality.

A competing risk is an event whose occurrence precludes the occurrence of the primary event of interest and alters the chances to observe the primary event[10]. When proportion of participants experiencing a competing risk is equal or greater to the proportion of participants experiencing the primary outcome, or when follow-up exceeds five years, a failure to consider competing risks can lead to biased results[11]. To reduce this bias in the present study, stroke death and non-stroke death were considered as a primary event of interest and as a competing risk event, respectively.

Therefore, the purpose of the present study was to determine the factors predicting stroke mortality, accounting for non-stroke death as a competing risk, using data over a 12-year follow-up period of the Thai Epidemiologic Stroke (TES) Study.

Materials and Methods

Study population

The TES Study is a prospective community-based cohort study, an ongoing process to investigate the relationships among various risk factors, lifestyles, and stroke in Thailand. A general population cohort aged 45 to 80 years (n=19,997) was enrolled on the voluntary basis from the following five geographic regions of the country, Bangkok (capital city), Chiang Mai Province (northern region), Khon Kaen Province (northeastern region), Chachoengsao Province (central region), and Nakhon Si Thammarat Province (southern region). Although the study sample was not established by random sampling, it covered all major demographic strata of the Thai general population aged 45 to 80 years[12]. In the present study, the authors limited the analyses to participants who were free of stroke at baseline (n=19,620). The study was approved by the Ethical Review Committee for Research in Human Subjects, Ministry of Public Health, Thailand (Ref. no. 94/2547 and 25/2558). Written, informed consents were obtained from all participants.

Baseline survey

Baseline survey data were collected at a community place between 2004 and 2006. Blood pressure and anthropometric data measurements, blood sampling after overnight fasting, and face-to-face interviews assessing demographic information, health behavior, and medical history were performed under standard operating procedures by a well-trained staff. The amount of alcohol consumption was estimated using responses to the question items on frequency, average daily amount, and type of alcoholic beverages. Based on the stroke screening questionnaire, participants who were suspected to have a stroke were interviewed and examined by board-certified neurologists for determining stroke status. The methodological details have been described in the authors' previous publications[12,13]. In brief, blood pressure was measured three times with one minute between measurement using an automated blood pressure device (Omron HEM-907; Omron Healthcare, Singapore) after participants had rested for at least five minutes. Height and weight were measured in light clothes without shoes to the nearest 0.1 cm and 0.1 kg, respectively. Digital weight measurement machine (TANITA BWB-800; TANITA Corporation, Japan) was used. Venous blood samples were obtained after a 12-hour overnight fast. Analyses for glucose and lipid profile were performed at the Division of Clinical Chemistry, Faculty of Medicine, Ramathibodi Hospital, which was certified by the Centers for Disease Control, USA - National Heart, Lung and Blood Institute Lipid Standardization Program.

Follow-up and ascertainment of stroke death cases

After the baseline survey, by using the unique 13-digit identification number of Thai citizen, the vital status of each participant was monitored twice a year through the National Death Registration Database established by the Department of Provincial Administration, Ministry of Interior, supplemented by annual home visits by trained village health volunteers. By December 31, 2016, 3,481 participants died. Of these, 2,298 (66.0%) participants died outside a hospital. To obtain a complete and community-based case ascertainment, the authors reviewed multiple overlapping sources of data to identify the cause of death, including hospital medical records (n=466), verbal autopsy (n=2,458), official death certificate (n=3,481), and hospital discharge summary (n=657) identified through the national database system, which covers 95.5% of Thai population who are under health security schemes[14]. For verbal autopsy, trained health personnel interviewed close relatives of the deceased using the standard verbal autopsy instrument developed by the World Health Organization[15]. The verbal interview reports were reviewed by two board-certified neurologists independently to determine the cause of death. If there was any disagreement, a third senior board-certified neurologist would review the case and determine the cause of death. Hospital medical records were also reviewed independently

by two board-certified neurologists to determine the cause of death and a third senior board-certified neurologist would review the case and determine the cause of death, if there was any disagreement.

