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Original article

Effects of fine particulate matter on hospital admission due to stroke in a business city of Thailand

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Background: About 99.0% of global population was living in the area where air pollutant levels exceed World Health Organization Standard. Particulate matter whose diameter is equal to or less than 2.5 microns ($PM_{2.5}$), is an important risk factor for chronic diseases including chronic respiratory diseases, heart diseases and lung cancer. However, the association between $PM_{2.5}$ and cerebrovascular event is still controversial, especially in Asian populations.

Objective: To assess the association between $PM_{2.5}$ and hospital admissions due to stroke.

Methods: A retrospective study was conducted using air monitoring and health data during 2017 - 2019 in Hatyai, a business city in Thailand. The daily mean concentrations of $PM_{2.5}$ were obtained from the Thai Pollution Control Department. The daily numbers of hospital admissions due to stroke such as ischemic stroke, hemorrhagic stroke and all stroke were obtained from the Thai National Health Security Office Regional Office 12. The association between $PM_{2.5}$ and outcome were assessed using Zero-inflated Negative Binomial regression, applied with the lag time of 0 to 4. For sensitivity analysis, the subgroup analysis by age and sex was performed.

Results: The mean daily concentration of $PM_{2.5}$ during the study period was 17.10 $\mu g/m^3$ (4.00 - 74.10 $\mu g/m^3$). Every 10 $\mu g/m^3$ increase in daily concentration of $PM_{2.5}$ was associated with incidence rate ratio (95%CI) of hospital admissions due to hemorrhagic stroke of 1.26 (1.09 - 1.46), 1.27 (1.10 - 1.48) and 1.18 (1.02 - 1.38) at lag0, lag1 and lag2, respectively. No association was observed between the daily concentration of $PM_{2.5}$ and ischemic stroke. According to sensitivity analysis, only positive association between $PM_{2.5}$ and stroke were found in male sex subgroup at lag0.

Conclusion: Exposure to $PM_{2.5}$ was associated with hemorrhagic stroke, a severe clinical condition. Therefore, health surveillance should also include monitoring the incidence of the hemorrhagic stroke, especially when the $PM_{2.5}$ exceeds standard limits.

Keywords: Fine particulate matter, $PM_{2.5}$, hemorrhagic stroke, ischemic stroke.

Air pollutants especially the fine ($PM_{2.5}$) and ultrafine particulate ($PM_{0.1}$) matter have been an important health issue for decades. According to the World Health Organization (WHO) report in 2018, 99.0% global population was living in the area where air pollutant levels exceeds WHO's standard.[(1)] About 3.1 million premature deaths of global population in 2010 was attributable to $PM_{2.5}$.[(2)] The mortality rate due to $PM_{2.5}$ varies differed among different ethnicities and regions of the world. Total and per-capita mortality due to $PM_{2.5}$ are highest in the Asian region 63 deaths per hundred thousand.[(2)] These might be due to the exacerbation of multi-factorial diseases due to $PM_{2.5}$ such as cerebrovascular diseases whose severities differed among ethnicities and culture.[(3)]

Previous studies found that continuously exposure to $PM_{2.5}$ is an indisputable risk factors for chronic diseases including asthma [(4 - 7)], chronic obstructive pulmonary disease [(4, 8)], pneumonia[(4)], upper respiratory tract infection[(7)], ischemic heart diseases[(9)], arrythmia[(9)], heart failure [(9, 10)] and lung cancer.[(11)]

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However, the associations between exposure to $PM_{2.5}$ and cerebrovascular diseases are still controversial especially across ethnicities.

Various studies from Europe and North America did not show association between $PM_{2.5}$ and cerebrovascular diseases. Byrne CP, *et al*. conducted a cross-sectional study in Ireland and reported no association between numbers of hospital admission due to all stroke and ischemic stroke and daily concentration of $PM_{2.5}$ in 2013 - 2017. (12) Similarly, studies in Villeneuve PJ, *et al*. (13) and Fisher JA, *et al*. (14), revealed that no association was found between all stroke, ischemic stroke, hemorrhagic stroke and daily concentration of $PM_{2.5}$. In contrast, a study in Portugal found that every increase in 10 µg/m^3 was associated with the increase in numbers of inpatients due to spontaneous intracerebral hemorrhage (SICH) by 1.064 (1.009 - 1.122) time in patients aged 70 years or younger and 1.051 (1.002 - 1.103) time in patients aged older than 70 years.

