



Association between Air Pollution Relating to Agricultural Residue Burning and Morbidity of Acute Cardiopulmonary Diseases in Upper Northern Thailand

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Received: 11 Oct 2023; Revised: 1 Dec 2023; Accepted: 12 Jan 2024

<https://doi.org/10.59096/osir.v17i1.265861>

Abstract

In Northern Thailand, increasing seasonal agricultural residue burning has led to public concern about health risks. This study aimed to examine the associations between air pollutants related to agricultural residue burning and morbidity from acute cardiopulmonary diseases in upper Northern Thailand in 2018. An ecological study was conducted. Emergency room visits and hospitalizations for chronic obstructive pulmonary disease (COPD), stroke, myocardial infarction (MI), and asthma were extracted from the National Electronic Health Record database. We interpolated air pollution data to estimate weekly pollutant concentrations, including PM₁₀, PM_{2.5}, carbon monoxide, nitrogen dioxide, sulfur dioxide and ozone from 1 Jan to 31 Dec 2018. Associations between air pollution and health outcomes were analyzed using a mixed effect model incorporating different lag structures. Overall pollutant concentrations exceeded WHO air quality standard levels throughout March and April, which is the end of forest burning prohibition campaign. Morbidity from COPD, stroke, MI and asthma slightly increased over March–April. For every increase in PM_{2.5} level of 10 µg/m³, the relative risk of COPD, stroke, MI and asthma 1 week later was 1.10 (95% CI 1.09–1.12), 1.06 (1.05–1.08), 1.06 (1.04–1.08) and 1.06 (1.01–1.12), respectively. The effects of agricultural residue burning should be highlighted and policies should be developed to deter this practice.

Keywords: air pollution, acute cardiopulmonary diseases, agricultural residue burning, burning prohibition campaign

Introduction

Air pollution is one of the leading contributors to the global burden of diseases. Approximately 98% of Southeast Asia's population live in places where air quality does not meet WHO air quality standard levels.^{1,2} Exposure to ambient particulate matter is the fifth leading risk factor for deaths worldwide.³ Air pollution in both urban and rural areas was estimated to cause more than four million premature deaths worldwide in 2016.^{1,3} Approximately 90% of premature deaths from air pollution are from people living in low and middle income countries, including Thailand.¹ Exposure to air pollution has been known to increase morbidity and mortality of cardiopulmonary diseases.^{4,5} Specifically, an increase in fine particulate matter (PM_{2.5}) of 10 µg/m³ was associated with a 6% increased risk of cardiopulmonary death.⁵

Major sources of air pollution include industry, road traffic, households, and agricultural residue burning. However, satellite remote sensing of active fire data suggests that air pollution in Southeast Asia, particularly Myanmar, Lao PDR, Cambodia and upper Northern Thailand, is unique; and occurs principally from wildfires.^{6–8} Wildfires can emit multiple air pollutants including particulate matter, carbon monoxide (CO), nitrogen dioxide (NO₂), sulfur dioxide (SO₂) and ozone-forming chemicals (O₃).^{9–11} In upper Northern Thailand, wildfires occur almost every year and affect people's health, property, the regional economy, society and the environment.^{6–8} Each year, the wildfire season, which causes air pollutant emissions during January to May, has a negative impact on respiratory health and vision.⁸ Gathering of forest products, such as fuel wood, mushrooms and

bamboo, and agricultural residue burning for land clearing are the major contributing factors.⁷ Concern is growing as air pollution levels in upper Northern Thailand poses a threat to the population's health.

Although several studies reporting the association between air pollution and cardiopulmonary diseases have been conducted, only a few studies have investigated the health effects caused by agricultural residue burning. This information could help policymakers prepare medical resources for patients with acute cardiopulmonary disease, especially within the week after air pollution levels rise. This study aimed to describe the levels and dynamics of air pollutants, morbidity of acute cardiopulmonary diseases, and examine associations between air pollutants and morbidity for acute cardiopulmonary diseases in the upper northern area of Thailand.

Methods

Overview of Study

This was an ecological study using secondary time series data and including two datasets; air pollution data and health outcome data. The study population were people visiting an emergency room (ER) or admitted to hospital and diagnosed with acute cardiopulmonary diseases in eight provinces (Chiang Mai, Chiang Rai, Nan, Phrae, Lampang, Lamphun,

Phayao and Mae Hong Son) in the upper northern region of Thailand from 1 Jan to 31 Dec 2018. Health outcomes were defined based on the international classification of diseases-10th revision (ICD-10). We identified cardiopulmonary diseases including chronic obstructive pulmonary disease (COPD) (J44), cerebrovascular diseases (stroke) (I60–I69), myocardial infarction (MI) (I20–I24) and asthma (J45–J46). Regarding air pollution data, six pollutants, including coarse particulate matter (PM₁₀), fine particulate matter (PM_{2.5}), CO, NO₂, SO₂, and O₃, were collected and integrated into spatial interpolation models to estimate weekly air pollutant concentrations. Associations between the air pollutants and health outcomes were analyzed using district-week as the unit of analysis.

Estimation and Pattern of Air Pollution

In order to estimate the spatiotemporal distribution of air pollution, national air pollution records provided by the Pollution Control Department, Ministry of Natural Resources and Environment were extracted. Date were recorded hourly from all air quality monitoring stations in Thailand and gathered at the Data Center in the Bureau of Air Quality and Noise Management, Pollution Control Department, Ministry of Natural Resources and Environment.