Definitions

Stroke was defined according to the World Health Organization clinical definition as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin"[16]. Education, occupation, and personal income were used as indicators of socioeconomic status. Education was classified as illiterate, primary, secondary, and university levels. Occupation was classified as non-manual, manual class, agricultural class, and unemployed or housework class. Personal income was categorized using monthly income cutoffs at less than 2,000 Thai Baht as low personal income (35 Thai Baht ≈ 1 US dollar in 2009 and 30 Thai Baht ≈ 1 US dollar in 2019). Non-smokers were those who had never smoked at all or had smoked less than 100 cigarettes in their lifetime. Current smoker was defined as having smoked 100 or more cigarettes in a lifetime and smokes cigarettes currently. Participants who smoked 100 or more cigarettes in their lifetime but currently do not smoke at all were defined as ex-smokers. The history of snoring was categorized as "always or almost always" (habitual snoring), "often", "occasionally", or "never". Those who reported snoring habitually or often were defined as "snoring", and the rest of the participants were defined as "non-snoring". For hypertension, the average of the three measurements was used in the present study analysis, and hypertension was defined as blood pressure of 140/90 mmHg or more or self-reported use of antihypertensive medication. Fasting plasma glucose of 7.0 mmol/L (126 mg/dL) or more or history of treatment for diabetes was defined as diabetes. Hypercholesterolemia was defined as fasting total cholesterol of 5.2 mmol/L (200 mg/dL) or more or self-reported use of medication for hypercholesterolemia.

Statistical analysis

Baseline characteristics were demonstrated as percentages for categorical variables, and as mean ± standard deviation (SD) for continuous variables. To estimate the association between baseline characteristics and stroke death, the number of person-years of follow up for each participant was counted from the date of study entry until the date of death (n=3,481), or the end of follow-up of December 31, 2016 (n=16,139), whichever came first. The survival time for participants were regarded as censored if the participants were alive by the end of follow-up. A univariate Fine and Gray competing risk regression model[17] was used to examine the individual relationship between each variable and stroke death, with non-stroke deaths considered as competing event. After each variable was tested independently in a univariate regression model, those that achieved a p-value less than 0.20 were selected for testing in multivariate Fine and Gray competing risk regression model[17]. Subdistribution hazard ratio (SHR) and 95% confidence intervals (CIs) were used to illustrate the associations between potential risk factors and stroke death. The proportional sub-hazards assumption for each potential prognostic factor was assessed and satisfied by including interaction time-dependent terms in the regression analysis[18]. All probability values were two sided and level of significance was set at p-value of less than 0.05. All statistical analyses were performed using Stata, version 13.1 (StataCorp, Texas, USA).

Results

Baseline characteristics of participants are shown in Table 1. Nineteen thousand six hundred twenty participants (33.7% were men), free of stroke at baseline, with a mean age of 58.9 years (standard deviation 9.0 years) and age range of 45 to 80 years, were included in the present study. Most were married (71.4%), primary educational level (78.7%), manual class occupation (35.4%), and living in northeastern region (31.0%). There were 13.9% current smoker, 27.1% snoring, 41.3% overweight, 43.2% hypertension, 16.0% diabetes mellitus, and 65.7% hypercholesterolemia.

Participants of the present study were followed for a median period of 11.1 years (interquartile range 10.3 to 11.7), leading to 202,803 person-years of observation. During the follow-up period, 16,139 (82.3%) participants remained alive and 3,481 (17.7%) participants died (Table 1). Of the participants who died, 305 (8.8%) participants died of stroke, and 3,176 (91.2%) participants died of non-stroke cause. The stroke mortality rate was 150.4 per 100,000 person-years (95% CI 134.4 to 168.2).