On the other hand, studies in Asia which were mostly from China showed positive association between $PM_{2.5}$ and cerebrovascular events. Zhang R, *et al*. demonstrated that the increases in $PM_{2.5}$ by 10 µg/m^3 were association with 0.3%, 0.2%, and 0.4% increase in mortality due to all stroke, ischemic stroke and hemorrhagic stroke, respectively.(15) A population studies of Gu J, *et al*. from 248 Chinese cities reported positive association between $PM_{2.5}$ and all stroke and ischemic stroke.(16) In addition, Yorifuji T, *et al*. conducted a study in Japan and reported only positive association between $PM_{2.5}$ and mortality due to subarachnoid hemorrhage.(17)

The magnitude and direction of the association between $PM_{2.5}$ concentration and incidence of stroke differed between studied from various racial/ethnicities. This might be explained by the genetic variation or the differences in life styles across cultures.

In Thailand, various studies including Denduangchai S, *et al*.(18) and Pothirat C, *et al*. (19) were conducted and explored the association between the $PM_{2.5}$ and stroke. However, all of the studies so far were focused on the cities or area with high concentration of $PM_{2.5}$. Some studies were conducted for short amount of time. None of the study were performed in the city where $PM_{2.5}$ concentration was generally below the Thai standard. This study was conducted in Hat Yai, a business city, in Songkhla province with generally low levels of air pollutants.

The city had an air monitoring station of the Thai Pollution Control Department (PCD) coupling with tertiary hospitals established for decades. Therefore, the $PM_{2.5}$ and health related data are rich enough to assess the association between the air pollutant level and health effects. Daily $PM_{2.5}$ ambient concentrations were between 4 - 5 µg/m^3 and as high as 75 µg/m^3 during transboundary haze season in July to September every other years.

Although the city's ambient concentrations of $PM_{2.5}$ were generally lower than the Thai standard limits which set at < 50 µg/m^3 throughout the year, the health effects from $PM_{2.5}$ were not negligible. Studies showed that cerebrovascular diseases, a possible health effect of $PM_{2.5}$ were varied by ethnicities and regions and might be possible to be exacerbated in vulnerable population including people with hypertension and diabetes even at the levels of daily $PM_{2.5}$ below WHO (< 15 µg/m^3) or Thai (< 50 µg/m^3) standard limits. Therefore, this study assessed the effects of $PM_{2.5}$ in a city with low to high air pollutant level by linking the changes of daily stroke incidence to the daily ambient concentration of $PM_{2.5}$.

Study design and settings

A retrospective study of time-series data was conducted using air quality and health data between 1st January 2017 - 31st December 2019 in Hatyai a business district in Songkhla province. The total study period was 3 consecutive years. The study protocol was approved by Human Research Ethics Committee of Faculty of Medicine, Prince of Songkla University. The ethical approval number is REC 65-062-9-4.

Fine particulate matter ($PM_{2.5}$) and atmospheric data source

The hourly concentrations of $PM_{2.5}$ were retrieved from an air monitoring station owned by the PCD, Ministry of Natural Resources and Environment. The concentration of $PM_{2.5}$ was measured in µg/m^3 using EPA recommended methods which are beta attenuation monitoring (BAM). The hourly concentration of $PM_{2.5}$ were later average into daily concentration in the final analysis.

The atmospheric data were obtained from the Thai Meteorological Department (TMD) using continuous air monitoring station. The 5 meteorological variables including temperature in degree Celsius (°C), atmospheric pressure in hectopascal (hPa), relative humidity in percent (%), dew points in degree Celsius (°C) and wind speed in kilometers per hour (km/hr) were measured using stationary air monitoring of TMD for every 3 hours. The data were then average to daily average of these variables.