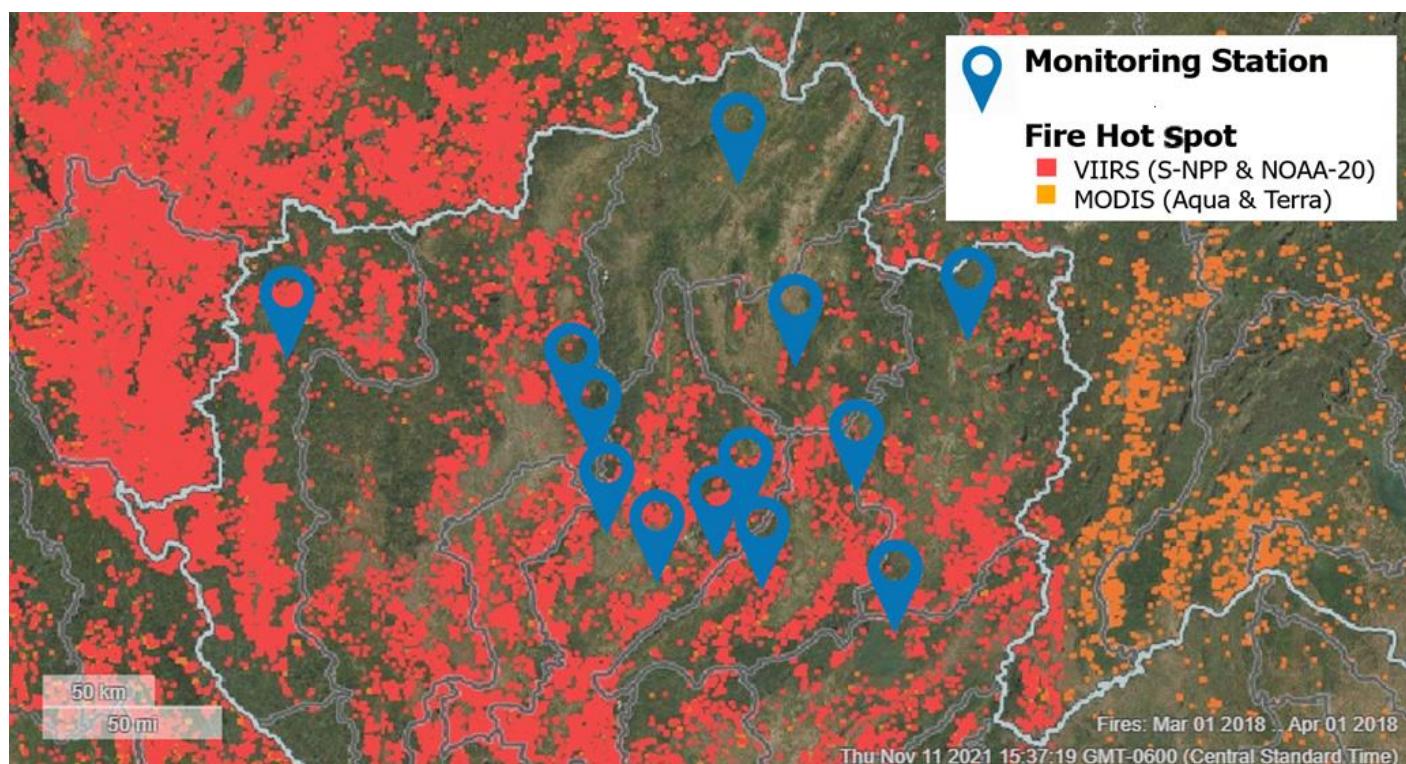


Figure 1. Distribution of air pollution monitoring stations and fire hot spots in the upper Northern Thailand, March–April 2018¹²

We obtained hourly air pollutant data from 13 monitoring stations in upper Northern Thailand to describe the seasonal pattern of air pollution between 2013–2018 to observe seasonality (Figure 1).¹² For each monitoring station, the pollutant level within each station on an hourly basis each day was aggregated. If the hourly pollutant level was not recorded, a 3-hour moving average was used to impute the missing data before calculating a daily average pollution level. Spearman's correlation was used to assess the correlation among each pollutant. We used a Simple Kriging interpolation model¹³ in order to estimate the spatial distribution of air pollution concentration in 10,000 grids (100×100). Air pollution concentrations were then aggregated into districts using zonal statistics and averaged from daily to weekly time units. We used the R language and environment (packages: gstat, raster, maptools, sp, field) to analyze the data.¹³⁻¹⁴

To better understand patterns of wildfire in the study area, we obtained fire hot spots during exceeding pollution period in 2018 from Fire Information for Resource Management System which is provided by National Aeronautics and Space Administration (NASA) (<https://firms.modaps.eosdis.nasa.gov>).

Spatiotemporal Distribution of Health Outcomes in 2018

Morbidity from acute cardiopulmonary diseases was calculated by extracting the secondary health data from the National Electronic Health Record (NEHR) database. NEHR was provided by the Health Data Center, Ministry of Public Health. All medical institutions of the Ministry of Public Health in Thailand have the authority to report individual health records into the which were coded by diagnosis according to the ICD-10. We obtained daily counts of acute cardiopulmonary diseases in each district. Aggregation of healthcare facility address and week of onset by district-week was performed to estimate the spatiotemporal distribution of diseases in each district-week unit.

Association between Air Pollution and Health Outcomes

As this time series data of health outcomes had repeated measurements in the same district in different weeks, mixed effects models, which contain both fixed and random effects, were selected for analysis in this setting where repeated measurements were made on the same statistical units.^{15,16} Districts were treated as a random effect.