In univariate Fine and Gray competing risk regression analysis, accounting for the competing risk of non-stroke death, all baseline variables, except for snoring, were statistically significantly ($p<0.05$)

Table 1. Baseline characteristics of participants, overall, and divided by outcomes

Variables	Total (n=19,620)	Alive (n=16,139)	Stroke death (n=305)	Non-stroke death (n=3,176)
Sex: male	33.7%	30.8%	45.6%	47.2%
Age (years)				
45 to 59	56.2%	62.6%	22.3%	26.8%
60 to 69	28.5%	27.4%	39.0%	32.9%
70 to 80	15.3%	10.0%	38.7%	40.3%
Mean (SD)	58.9 (9.0)	57.5 (8.3)	66.0 (8.4)	65.6 (9.0)
Marital status				
Single	5.8%	6.2%	4.3%	4.2%
Married	71.4%	72.9%	61.3%	65.1%
Widow/widower	17.3%	15.2%	29.8%	26.3%
Separated	5.5%	5.7%	4.6%	4.4%
Education level				
Illiterate	2.7%	2.3%	7.2%	4.4%
Primary	78.7%	77.3%	80.7%	85.1%
Secondary	11.7%	12.5%	9.5%	8.1%
University	6.9%	7.9%	2.6%	2.4%
Occupation				
Non-manual class	5.4%	6.3%	2.0%	1.5%
Manual class	35.4%	37.0%	27.2%	28.4%
Agricultural class	30.7%	31.5%	23.9%	27.0%
Unemployed/house work	28.5%	25.2%	46.9%	43.1%
Low personal income (<2,000 Thai Baht*/month)	37.2%	32.7%	55.5%	57.8%
Geographic region				
Bangkok	10.6%	11.1%	6.9%	8.5%
Central	24.2%	25.7%	22.6%	16.3%
Northern	22.0%	21.3%	19.3%	26.0%
Northeastern	31.0%	29.2%	41.7%	39.2%
Southern	12.2%	12.7%	9.5%	10.0%
Smoking status				
Non-smoker	70.4%	74.1%	56.1%	52.7%
Ex-smoker	15.7%	13.9%	22.3%	24.6%
Current smoker	13.9%	12.0%	21.6%	22.7%
Alcohol consumption (g/day)				
0	67.5%	66.5%	75.1%	71.6%
0.1 to 9.9	26.1%	27.0%	19.6%	22.4%
10.0 to 29.9	3.8%	3.9%	3.3%	3.3%
≥30.0	2.6%	2.6%	2.0%	2.7%
Snoring	27.1%	27.4%	26.7%	25.6%
Body mass index (kg/m^2)				
Underweight (<18.5)	6.9%	5.1%	12.3%	15.7%
Normal (18.5 to 24.9)	51.8%	51.2%	53.3%	54.4%
Overweight (≥ 25.0)	41.3%	43.7%	34.4%	29.9%
Hypertension	43.2%	40.6%	65.6%	54.2%
Diabetes mellitus	16.0%	13.9%	22.7%	25.9%
Hypercholesterolemia	65.7%	67.2%	58.4%	58.7%

SD=standard deviation

* 35 Thai Baht ≈ 1 US dollar in 2009, and 30 Thai Baht ≈ 1 US dollar in 2019

Table 2. Predictors of stroke mortality, using univariate competing risk regression model

Variables	SHR	95% CI	p-value
Sex: male	1.66	1.32 to 2.08	<0.001
Age (years)			<0.001
45 to 59	1.00	-	
60 to 69	3.48	2.59 to 4.69	
70 to 80	6.47	4.80 to 8.72	
Marital status			<0.001
Single	1.00	-	
Married	1.20	0.68 to 2.11	
Widow/widower	2.44	1.36 to 4.36	
Separated	1.17	0.55 to 2.49	
Education level			<0.001
Illiterate	7.37	3.30 to 16.46	
Primary	2.84	1.42 to 5.71	
Secondary	2.20	1.01 to 4.80	
University and higher	1.00	-	
Occupation			<0.001
Non-manual class	1.00	-	
Manual class	2.19	0.96 to 5.01	
Agricultural class	2.28	1.00 to 5.24	
Unemployed/house work	4.73	2.09 to 10.70	
Low personal income (<2,000 Thai Baht*/month)	2.13	1.70 to 2.68	<0.001
Geographic region			<0.001
Bangkok	1.00	-	
Central	1.47	0.90 to 2.39	
Northern	1.38	0.84 to 2.27	
Northeastern	2.19	1.38 to 3.47	
Southern	1.24	0.71 to 2.18	
Smoking status			<0.001
Non-smoker	1.00	-	
Ex-smoker	1.79	1.35 to 2.37	
Current smoker	1.96	1.48 to 2.61	
Alcohol consumption (g/day)			0.044
0	1.00	-	
0.1 to 9.9	0.67	0.51 to 0.90	
10.0 to 29.9	0.78	0.42 to 1.48	
≥30.0	0.68	0.30 to 1.53	
Snoring	0.98	0.75 to 1.28	0.885
Body mass index (kg/m^2)			<0.001
Underweight (<18.5)	1.00	-	
Normal (18.5 to 24.9)	0.58	0.40 to 0.82	
Overweight (≥ 25.0)	0.47	0.32 to 0.68	
Hypertension	2.52	1.99 to 3.19	<0.001
Diabetes mellitus	1.56	1.19 to 2.03	0.001
Hypercholesterolemia	0.72	0.58 to 0.91	0.005