Data management and missing data imputation

All data managements and missing data imputation were performed in R version 3.4.1.

The missing data were explored, and their patterns were analyzed and imputed. The missing data percentage of hourly concentration of $PM_{2.5}$ from a PCD station was 29.1%. Two observe missing data patterns of $PM_{2.5}$ were either randomly missing for each hour or entire days, respectively. The 4 time periods when the $PM_{2.5}$ were missing for entire days were Period 1: 30th September 2017 - 27th October 2017, Period 2: 7th November 2017 - 29th November 2017, Period 3: 8th October 2018 - 13th October 2018 and Period 4: 24th October 2018 - 12th June 2019. The entire periods missing were from mechanical errors of the air sensors where PCD had to fix or replace the sensor. Whereas the random hourly missing data were from occasionally WIFI breakdown.

To deal with the entire period missing, the imputation using Inverse Distance Weighting (IDW) average of $PM_{2.5}$ from the nearby stations including Piman subdistrict of Satun province, Sateng subdistrict of Yala province and Bangnak subdistrict of Narathiwat province. The random hourly missing data were imputed using K-Nearest Neighbor (KNN) algorithm based on the hourly data of the same station within the same day, the day before and the day after the missing data points.

For atmospheric data, the missing data were about 0.1% for all atmospheric parameters. The 3 hour missing data points were imputed using K-Nearest Neighbor (KNN) algorithm based on the 3-hour data of the same station within the same day, the day before and the day after the missing data points.

Study population

The patient under Thai government Universal Health-care Coverage Scheme (UCS) aged 20 years and older were included in this study. The total number of people under UCS in Hatyai in the database was 310,101 people which was accounted for 67.7% of the total population of Hatyai of 457,945 people.

Outcome ascertainment

The main outcome data, numbers of hospital admissions due to stroke each day were calculated based on individual admission retrieved from the 43-folder database of Thai National Health Security Office (NHSO) Regional Office 12. The 43-folder database was a database used primarily for medical reimbursement of patients under UCS. The individual admission was recorded as a longitudinal format where the physician diagnosis was translated and coded using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems - Thailand Modification (ICD-10-TM).

The data of patients who had visited hospitals of all sizes in Hatyai district from 1st January 2017 to 31st December 2019 were retrieved from the 43-folder health database. The diagnoses of stroke were identified separately into ischemic and hemorrhagic stroke with the ICD-10-TM: I63x and I60x-I62x, respectively. The ‘all stroke group’ was defined as the admission with either ICD-10-TM: I63x or I60x - I62x, respectively. The total daily numbers of admission due to all, ischemic and hemorrhagic stroke were count and calculated for each day. The intracerebral hemorrhage from other causes including S06.4 epidural hemorrhage, S06.5 traumatic subdural hemorrhage, S06.6 traumatic subarachnoid hemorrhage were excluded from this study.

Statistical analysis

The continuous atmospheric data including daily concentration of $PM_{2.5}$, temperature, atmospheric pressure, relative humidity, dew points and wind speed were described by their corresponding mean, maximum and minimum values. The categorical data including age group, gender, and total numbers of admission due to stroke were described by numbers and percentages.

The association between the daily ambient concentration of $PM_{2.5}$ and the daily admissions due to stroke was assessed using Zero-inflated negative binomial (ZNB) models to account for excess zero daily incidence and since the test of over dispersion as described by Cameron AC, *et al.*[20] The adjust variables in the models were Thai national holidays, atmospheric parameters including temperature, atmospheric pressure, relative humidity, dew points and wind speed. The offsets of the ZNB models were the mid-year population estimates in Hatyai in 2017, 2018 and 2019, respectively, which were retrieved from the Thai Official Statistics Registration Systems, Department of Provincial Administration, Ministry of Interior. Using the offset, the incident rate ratios with their corresponding 95% confidence interval were then calculated, accounting for lag time of 0 up to 4 days because studies found association of $PM_{2.5}$ and stroke up to 4 days after exposure.[21] Due to fact that the study was conducted for the relatively short duration of 3 years, the distribution of demographic characteristics was assumed constant over the study duration. For sensitivity analysis, subgroup analysis by gender and age group of 20 - 44 years old and 45 years old and older were performed with ZNB models to account for stroke in the young and stroke in at risk age group and risk difference between male and female. The statistically significant was determined based on *P* - value < 0.05.