Various lag structures between air pollution and health outcomes have been identified in previous

studies, therefore, we initially examined separate models with different lag structures, including single-week lag from lag-0 to lag-2 (lag-0 refers to the air pollution in the current week and lag-1 and lag-2 refer to 1 and 2 weeks prior to the current week, respectively).^{17,18} Furthermore, models assessing the associations between health outcomes and both single- and multiple-pollutants were fit. PM₁₀, PM_{2.5}, CO, NO₂, SO₂ and O₃, were included in the single-pollutant models while PM_{2.5}, adjusted for the other pollutants, was included in the multiple-pollutants models. A variance inflation factor (VIF) was estimated to identify the severity of multicollinearity. All pollutants with a VIF greater than 10 were excluded from the multiple-pollutant models. All of these models were fit using different lag structures.

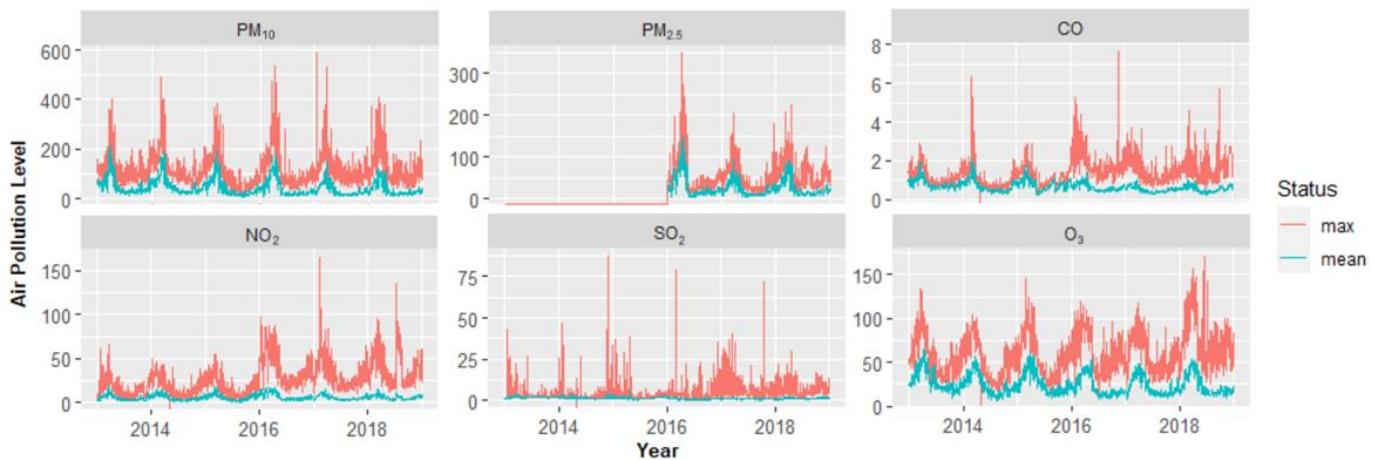
After establishing various models, concentration response (CR) relationships were developed to estimate the relative risk (RR) which was calculated based on the relationship between RR, CR-coefficients and a 20% change in air pollution concentrations.¹⁸ A CR-coefficient was assigned as the slope of the log-linear relationship between ambient air pollution concentrations and morbidity, while a 20% change in air pollution concentrations was defined as a 20% difference in maximum concentration and mean concentration of each pollutant in that year.¹⁸ The CR at each change in air pollution concentration was visualized with curves of the central estimation of RR and their 95% uncertainty intervals.

Results

Estimation and Pattern of Air Pollution

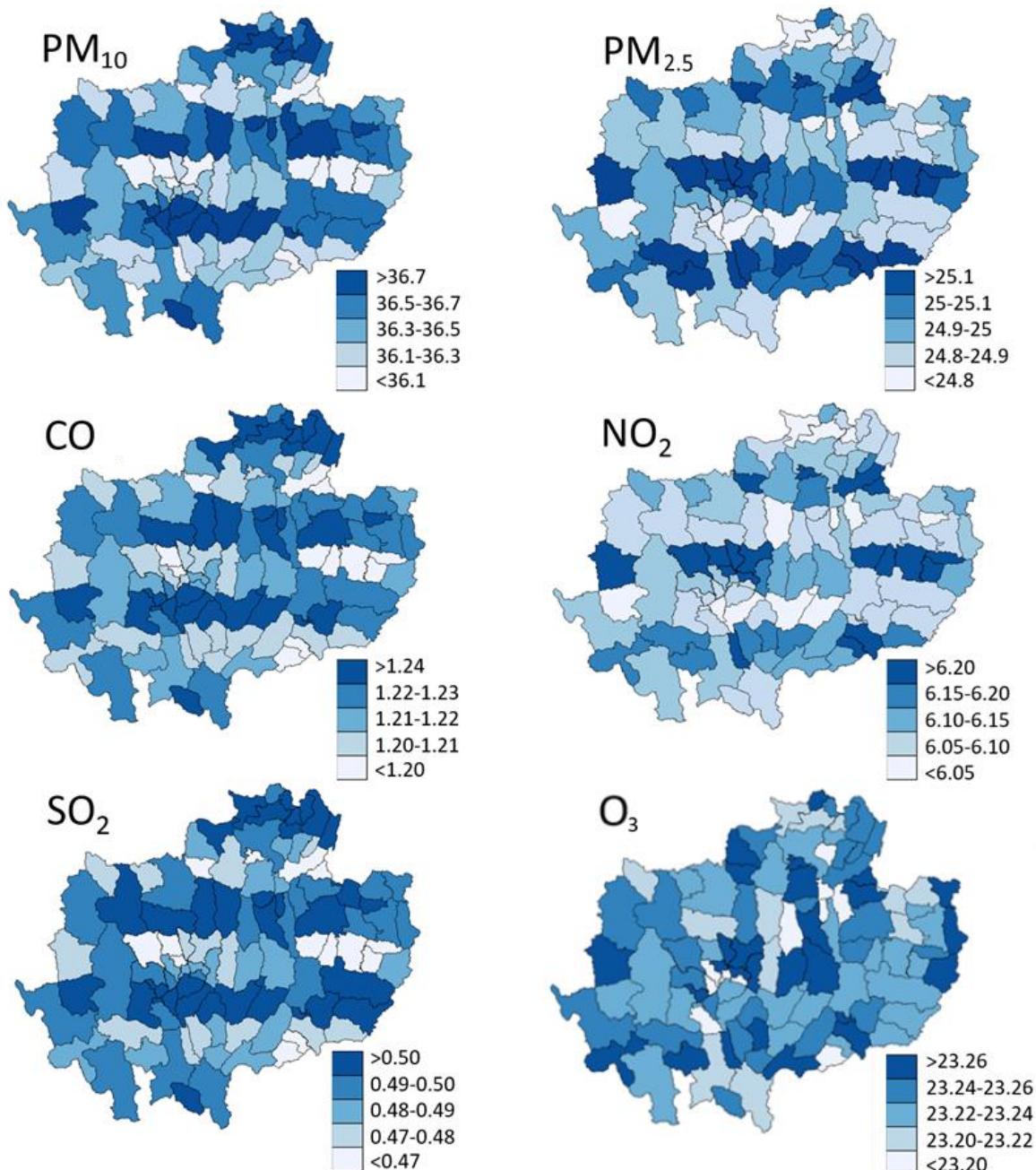
Air pollution data were obtained from 12 of the 13 monitoring stations; the station in Mae Hong Son Province (located in the farthest northwest) was not functioning on the required days. Most pollutant concentrations were monitored by at least 10 stations.