SHR=subdistribution hazard ratio; CI=confidence interval

* 35 Thai Baht ≈ 1 US dollar in 2009, and 30 Thai Baht ≈ 1 US dollar in 2019

associated with stroke death (Table 2). Multivariate Fine and Gray competing risk regression model (Table 3), which included all variables with p<0.20 in the univariate analysis in the model, showed that men (p=0.043), age (p<0.001), geographic region (p=0.001), smoking status (p=0.003), and hypertension (p<0.001) were significantly associated with a higher risk of stroke death. Among these factors, older age had the highest SHR (3.37, 95% CI 2.25 to 5.04, and 2.28, 95% CI 1.61 to 3.23 in 70 to 80 years and 60 to 69 years age group, respectively), followed by geographic region, that was, living in northeastern region (SHR 2.05, 95% CI 1.26 to 3.34), hypertension (SHR 2.05, 95% CI 1.56 to 2.68), current smoker (SHR 1.97, 95% CI 1.33 to 2.91), and men (SHR 1.46, 95% CI 1.01 to 2.10). Hypercholesterolemia was significantly associated with a lower risk of stroke death (SHR 0.74, 95% CI 0.57 to 0.96, p=0.021). Marital status, education level, occupation, low personal income, alcohol consumption, body mass index (BMI), diabetes mellitus, and snoring were not significant predictors of stroke mortality.

Discussion

In the present prospective community-based cohort study of the Thai general population (n=19,620), including 202,803 person-years of observation with 305 deaths from stroke, the authors found that men, older age, geographic region, smoking status, and hypertension were significantly associated with a higher risk of stroke mortality, after controlling for several potential confounders and accounting for non-stroke death as a competing risk (Table 3). Among these associated factors, older age had the highest SHR, followed by geographic region, that was, living in northeastern region, hypertension, current smoker, and men. Whereas hypercholesterolemia was significantly associated with a lower risk of stroke mortality (Table 3). Marital status, education level, occupation, low personal income, alcohol consumption, BMI, diabetes mellitus, and snoring were not found to be predictors of stroke mortality.

In general, stroke has been considered as a disease of aging[19]. The incidence of stroke increases with age, with the incidence doubling for each decade after 55 years of age[1]. The present study showed that older age was a strong predictor of stroke mortality, which was consistent with the previous studies[20-22].

Geographic variation in stroke mortality has been observed in some regions such as the United States[23], China[24], and Korea[25]. The present study

Table 3. Predictors of stroke mortality, using multivariate competing risk regression model