Results

Throughout the 3 - year study period, the total numbers of patients admitted to hospitals due to stroke in Hatyai city were 6,361 persons, consisting of 3,632 males and 2,729 females. Majority (60.0%) of the patients' ages were 60 years old and older. Patients with ischemic stroke were older than those with hemorrhagic stroke (*P* < 0.001) (Table 1).

The outcome which are all stroke, ischemic stroke and hemorrhagic stroke exhibited seasonal trend (data not shown). The average standard deviation (SD) daily numbers of inpatients due to all, ischemic and hemorrhagic stroke were demonstrated in Table 1.

The daily mean concentration of $PM_{2.5}$ was 17.13 $\mu g/m^3$, the minimum was at 4.00 $\mu g/m^3$ and the maximum was at 74.13 $\mu g/m^3$ (Figure 1 and Table 2). The highest concentration of the $PM_{2.5}$ was observed during the Indonesian haze in September 2019. The distributions of the atmospheric parameters exhibit seasonality trend as shown in Figure 1 and Table 2.

From the zero - inflated negative binomial (ZNB) regression, the increases in $PM_{2.5}$ by 10 $\mu g/m^3$ was associated with the increase in the incidence rate of hospital admissions due to hemorrhagic stroke by 1.26 (1.09 - 1.46), 1.27 (1.10 - 1.48), 1.18 (1.02 - 1.38) time (Incidence Rate Ratio: IRR) the background numbers of the hospital admissions at lag time of 0, 1 and 2 days, respectively, adjusted for holiday and atmospheric parameters. However, association between the daily $PM_{2.5}$ concentration and the overall stroke and ischemic stroke in any time lags were not observed (Table 3).

Table 1. Distribution of hospital admission due to stroke in Hatyai during 1st January 2017 – 31st December 2019 by classification of stroke using ICD-10-TM.

Demographic factors	**Hemorrhagic stroke n (%)**	**Ischemic stroke n (%)**	**All stroke n (%)**	***P* - value**
Total	2,276 (35.8)	4,085 (64.2)	6,361 (100.0)	
Mean (SD)	0.79 (1.1)	1.41 (1.3)	2.20 (1.4)	
Minimum	0.00	0.00	1.00	
Maximum	10.00	10.00	12.00	
Gender				0.196
Male	1,324 (58.2)	2,308 (56.5)	3,632 (57.1)	
Female	952 (41.8)	1,777 (43.5)	2,729 (42.9)	
Age (years)				
Mean age (SD)	59.14 (17.0)	64.09 (14.1)	62.29 (15.4)	< 0.001
Age groups				< 0.001
20 - 29 years old	64 (2.8)	23 (0.6)	87 (1.4)	
30 - 39 years old	119 (5.2)	121 (3.0)	240 (3.8)	
40 - 49 years old	345 (15.2)	418 (10.2)	763 (12.0)	
50 - 59 years old	575 (25.3)	878 (21.5)	1,453 (22.8)	
≥ 60 years old	1,173 (51.5)	2,645 (64.8)	3,818 (60.0)	