As shown in Figure 1, the fire hot spots distributed throughout the northern parts of Thailand and the neighboring countries exceeded WHO pollution levels in March and April 2018. All air pollutants, especially PM₁₀ and PM_{2.5}, exceeded WHO standards from the middle of February to the end of April from 2013–2018 (Figure 2). The annual average air pollution concentration in 2018 from 97 districts in the eight provinces is illustrated in Figure 3. There were strong to very strong correlations among most pollutants with correlation coefficients ranging from 0.68–0.99 (all *p*-values <0.01), while CO exhibited correlations ranging from 0.25–0.40 (all *p*-values <0.01).



The units for PM_{10} and $PM_{2.5}$ are $\mu\text{g}/\text{m}^3$; CO is parts per million; NO_2 , SO_2 and O_3 are parts per billion.

Figure 2. Time series of air pollution concentrations of PM_{10} , $PM_{2.5}$, CO , NO_2 , SO_2 and O_3 in upper Northern Thailand, 2013–2018



The units for PM_{10} and $PM_{2.5}$ are $\mu\text{g}/\text{m}^3$; CO is parts per million; NO_2 , SO_2 and O_3 are parts per billion.

Figure 3. Annual average air pollution concentrations in 97 districts in upper Northern Thailand, 2018

Spatiotemporal Distribution of Health Outcomes

Air pollution related morbidities from 97 districts in the eight provinces were extracted and then each district data were aggregated into 5,044 (97×52) district-week units. However, the number of ER visits and hospitalizations dropped to nearly zero during August and September 2018 (Figure 4).

The number of ER visits and hospitalizations for patients with acute cardiopulmonary diseases in this

region was 53,668, including 31,706 for COPD (537 per 100,000 populations), 12,190 for stroke (206 per 100,000 populations), 6,164 for MI (104 per 100,000 populations) and 3,416 for asthma (22.8 per 100,000 populations). Each disease showed a minimal fluctuation in the number of ER visits month by month with a slightly higher number of visits early in the year for COPD, stroke and MI. The annual incidence of these four diseases in the 97 districts is illustrated in Figure 5.

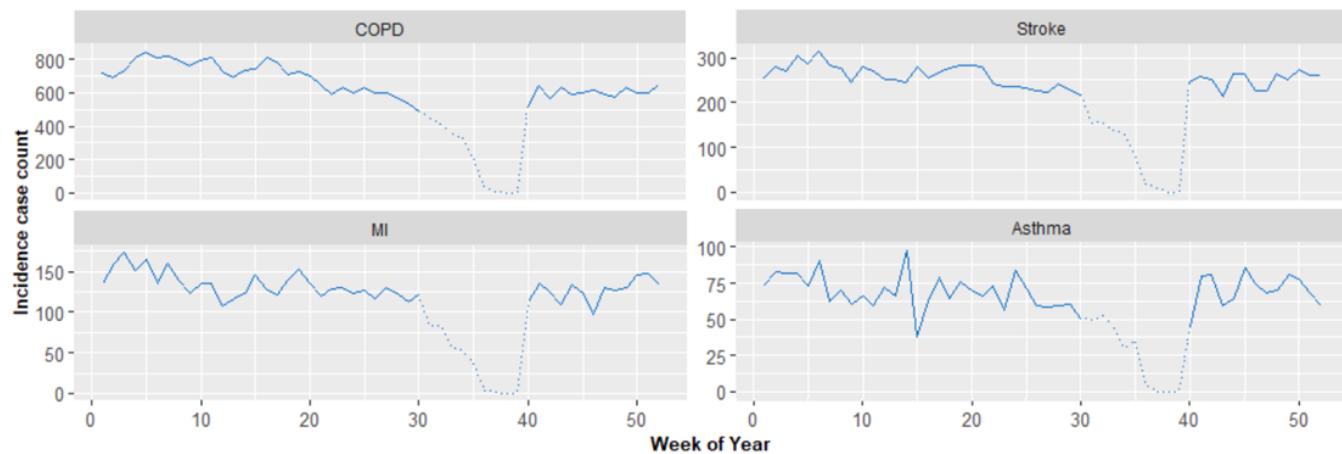


Figure 4. Incidence of chronic obstructive pulmonary disease (COPD), stroke, myocardial infarction (MI) and asthma admissions or emergency room visits by month of onset, upper Northern Thailand, 2018