Variables	SHR	95% CI	p-value
Sex: male	1.46	1.01 to 2.10	0.043
Age (years)			<0.001
45 to 59	1.00	-	
60 to 69	2.28	1.61 to 3.23	
70 to 80	3.37	2.25 to 5.04	
Marital status			0.129
Single	1.00	-	
Married	1.15	0.60 to 2.19	
Widow/widower	1.59	0.82 to 3.11	
Separated	1.45	0.64 to 3.26	
Education level			0.077
Illiterate	2.85	1.00 to 8.13	
Primary	1.59	0.62 to 4.07	
Secondary	1.54	0.60 to 3.98	
University and higher	1.00	-	
Occupation			0.297
Non-manual class	1.00	-	
Manual class	0.82	0.28 to 2.41	
Agricultural class	0.65	0.21 to 1.98	
Unemployed/house work	0.91	0.31 to 2.66	
Low personal income (<2,000 Thai Baht*/month)	1.12	0.86 to 1.47	0.394
Geographic region			0.001
Bangkok	1.00	-	
Central	1.64	0.99 to 2.71	
Northern	1.15	0.67 to 1.96	
Northeastern	2.05	1.26 to 3.34	
Southern	1.32	0.73 to 2.38	
Smoking status			0.003
Non-smoker	1.00	-	
Ex-smoker	1.30	0.90 to 1.88	
Current smoker	1.97	1.33 to 2.91	
Alcohol consumption (g/day)			0.128
0	1.00	-	
0.1 to 9.9	0.68	0.50 to 0.94	
10.0 to 29.9	0.84	0.43 to 1.66	
≥30.0	0.76	0.34 to 1.74	
Body mass index (kg/m^2)			0.608
Underweight (<18.5)	1.00	-	
Normal (18.5 to 24.9)	0.93	0.62 to 1.40	
Overweight (≥ 25.0)	0.82	0.51 to 1.31	
Hypertension	2.05	1.56 to 2.68	<0.001
Diabetes mellitus	1.26	0.94 to 1.68	0.128
Hypercholesterolemia	0.74	0.57 to 0.96	0.021

SHR=subdistribution hazard ratio; CI=confidence interval

* 35 Thai Baht ≈ 1 US dollar in 2009, and 30 Thai Baht ≈ 1 US dollar in 2019

also demonstrated that a geographic region was associated with stroke mortality with the highest SHR (2.05, 95% CI 1.26 to 3.34) in northeastern region. This geographical difference in stroke mortality may be related to differences in lifestyles, health seeking behaviors, and the prevalence of other stroke risk factors between the regions.

Hypertension is a major risk factor for both cerebral infarction and intracerebral hemorrhage[4]. In a meta-analysis of 61 prospective observational studies involving one million adults with no previous vascular disease at baseline, researchers found that in people between the ages of 40 and 69 years, beginning with systolic blood pressure (SBP) of 115 mmHg and diastolic blood pressure (DBP) of 75 mmHg, each incremental rise of 20 mmHg in SBP and 10 mmHg in DBP was associated with more than a twofold increase in death rate from stroke[26]. In the present study, hypertension (SHR 2.05, 95% CI 1.56 to 2.68) was the strongest modifiable predictor of stroke mortality.

Several studies have identified cigarette smoking as a potent risk factor for ischemic stroke[4]. A recent meta-analysis included 14 studies involving 303,134 subjects, demonstrated that smokers had an overall increased risk of stroke compared with non-smokers, with a pooled odds ratio (OR) of 1.61 (95% CI 1.34 to 1.93)[27]. The present study found that current smoker was a potent predictor of stroke mortality (SHR 1.97, 95% CI 1.33 to 2.91), which was consistent with the previous studies[20,28,29].

The present study revealed that men was a significant predictor (SHR 1.46, 95% CI 1.01 to 2.10) of stroke mortality, which was in line with some previous studies[22,30]. Sex differences in risk factor prevalence and lifestyle may explain this finding.

The relationship between lipids and stroke is complex. In most epidemiological cohorts, there is a direct relationship between cholesterol levels and ischemic stroke[31]. However, this relationship varies by ischemic stroke subtype, with associations strongest for atherosclerotic subtypes[31]. Conversely, there is an increased risk of intracerebral hemorrhage at low cholesterol levels[31,32], and there is evidence that small vessel disease may share a similar profile of inverse association with lipid levels[31]. The present study showed that hypercholesterolemia was inversely associated with stroke mortality (SHR 0.74, 95% CI 0.57 to 0.96, p=0.021). An explanation for this finding may be because it was not possible to distinguish between ischemic stroke and hemorrhagic stroke in the present study. Moreover, in Thailand, there is higher proportion of hemorrhagic stroke

comparing with Caucasian populations[8]. Therefore, a positive association between increased cholesterol and ischemic stroke may be counterbalanced by the inverse association between low cholesterol and hemorrhagic stroke.