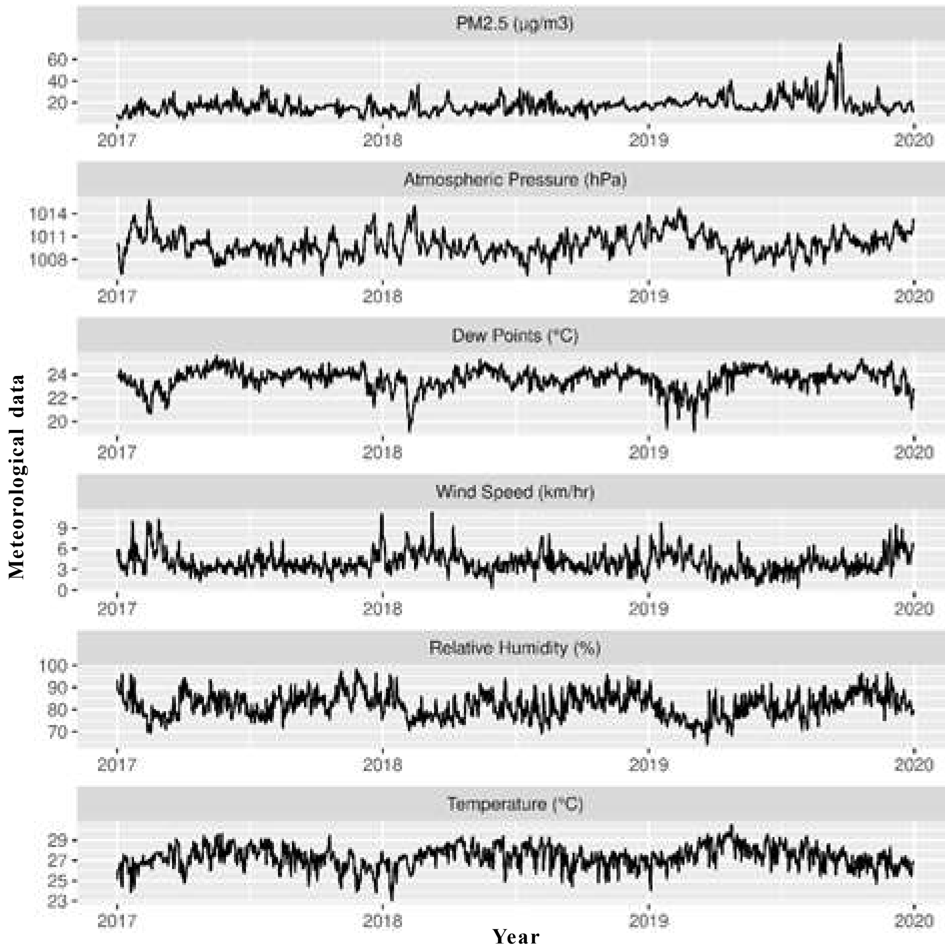

Figure 1. Daily concentration of $PM_{2.5}$ and mean meteorological data during the 3-year study period from 1st January 2017 to 31st December 2019.

Table 2. Distribution of daily concentration of $PM_{2.5}$ and atmospheric parameters during the 3-year study period from 1st January 2017 to 31st December 2019.

Parameters	Mean	Minimum	Maximum
Daily concentration of $PM_{2.5}$ (µg/m³)	17.10	4.00	74.10
Atmospheric pressure (hPa)	1,010.00	1,005.90	1,015.80
Dew points (°C)	23.60	19.10	25.60
Wind speed (km/hr.)	4.00	0.30	11.30
Relative humidity (%)	81.90	64.25	98.50
Temperature (°C)	27.31	23.06	30.54

As for sensitivity analysis, the subgroup analysis by age (Table 4) and gender (Table 5) was performed using ZNB adjusted for holiday and atmospheric parameters similar to the analysis done for Table 3. Only positive association was found in male sex subgroup. For male, the increase in $PM_{2.5}$ by 10 µg/m³ was associated with the increase in the incidence rate of hospital admissions due to hemorrhagic stroke by 1.38 (1.04 - 1.83) time of background hospital admissions at lag time of 0 day (Table 5). Of subgroup analysis by age, no significant association between the daily concentration of $PM_{2.5}$ and incidence rate of hospital admission due to stroke was observed. The association between the $PM_{2.5}$ and hospital admissions due to hemorrhagic stroke were marginally significant in age group of 45 years old and older at lag time of 0 ($P = 0.077$) and in age group of younger than 45 years old at lag time of 3 ($P = 0.057$), respectively (Table 4).