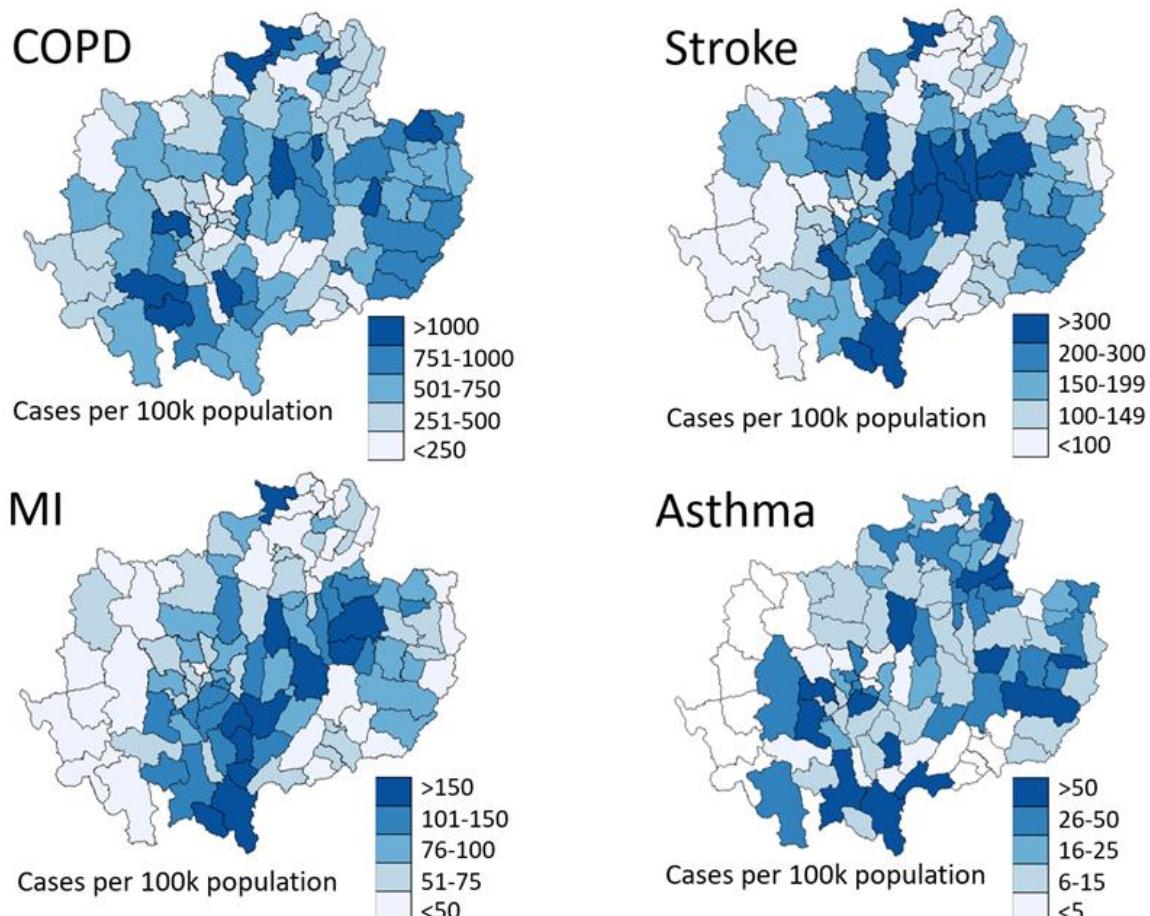


Figure 5. Incidence of chronic obstructive pulmonary disease (COPD), stroke, myocardial infarction (MI) and asthma admissions or emergency room visits in 97 districts of upper Northern Thailand, 2018

Associations between Air Pollution and Health Outcomes

Morbidity data in August and September were excluded due to an unexplainable decline during those two months. Therefore, the other 4,074 district-week units were included in the analysis. In order to estimate relative risks, a 20% difference between the maximum pollutant levels and mean pollutant levels were determined, which were $11 \mu\text{g}/\text{m}^3$, $10 \mu\text{g}/\text{m}^3$, 0.12 ppm, 0.86 ppb, 0.06 ppb and 5.08 ppb for PM_{10} , $\text{PM}_{2.5}$, CO, NO_2 , SO_2 , and O_3 , respectively.

For the single-pollutant model, all pollutants were identified as significant risk factors to develop all cardiopulmonary diseases in all selected lag structures, except for asthma at lag-0. For pollutants,

the 20% difference between maximum pollutant and mean pollutant change of PM_{10} and $\text{PM}_{2.5}$ had the highest impact on all cardiopulmonary diseases (relative risks 1.02–1.18), whereas CO had the lowest impact on cardiopulmonary diseases (relative risks 1.01–1.05). In addition, CO was not statistically associated with MI and asthma at lag-0 and the moving average lag (Table 1).