Recently, a meta-analysis of 34 studies has demonstrated the influence of marital status on the stroke mortality[33]. The results of this meta-analysis demonstrated that unmarried participants had increased odds of stroke death (OR 1.55, 95% CI 1.16 to 2.08), compared with married participants. In present study, marital status was a significant predictor of stroke mortality in univariate ($p<0.001$), but not in multivariate analysis adjusted for conventional risk factors and other potential confounders. This finding suggested that marital status may be a surrogate marker for adverse health behavior or cardiovascular risk factor profiles rather than being a risk factor in itself.

Several studies demonstrated that socioeconomic status inversely associated with stroke mortality[34]. In present study, socioeconomic status, measured by education level, occupation, and low personal income, was also inversely associated with stroke mortality in univariate analysis ($p<0.001$). However, these associations were not statistically significant after adjustment for potential confounders, including major cardiovascular risk factors such as smoking, hypertension, diabetes, and hypercholesterolemia. These findings suggested that the mechanisms through which socioeconomic status affected stroke mortality may be due to differences in major cardiovascular risk factor prevalence.

A recent meta-analysis based on 27 prospective studies demonstrated that light and moderate alcohol consumption was inversely associated only with ischemic stroke, whereas heavy drinking was associated with increased risk of all stroke type with a stronger association for hemorrhagic strokes[35]. The present study found no association between alcoholic consumption and stroke mortality in multivariate analysis. This finding may be because alcohol consumption had divergent effects on different stroke subtypes[35] and the present study used all stroke mortality as the outcome.

Previous prospective studies have reported on the relation between BMI and stroke mortality, but the findings have been inconsistent, including a positive association[36], no association[28], a U-shaped association[37], or even an inverse association[38]. In the present study, BMI was not related to stroke mortality in the multivariate model.

In multivariate analysis, the present study found no significant association of diabetes with stroke mortality, which was similar to some studies[20,28]. Other previous prospective studies[22,29,39] have implicated diabetes as a significant predictor for stroke mortality. However, previous studies that distinguished types of stroke found a significant positive association of diabetes with ischemic stroke, but a negative association with hemorrhagic stroke[40-42]. In present study, the authors used all stroke death as the outcome because it was not possible to distinguish between ischemic stroke and hemorrhagic stroke, therefore, the differences in relationship of diabetes with different types of stroke may explain the present finding.

A meta-analysis based on eight prospective observational studies with 65,037 participants revealed that self-reported habitual snoring was a mild but statistically significant risk factor for stroke, but not for cardiovascular disease and all-cause mortality[43]. The present study found no association between snoring and stroke mortality, which was similar to a previous study[44].

The strengths of the present study include its prospective design and enrollment of participants from the general population in five regions around Thailand rather than a selected population. The authors used multiple overlapping sources of data to verify cause of death, which was verified by board-certified neurologists. However, the present study has certain limitations. Participants were recruited on a voluntary basis, so the study sample was not established by random sampling. Nonetheless, it covers all major demographic strata of the Thai general population aged 45 to 80 years[12]. The authors were unable to segregate ischemic from hemorrhagic stroke during the subsequent follow-up period. Finally, although several potential confounders have been adjusted, unknown confounders may not have been included in the analyses.

Conclusion

The authors found that older age, geographic region (northeastern region), hypertension, current smoker, and men were significant predictors of higher risk of stroke mortality. Whereas hypercholesterolemia was significantly associated with a lower risk of stroke mortality, which could be partially explained by the authors' inability to segregate ischemic from hemorrhagic stroke during the subsequent follow-up period. No associations were seen with marital status, education level, occupation, low personal income,

alcohol consumption, BMI, diabetes mellitus, and snoring. Therefore, identifying the individuals who have higher risk of stroke mortality by using the high-risk predictors could be warranted. Clinical preventive focus targeting these groups may reduce the stroke mortality in the Thai population.

What is already known on this topic?