Table 3. The association (Incidence Rate Ratio: IRR) between $PM_{2.5}$ and hospital admission due to all, ischemic and hemorrhagic stroke from Zero-Inflated Negative Binomial Regression (ZNB).

Classification of stroke	Lag 0 (95%CI)	Lag 1 (95%CI)	Lag 2 (95%CI)	Lag 3 (95%CI)	Lag 4 (95%CI)
All stroke	0.98 (0.95 - 1.01)	0.98 (0.95 - 1.01)	0.98 (0.95 - 1.01)	0.98 (0.95 - 1.02)	0.97 (0.94 - 1.01)
Ischemic stroke	1.00 (0.96 - 1.05)	1.01 (0.97 - 1.06)	1.00 (0.96 - 1.05)	0.99 (0.95 - 1.04)	0.98 (0.93 - 1.02)
Hemorrhagic stroke	1.26** (1.09 - 1.46)	1.27** (1.10 - 1.48)	1.18* (1.02 - 1.38)	1.11 (0.95 - 1.30)	1.06 (0.90 - 1.25)

*Denote the $P < 0.05$,** Denote the $P < 0.01$, Lag is the numbers of days since the daily $PM_{2.5}$ concentration.

Table 4. The association (Incidence Rate Ratio: IRR) between $PM_{2.5}$ and hospital admission due to all, ischemic and hemorrhagic stroke from Zero-Inflated Negative Binomial Regression (ZNB) stratified by age group.

Classification of stroke	Age group	Lag 0 (95% CI)	Lag 1 (95% CI)	Lag 2 (95% CI)	Lag 3 (95% CI)	Lag 4 (95% CI)
All stroke	< 45 years old	1.00 (0.90 - 1.11)	1.03 (0.92 - 1.13)	0.98 (0.88 - 1.08)	0.98 (0.88 - 1.09)	0.99 (0.90 - 1.11)
	≥ 45 years old	0.99 (0.95 - 1.03)	0.98 (0.94 - 1.02)	1.00 (0.96 - 1.05)	1.00 (0.96 - 1.04)	1.00 (0.96 - 1.04)
Ischemic stroke	< 45 years old	0.98 (0.83 - 1.13)	0.91 (0.76 - 1.07)	0.92 (0.78 - 1.08)	0.92 (0.78 - 1.08)	0.91 (0.77 - 1.07)
	≥ 45 years old	1.02 (0.96 - 1.08)	0.99 (0.94 - 1.05)	1.02 (0.96 - 1.08)	1.00 (0.95 - 1.06)	1.00 (0.95 - 1.06)
Hemorrhagic stroke	< 45 years old	1.36 (0.94 - 1.96)	1.24 (0.86 - 1.79)	1.36 (0.96 - 1.92)	1.45 (0.99 - 2.12)	1.22 (0.82 - 1.82)
	≥ 45 years old	1.27 (0.97 - 1.67)	1.22 (0.94 - 1.59)	1.18 (0.91 - 1.53)	0.90 (0.58 - 1.39)	0.84 (0.51 - 1.38)

*Denote the $P < 0.05$, Lag is the numbers of days since the daily $PM_{2.5}$ concentration.

Table 5. The association (Incidence Rate Ratio: IRR) between $PM_{2.5}$ and hospital admission due to all, ischemic and hemorrhagic stroke from Zero-Inflated Negative Binomial Regression (ZNB) stratified by gender.