Analysis of the different lag structures revealed that lag-1 had the highest association between all cardiopulmonary diseases and PM_{10} and $\text{PM}_{2.5}$, while lag-2 had the highest corresponding associations for CO, NO_2 , SO_2 , and O_3 , compared to lag 0 and the moving average lag (Table 1).

Table 1. Summary of relative risks for chronic obstructive pulmonary disease (COPD), stroke, myocardial infarction (MI) and asthma for a 20% change in mean ambient air pollution concentration, upper Northern Thailand, 2018

Pollutant	Lag structure	COPD				Stroke				MI				Asthma		
		RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
PM_{10}	L0	1.06	1.05	1.07	1.02	1.01	1.04	1.02	1.00	1.04	1.02	0.97	1.08			
	L1	1.10	1.09	1.11	1.06	1.05	1.08	1.06	1.04	1.08	1.06	1.01	1.12			
	L2	1.10	1.09	1.11	1.06	1.04	1.07	1.07	1.05	1.08	1.07	1.02	1.12			
$\text{PM}_{2.5}$	L0	1.06	1.05	1.07	1.02	1.01	1.04	1.02	1.00	1.03	1.02	0.96	1.08			
	L1	1.10	1.09	1.12	1.06	1.05	1.08	1.06	1.04	1.08	1.06	1.01	1.12			
	L2	1.10	1.09	1.11	1.06	1.04	1.07	1.06	1.05	1.08	1.07	1.02	1.12			
CO	L0	1.01	1.00	1.02	1.01	1.00	1.03	1.01	0.99	1.03	1.01	0.97	1.06			
	L1	1.05	1.05	1.06	1.05	1.04	1.06	1.04	1.03	1.06	1.05	1.01	1.10			
	L2	1.04	1.03	1.04	1.03	1.01	1.04	1.02	1.01	1.04	1.04	0.99	1.09			
NO_2	L0	1.05	1.04	1.05	1.02	1.01	1.03	1.02	1.01	1.04	1.03	0.99	1.08			
	L1	1.10	1.09	1.11	1.07	1.06	1.09	1.08	1.07	1.10	1.10	1.05	1.15			
	L2	1.09	1.08	1.10	1.07	1.06	1.08	1.08	1.06	1.09	1.12	1.07	1.17			
SO_2	L0	1.05	1.05	1.06	1.03	1.01	1.04	1.03	1.01	1.04	1.05	1.00	1.09			
	L1	1.07	1.06	1.08	1.04	1.03	1.06	1.04	1.03	1.06	1.07	1.02	1.11			
	L2	1.05	1.04	1.06	1.02	1.01	1.04	1.03	1.02	1.05	1.06	1.00	1.00			
O_3	L0	1.06	1.05	1.07	1.03	1.01	1.04	1.02	1.00	1.04	1.01	0.96	1.05			
	L1	1.09	1.08	1.10	1.06	1.04	1.07	1.05	1.04	1.07	1.05	1.00	1.10			
	L2	1.09	1.08	1.10	1.06	1.04	1.07	1.05	1.04	1.07	1.06	1.01	1.10			

20% change in mean ambient air pollution level for PM_{10} : $11 \mu\text{g}/\text{m}^3$, $\text{PM}_{2.5}$: $10 \mu\text{g}/\text{m}^3$, CO: 0.12 PPM, NO_2 : 0.86 parts per billion (PPB), SO_2 : 0.06 PPB, and O_3 : 5.08 PPB. COPD: chronic obstructive pulmonary disease. MI: myocardial infarction. RR: relative risk. LCI: lower confidence interval. UCI: upper confidence interval.

For multiple-pollutants models, PM_{10} and O_3 were excluded due to VIF exceeding 10. After adjusting for CO, NO_2 , and SO_2 , $\text{PM}_{2.5}$ was significantly associated with COPD. However, there were no associations between $\text{PM}_{2.5}$ and stroke or MI after adjusting for SO_2

or SO_2 combined with other pollutants (Table 2). We illustrated the association between cardiopulmonary diseases and $\text{PM}_{2.5}$ adjusting for CO at lag-0 using CR-curves and found a slight exponential relationship (Figure 6).

Table 2. Summary of relative risks of chronic obstructive pulmonary disease (COPD), stroke, myocardial infarction (MI) and asthma for a 20% change in mean PM_{2.5} adjusting for CO (lag-0), NO₂ and SO₂, upper Northern Thailand, 2018

Main Pollutant	Adjusted Pollutant	COPD			Stroke			MI			Asthma		
		RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
PM _{2.5}	CO	1.13	1.11	1.16	1.03	1.01	1.05	1.02	1.00	1.04	1.02	1.00	1.03
	SO ₂	1.06	1.02	1.10	0.97	0.95	1.00	0.96	0.92	1.00	1.01	0.98	1.03
	NO ₂	1.13	1.09	1.16	1.02	0.99	1.04	1.00	0.97	1.03	0.97	0.95	1.00
	CO+SO ₂	1.06	1.02	1.10	0.97	0.95	1.00	0.95	0.92	0.99	1.01	0.98	1.04
	CO+NO ₂	1.12	1.07	1.16	1.01	0.99	1.04	1.00	0.97	1.03	0.97	0.94	1.00
	NO ₂ + SO ₂	1.06	1.02	1.11	0.97	0.94	1.00	0.94	0.91	0.98	0.96	0.94	1.00
	NO ₂ + SO ₂ + CO	1.06	1.02	1.11	0.97	0.94	1.00	0.94	0.91	0.98	0.97	0.94	1.00

We excluded PM₁₀ and O₃ due to a variance inflation factor (VIF) >10. COPD: chronic obstructive pulmonary disease. MI: myocardial infarction. RR: relative risk. LCI: lower confidence interval. UCI: upper confidence interval.