Stroke is a major health problem worldwide. In Thailand, stroke is the first leading cause of death in both sexes. It carries the first rank for disease burden in Thailand measured by DALYs lost in female and the third in male. To reduce the stroke mortality, it is essential to identify the factors predicting stroke mortality. Despite a significant and increasing amount of research on this issue in developed countries, good quality data on stroke risk factors in developing countries including Thailand are lacking.

What this study adds?

The present study demonstrated that older age, geographic region (northeastern region), hypertension, current smoker, and men were significant predictors of a higher risk of stroke mortality. Marital status, education level, occupation, low personal income, alcohol consumption, BMI, diabetes mellitus, and snoring were not significantly related to stroke mortality. These finding are likely to be very important in the development of policies or tailored strategies for reduction of stroke mortality.

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Conflicts of interest

The authors declare no conflict of interest.

References

1. Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, 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.
2. 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;54:171-9.
3. Kalkonde YV, Alladi S, Kaul S, Hachinski V. Stroke prevention strategies in the developing world. Stroke 2018;49:3092-7.
4. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:3754-832.
5. Kulshreshtha A, Anderson LM, Goyal A, Keenan NL. Stroke in South Asia: a systematic review of epidemiologic literature from 1980 to 2010. Neuroepidemiology 2012;38:123-9.
6. Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke epidemiology in South, East, and South-East Asia: a review. J Stroke 2017;19:286-94.
7. Porapakkham Y, Rao C, Pattaraarchachai J, Polprasert W, Vos T, Adair T, et al. Estimated causes of death in Thailand, 2005: implications for health policy. Popul Health Metr 2010;8:14.
8. Suwanwela NC. Stroke epidemiology in Thailand. J Stroke 2014;16:1-7.
9. Bundhamcharoen K, Odton P, Phulkerd S, Tangcharoensathien V. Burden of disease in Thailand: changes in health gap between 1999 and 2004. BMC Public Health 2011;11:53.
10. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133:601-9.
11. Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing risk of death: an important consideration in studies of older adults. J Am Geriatr Soc 2010;58:783-7.
12. Hanchaiphiboolkul S, Poungvarin N, Nidhinandana S, Suwanwela NC, Puthkhao P, Towanabut S, et al. Prevalence of stroke and stroke risk factors in Thailand: Thai Epidemiologic Stroke (TES) Study. J Med Assoc Thai 2011;94:427-36.
13. Hanchaiphiboolkul S, Suwanwela NC, Poungvarin N,