Classification of stroke	Gender	Lag 0 (95% CI)	Lag 1 (95% CI)	Lag 2 (95% CI)	Lag 3 (95% CI)	Lag 4 (95% CI)
All stroke	Male	0.95 (0.91 - 1.00)	0.96 (0.92 - 1.00)	0.96 (0.92 - 1.00)	0.96 (0.92 - 1.00)	0.96 (0.91 -1.00)
	Female	1.03 (0.97 - 1.08)	1.01 (0.96 - 1.06)	1.01 (0.96 - 1.06)	1.01 (0.96 - 1.07)	1.01 (0.96 - 1.06)
Ischemicstroke	Male	0.99 (0.93 - 1.05)	1.00 (0.94 - 1.06)	1.00 (0.94 - 1.06)	0.98 (0.93 - 1.04)	0.98 (0.92 - 1.04)
	Female	1.03 (0.95 - 1.10)	1.03 (0.96 - 1.10)	1.01 (0.94 - 1.09)	1.00 (0.93 - 1.08)	0.98 (0.91 - 1.05)
Hemorrhagicstroke	Male	1.38 * (1.04 - 1.83)	1.32 (0.99 - 1.76)	1.22 (0.90 - 1.64)	1.09 (0.79 - 1.51)	0.96 (0.65 - 1.43)
	Female	1.16 (0.91 - 1.49)	1.28 (1.00 - 1.63)	1.19 (0.93 - 1.52)	1.12 (0.86 - 1.45)	1.05 (0.82 - 1.35)

*Denote the $P < 0.05$, Lag is the numbers of days since the daily $PM_{2.5}$ concentration.

Discussion

This study assessed the association between $PM_{2.5}$ and stroke by linking the daily ambient concentration of $PM_{2.5}$ and the hospital admissions due to stroke in Hatyai, a business city of Thailand where the $PM_{2.5}$ was generally low. Nonetheless, this study observed significant association between the daily concentration of $PM_{2.5}$ and hospital admissions due to hemorrhagic stroke in this city at lag time of 0, 1 and 2 days after the exposure. In the subgroup analysis by sex, in male, the positive association was found between the daily concentration of $PM_{2.5}$ and hospital admission due to hemorrhagic stroke at lag 0. No association were observed between $PM_{2.5}$ and all and ischemic stroke.

Studies from countries, reported controversial results. Similar to this study, studies from Asian countries reported positive association between $PM_{2.5}$ and stroke. A study in China of Chiu HF, *et al*. reported that the 1 inter quartile range increase in $PM_{2.5}$ was associated with the 1.04 and 1.12 increases in the hospital admissions due to hemorrhagic stroke in cold and hot temperature days, respectively.[22] Several studies using death registries from China and Japan also observed association between $PM_{2.5}$ and mortality due to hemorrhagic stroke.[15, 17] In contrast, most studies in Europe and America reported no association between $PM_{2.5}$ and hemorrhagic stroke. Outcome ascertainments of these studies included the used of medical records of emergency room visits [13], self-reported questionnaires [23], hospital admissions [12] and death certificates.[17] Meanwhile, a case-crossover study from Portugal reported a positive association between $PM_{2.5}$ and hemorrhagic stroke. The study found that every increase in 10 $\mu g/m^3$ was associated with the increase in numbers of inpatients due to spontaneous intracerebral hemorrhage (SICH) by 1.064 (1.009 - 1.122) time in patients aged 70 years or younger and 1.051 (1.002 - 1.103) time in patients aged older than 70 years.

The effects of $PM_{2.5}$ that increase the likelihood of hemorrhagic stroke might be explainable through the stimulation of autonomic nervous system and inflammation processes.[23] An *in vitro* study showed that exposure to patticulater matter led to inflammation of the endothelial cells by various mechanisms including anti-tissue factor antibody synthesis, reactive oxygen species production and the Nox-4 enzyme.[24] This increased autonomic activities of the circulatory system and atherosclerosis formation of endothelial cells which included the vessels in brain. After exposing to $PM_{2.5}$, the body responses included systemic vasocontriction [23] and the increase in blood pressure [25] which are the predisposing factors for ruptured of cerebral arteries, leading to hemorrhagic stroke.

In this study, the sensitivity analysis by stratified analysis by sex and age. Sex may be an effect modifier for the effect of $PM_{2.5}$ on hemorrhagic stroke. The observed magnitudes of association (IRR) between $PM_{2.5}$ and hemorrhagic stroke at lag0 - lag2 in male were higher than in female. Similarly, a study of Qian Y, *et al*. reported that the male sex was an interaction term for the effects of $PM_{2.5}$ and mortality due to hemorrhagic stroke.[26] Male generally have more predisposing factors than female such as cigarette smoke and underlying diseases such as hypertension and heart diseases.