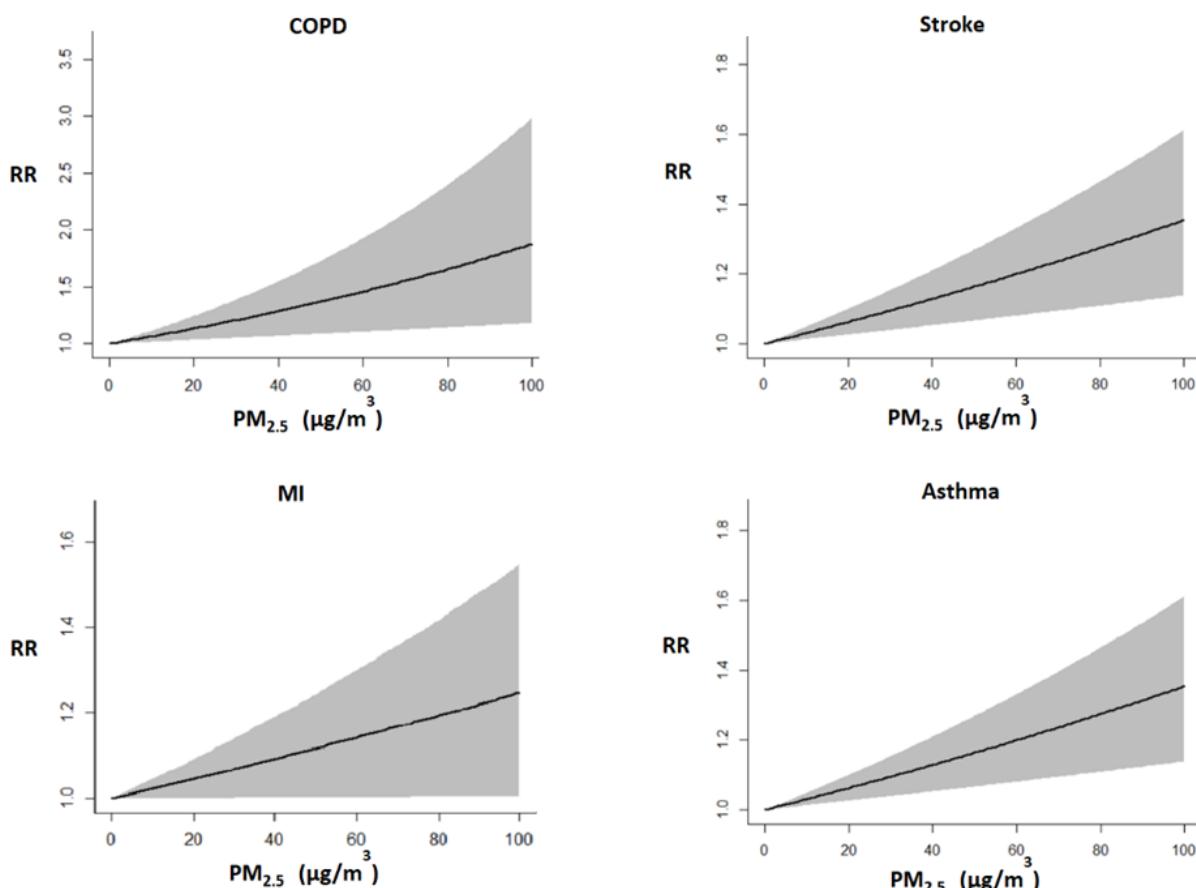


Figure 6. Concentration response relationship curves showing the adjusted relative risk of PM_{2.5} adjusting for CO and cardiopulmonary diseases in upper Northern Thailand, 2018. Shaded areas represent 95% confidence intervals

Discussion

This is one of the few studies on the acute and sub-acute effects from agricultural residue burning related to air pollution associated with cardiopulmonary diseases using data from a large disease registry. We illustrated the association of air pollution related to agricultural residue burning with other air pollutants.

The excessive pollutant levels are likely due to wildfires and is supported by other researchers.⁷⁻⁹ All pollutants had strong to very strong correlations with

each other, especially PM₁₀, PM_{2.5}, and O₃, which might originate from the same source of pollutants (wildfires), thus the analytic study was mindful of perfect collinearity among those pollutants. For all pollutants, the mean daily pollutant levels were higher than standard concentrations issued by the World Health Organization's Air Quality Guideline, especially after the end of forest burning prohibition campaign.¹⁸ This finding provides evidence that the campaign could be promoted to control air quality and should be expanded in both time and scope to include agricultural residue burning.

Corresponding with the excessive air pollution, the morbidity associated with acute cardiopulmonary diseases in upper Northern Thailand was high compared with previous annual reports of average morbidity in other regions of Thailand, based on the 2017 Thai Annual Epidemiological Surveillance Report (AESR) and the United States National Hospital Ambulatory Medical Care Survey (NHAMCS).^{20,21} On the other hand, morbidity from asthma was slightly lower than that reported by the AESR and much lower than the NHAMCS.^{20,21} Asthma morbidity from the National Electronic Health Record was likely to be underestimated, probably due to the strict diagnostic criteria in Thailand for patients that need pre-post bronchodilator for diagnosis.²² However, only a few community hospitals in Thailand have spirometers.²³ Moreover, we found an unexplained and abnormally large decline in the number of ER visits and hospitalizations from all diseases of interest during August and September, which might be due to errors of reporting during the beginning of the fiscal year.