Nidhinandana S, Puthkhao P, Towanabut S, et al. Risk of metabolic syndrome for stroke is not greater than the sum of its components: Thai Epidemiologic Stroke (TES) study. J Stroke Cerebrovasc Dis 2013;22:e264-70.
14. Kongbunkiat K, Kasemsap N, Thepsuthammarat K, Tiamkao S, Sawanyawisuth K. National data on stroke outcomes in Thailand. J Clin Neurosci 2015;22:493-7.
15. World Health Organization. Verbal autopsy standards: ascertaining and attributing cause of death [Internet]. 2007 [cited 2020 Apr 5]. Available from: https://apps.who.int/iris/handle/10665/43764.
16. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. Bull World Health Organ 1980;58:113-30.
17. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
18. Cleves M, Gould W, Gutierrez RG, Marchenko YV. Competing risks. In: Cleves M, Gould W, Gutierrez RG, Marchenko YV, editors. An introduction to survival analysis using Stata. 3rd ed. Texas: Stata Press; 2010. p. 365-91.
19. Boehme AK, Esenwa C, Elkind MSV. Stroke risk factors, genetics, and prevention. Circ Res 2017;120:472-95.
20. Khaw KT, Barrett-Connor E, Suarez L, Criqui MH. Predictors of stroke-associated mortality in the elderly. Stroke 1984;15:244-8.
21. Menotti A, Jacobs DR Jr, Blackburn H, Kromhout D, Nissinen A, Nedeljkovic S, et al. Twenty-five-year prediction of stroke deaths in the Seven Countries Study: the role of blood pressure and its changes. Stroke 1996;27:381-7.
22. Pham TM, Fujino Y, Tokui N, Ide R, Kubo T, Shirane K, et al. Mortality and risk factors for stroke and its subtypes in a cohort study in Japan. Prev Med 2007;44:526-30.
23. Lanska DJ, Kuller LH. The geography of stroke mortality in the United States and the concept of a stroke belt. Stroke 1995;26:1145-9.
24. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, incidence, and mortality of stroke in China: Results from a nationwide population-based survey of 480,687 adults. Circulation 2017;135:759-71.
25. Lee J, Bahk J, Kim I, Kim YY, Yun SC, Kang HY, et al. Geographic variation in morbidity and mortality of cerebrovascular diseases in Korea during 2011-2015. J Stroke Cerebrovasc Dis 2018;27:747-57.
26. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13.
27. Pan B, Jin X, Jun L, Qiu S, Zheng Q, Pan M. The relationship between smoking and stroke: a meta-analysis. Medicine (Baltimore) 2019;98:e14872.
28. Håheim LL, Holme I, Hjermann I, Leren P. Risk factors of stroke incidence and mortality: a 12-year follow-up of the Oslo Study. Stroke 1993;24:1484-9.
29. Knuiman MW, Vu HTV. Risk factors for stroke mortality in men and women: the Busselton Study. J Cardiovasc Risk 1996;3:447-52.
30. Holroyd-Leduc JM, Kapral MK, Austin PC, Tu JV. Sex differences and similarities in the management and outcome of stroke patients. Stroke 2000;31:1833-7.
31. Yaghi S, Elkind MSV. Lipids and cerebrovascular disease: research and practice. Stroke 2015;46:3322-8.
32. Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. Stroke 2013;44:1833-9.
33. Wong CW, Kwok CS, Narain A, Gulati M, Mihalidou AS, Wu P, et al. Marital status and risk of cardiovascular diseases: a systematic review and meta-analysis. Heart 2018;104:1937-48.
34. Marshall IJ, Wang Y, Crichton S, McKevitt C, Rudd AG, Wolfe CDA. The effects of socioeconomic status on stroke risk and outcomes. Lancet Neurol 2015;14:1206-18.
35. Larsson SC, Wallin A, Wolk A, Markus HS. Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. BMC Med 2016;14:178.
36. Zhou M, Offer A, Yang G, Smith M, Hui G, Whitlock G, et al. Body mass index, blood pressure, and mortality from stroke: a nationally representative prospective study of 212,000 Chinese men. Stroke 2008;39:753-9.
37. Oki I, Nakamura Y, Okamura T, Okayama A, Hayakawa T, Kita Y, et al. Body mass index and risk of stroke mortality among a random sample of Japanese adults: 19-year follow-up of NIPPON DATA80. Cerebrovasc Dis 2006;22:409-15.
38. Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, et al. Body mass index and mortality from cardiovascular disease among Japanese men and women: the JACC study. Stroke 2005;36:1377-82.
39. Tuomilehto J, Rastenyte D, Jousilahti P, Sarti C, Vartiainen E. Diabetes mellitus as a risk factor for death from stroke. Prospective study of the middle-aged Finnish population. Stroke 1996;27:210-5.
40. Burchfiel CM, Curb JD, Rodriguez BL, Abbott RD, Chiu D, Yano K. Glucose intolerance and 22-year stroke incidence. The Honolulu Heart Program. Stroke 1994;25:951-7.
41. Janghorbani M, Hu FB, Willett WC, Li TY, Manson JE, Logroscino G, et al. Prospective study of type 1 and type 2 diabetes and risk of stroke subtypes: the Nurses' Health Study. Diabetes Care 2007;30:1730-5.
42. Cui R, Iso H, Yamagishi K, Saito I, Kokubo Y, Inoue M, et al. Diabetes mellitus and risk of stroke and its subtypes among Japanese: the Japan Public Health Center Study. Stroke 2011;42:2611-4.
43. Li D, Liu D, Wang X, He D. Self-reported habitual

snoring and risk of cardiovascular disease and all-cause mortality. Atherosclerosis 2014;235:189-95.
44. Marshall NS, Wong KKH, Cullen SRJ, Knuiman MW, Grunstein RR. Snoring is not associated with all-cause mortality, incident cardiovascular disease, or stroke in the Busselton Health Study. Sleep 2012;35:1235-40.