In this study, the signicant association between $PM_{2.5}$ and ischemic stroke was not observed while the other studies found significant association.[27 - 30] This might be due to the fact that the daily concentration of $PM_{2.5}$ in Hatyai was generally low throughout the year and not at the levels which can cause ischemic stroke. In addition, formation of plaque in the vessels to cause ischemic stroke takes times which might not be observable during the 3-year study period. Another possible explanation might be the misclassification of medical records. The diagnoses of ischemic stroke were mostly done by non-contrast computed tomography of brain (CT-brain) and clinical criteria. Certain numbers of patients with ischemic stroke do not develop markedly hypodensity in CT-brain until hours or a day after brain tissue ischemia.[31, 32] The negative CT-brain was sometime diagnosed as early ischemic stroke. Therefore, a misclassification of patients with the transient ischemic attack or other diseases with facial palsy such as Bell's palsy with ischemic stroke is possible. Meanwhile, the hemorrhagic stroke was less likely to be misdiagnosed since the CT-brain always shown positive signs.

There are several limitations that should be noted when interpreting results of this study. The analysis used the secondary data which is electronic medical records called 43-folder of the National Health Security Office Regional Health 12, designed for medical claims and reimbursements. Therefore, information on risk factors such as smoking[33, 34], underlying diseases and medications at the time of stroke diagnosis, occupation and socio-economic status for each patients were lacking or not in detail enough for statistical analysis. Due to those limitations in this study, future studies should further explore the mechanism of the $PM_{2.5}$ on molecular levels or clinical parameters related to the pathogenesis of stroke including the blood pressure or vascular stiffness indexes by longitudinal data collection and analysis. In addition, since only data from a small city were used, the numbers of cases were limited. The results might be subject to type 2 error when null hypothesis might be incorrectly accepted.

Moreover, the study samples were those who were under the UCS which only accounted for 67.7% of the total population in Hatyai. Those who were excluded were the people under Civil Servant Medical Benefit Scheme (CSMBS), Social Security Scheme (SSS) and private health insurance. The people under CSMBS and private health insurance are people with high socio-economic status whose lifestyles and background risk factors might be different from those under UCS. Whereas the people under SSS are the working population who are relatively healthier and younger than people under UCS. Thus, the association between $PM_{2.5}$ and incidence of stroke might be a bit overestimate because only the data of people under UCS were assessed.

Nevertheless, this study one of a few studies assessing the effects of $PM_{2.5}$ on stroke. In addition, the missing data of air pollutants which were commonly found due to the sensor, internet or recording error were managed using rigorous statistics including several imputation methods. The inverse distance weighting (IDW) and K-nearest neighbor (KNN) were performed for entire day and hour missing data, respectively. These methods reduced the issue of selection bias due to missing variables and improve statistical power of the analysis.

The results from this study support the possible effects of $PM_{2.5}$ on hemorrhagic stroke in Asian population. In addition, the results also showed the usefulness of using ICD-10-TM to monitor the health effects of $PM_{2.5}$. The current Thai Acts related to $PM_{2.5}$, Control of Occupational Diseases and Environmental Diseases Act B.E. 2562 (2019) should include the ICD-10-TM for hemorrhagic stroke and diseases for monitoring health effects of $PM_{2.5}$.

Conclusion

Exposure to fine particulate matter ($PM_{2.5}$) was associated with hemorrhagic stroke, a severe clinical condition. Hemorrhagic stroke along with its diagnosis by ICD-10-TM should be listed as a possible disease, possibly affected, or caused by $PM_{2.5}$ in Thai environment-related acts such as Control of Occupational Diseases and Environmental Diseases Act B.E. 2562 (A.D. 2019).

Conflict of interest statement

The authors have each completed an ICMJE disclosure form. None of the authors declare any potential or actual relationship, activity, or interest related to the content of this article.

Data sharing statement

The present review is based on the reference cited. Further details, opinions, and interpretation are available from the corresponding authors on reasonable request.

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