We found that all pollutants had statistically significant associations with stroke, MI and COPD. For stroke, our findings were consistent with previous studies for PM₁₀ and PM_{2.5}.^{4,5,24} Comparing with different sources of air pollution, our strength of association for PM_{2.5} and stroke at lag-0 is similar to previous studies. The previous study in Ireland identified the pollutant source from domestic solid fuel burning during winter.²³ While, the previous study in China identified the pollutant source from industrial production and traffic congestion.²⁴ This finding may suggest that air pollution from wildfire contributes a similar impact on stroke compared to other sources of pollution. For MI, our findings are consistent with previous studies from around the world.^{4,5,26,27} We found that the strength of association between PM₁₀ and MI at lag-0 was slightly lower than reported in a previous study from Poland where pollution was identified from residential areas and small-industry, and in Beijing, China where pollution was identified from traffic and industry.^{26,27} This finding suggests that air pollution from wildfire has a slightly lower impact on MI compared to other sources, which could be explained from other hazardous chemical pollutants from traffic and industry-related pollutants such as benzene, perchloroethylene, and methylchloride.²⁸⁻³⁰

Concerning COPD, our findings are consistent with previous studies assessing its associations with PM₁₀, PM_{2.5} and NO₂ concentrations.^{4,5,16,31,32} Compared with different sources of air pollution, the strength of association between PM_{2.5} and COPD at lag-0 was slightly lower compared to a previous study in Beijing,

China which was associated from traffic and industry.³¹ It was also higher than in Taiwan where pollutant sources were identified from sea-land breezes and desert dust storms.³² For three of these diseases, with the same level of PM_{2.5}, air pollution due to agricultural residue burning had a similar, or perhaps higher, impact compared to other sources of air pollution. This could be explained by other confounders, for instance, chemical related pollutants, weather, or physical activities. Asthma, however, was not significantly associated with most of the other air pollutants, except SO₂, which could be due to a lack of consistency and accuracy of NEHR for reporting asthma.

According to our models which analyzed different lag structures, lag-1 had the highest relative risk on health outcomes for almost all pollutants, followed by lag-2 and lag-0. Therefore, the effect of air pollution on cardiopulmonary diseases does not peak during the initial period of air pollution, but was stronger during the week after the event. This finding is compatible with previous studies in the US, China, Brazil, and Thailand.^{16,33,34} This could be because of the natural history of diseases and delays in emergency room visits.

This study has several limitations which should be acknowledged. First, there were a limited number of air monitoring stations and some of them were clustered in particular areas. Interpolation methods were used to solve this limitation; however, accuracy may have been compromised. Secondly, the associations of health outcomes were estimated from modeled air pollutants, not from direct pollutant measures. Thirdly, ecological fallacy could potentially occur by inferring that associations at the aggregate level rather than the individual level: if we infer into aggregate level, ecological fallacy would not be the issue. Fourthly, confounding bias may have occurred if unmeasured potential confounders such as temperature, humidity, chemical related pollution, or physical activities in each area, are correlated with pollutants and the illnesses reported in this study.

Conclusion

In Northern Thailand, the morbidity from COPD, stroke, MI and asthma slightly increased since the middle of March, 2018, which is consistent with pollutant concentrations exceeding standard levels after March. This period marks the end of the agricultural residue burning season and the increasing air pollution levels were significantly associated with COPD, stroke and MI. Air pollution from agricultural residue burning had almost similar

or even higher health impacts compared to other sources of air pollution. Therefore, we suggest using air pollutant data to estimate and monitor the trend of air pollution-related diseases and increase the number of air pollution monitoring stations in Northern Thailand. Specifically, disease prevention and control authorities should use the air pollutant data in available areas to estimate and monitor the trend of air pollution-related diseases. The magnitude of air pollution-related diseases should be reported to authorities to monitor trends as part of disease surveillance systems. For healthcare facilities in the affected areas, after an increase in pollutants is detected, the number of air pollution-related diseases should be estimated using CR-curves. Adequate preparation for essential resources in hospitals is recommended. For national health data organization, consistency and accuracy of NEHR should be studied and closely monitored and forecasted. For the Pollution Control Department, due to the limited number of air pollution monitoring stations in the affected area, we recommend increasing the number of stations, especially in areas affected by wildfires. Forest burning prohibition campaign should be promoted, expanded its period, and should include neighboring countries.

Acknowledgements

We would like to thank the Pollution Control Department, Ministry of Natural Resources and Environment, Dr. Thammasin Ingviya, Dr. Rapeepong Suphanchaimat and Dr. Panupong Tantirat for their support.

Funding

This project was funded by the Field Epidemiology Training Program, Division of Epidemiology, Department of Disease control, Ministry of Public Health, Thailand.

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

Conceptualization, S.W., H.P. and P.T.; methodology, S.W., H.P. and P.T.; software, S.W. and C.J.; validation, S.W., P.T. and C.J.; formal analysis, S.W., C.J. and P.T.; resources, S.W. and P.T.; data curation, S.W. and C.J.; writing—original draft preparation, S.W. and C.J.; writing—review and editing, H.P. and P.T.; visualization, S.W. and C.J.; supervision, H.P. and P.T.; project administration, S.W.; All authors have read and agreed to the published version of the manuscript.

Suggested Citation

Wongsanuphat S, Praekunatham H, Jitpeera C, Thammawijaya P. Association between air pollution relating to agricultural residue burning and morbidity of acute cardiopulmonary diseases in upper Northern Thailand. OSIR. 2024 Mar;17(1):9–19. doi:10.59096/osir.v17i1.265861.

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