ORIGINAL RESEARCH

Time-Stratified Case Crossover Study of the Association of Outdoor Ambient Air Pollution With the Risk of Acute Myocardial Infarction in the Context of Seasonal Exposure to the Southeast Asian Haze Problem

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***Background*—**Prior studies have demonstrated the association of air pollution with cardiovascular deaths. Singapore experiences seasonal transboundary haze. We investigated the association between air pollution and acute myocardial infarction (AMI) incidence in Singapore.

***Methods and Results*—**We performed a time-stratified case-crossover study on all AMI cases in the Singapore Myocardial Infarction Registry (2010–2015). Exposure on days where AMI occurred (case days) were compared with the exposure on days where AMI did not occur (control days). Control days were chosen on the same day of the week earlier and later in the same month and year. We fitted conditional Poisson regression models to daily AMI incidence to include confounders such as ambient temperature, rainfall, wind-speed, and Pollutant Standards Index. We assessed relationships between AMI incidence and Pollutant Standards Index in the entire cohort and subgroups of individual-level characteristics. There were 53 948 cases. Each 30-unit increase in Pollutant Standards Index was association with AMI incidence (incidence risk ratio [IRR] 1.04, 95% CI 1.03–1.06). In the subgroup of ST-segment–elevation myocardial infarction the IRR was 1.00, 95% CI 0.98 to 1.03, while for non–ST-segment–elevation myocardial infarction, the IRR was 1.08, 95% CI 1.05 to 1.10. Subgroup analyses showed generally significant. Moderate/unhealthy Pollutant Standards Index showed association with AMI occurrence with IRR 1.08, 95% CI 1.05 to 1.11 and IRR 1.09, 95% CI 1.01 to 1.18, respectively. Excess risk remained elevated through the day of exposure and for >2 years after.

***Conclusions*—**We found an effect of short-term air pollution on AMI incidence, especially non–ST-segment–elevation myocardial infarction and inpatient AMI. These findings have public health implications for primary prevention and emergency health services during haze. **(*J Am Heart Assoc*. 2019;8:e011272. DOI: 10.1161/JAHA.118.011272.)**

Key Words: myocardial infarction • population • haze • Singapore • air pollution

The role of ambient air pollution in the pathogenesis of a diverse range of acute and chronic diseases is increasingly recognized.[1] Southeast Asian (SEA) transboundary haze because of forest fires is a major public health problem, exacting a large economic and health toll on the region. The Global Burden of Disease Study identified fine particulate matter (PM) in outdoor air to be the ninth leading risk factor for disease worldwide,[2] while the World Health Organization attributes 1 in every 8 deaths to air pollution.[3] There is growing epidemiological evidence that air pollution contributes a heterogeneous and currently poorly understood, yet important role in a range of health outcomes ranging from low birth weight to sudden cardiac death. The ubiquitous and involuntary exposure to air pollution makes it a formidable and highly relevant preventive medicine challenge.

Cardiovascular disease is the leading cause of death worldwide.[4] A 2010 update to a scientific statement from the American Heart Association concluded that the overall absolute risk for mortality because of particulate matter exposure is greater for cardiovascular disease compared with pulmonary disease after both short- and long-term exposures, and that the evidence for association of PM exposure was

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Clinical Perspective

What Is New?

- This nationwide registry study using a time-stratified case-crossover design found a transient effect of short-term air pollution on acute myocardial infarction incidence, especially non–ST-segment–elevation myocardial infarction and inpatient acute myocardial infarction, after adjusting for other meteorological indicators and stratifying by individual characteristics.

What Are the Clinical Implications?

- These findings have public health implications for acute myocardial infarction prevention and emergency health services delivery during haze, in particular, the Southeast Asian haze problem.

moderate for ischemic heart disease, heart failure, and ischemic stroke, and mixed for arrhythmia and cardiac arrest.[5] Acute myocardial infarction (AMI) is the main acute presentation of ischemic heart disease where there is irreversible myocardial ischemia leading to significant morbidity and mortality; therefore, understanding the relationship between ambient air pollution and AMI is of tremendous public health interest.

Short-term increase in air pollution has previously been shown to be capable of triggering acute coronary syndromes.[6–8] In a large comparative risk assessment study of the triggers of myocardial infarction, amongst all the potential triggers studied, the highest population attributable fractions (which comprise both the effect size and prevalence of a risk factor), were contributed by road traffic and concentration of PM with aerodynamic diameter <10 μm (PM_{10}).[9] These studies varied in the accuracy, completeness, and representativeness of both the pollution and disease data. Further, unanswered questions remain about the presence of susceptible populations, possible lag effects, and relevance in the context of the Southeast Asian (SEA) transboundary haze problem.

The SEA haze problem refers to periodic episodes of transboundary and large-scale air pollution episodes that have been recorded since 1972.[10] These events have exacted adverse health and economic impact in Indonesia, Singapore, Malaysia, Brunei Darussalam, southern Thailand, northern Laos, and as far as the southern Philippines.[11,12] Haze crises such as those that occurred in 1997, 2006, 2013, and 2015 have damaging effects on tourism, transport, food and water quality, urban and rural livelihood, and overall human productivity.[13] Unlawful industrial-scale slash-and-burn land-clearing agricultural practices in the region have been incriminated for sparking off forest fires which releases acrid smoke, dust, and particulate matter into the atmosphere.[14] The haze situation surfaces recurrently in Singapore, usually coinciding with the dry season from July to September, when the southwest monsoon also shifts haze towards Singapore. These episodes have been implicated in damages amounting to an estimated of US $4.5 billion for the fire episodes in 1997 alone.[15] These included health impacts, reduced crop yield, preventive expenditures, accidents, loss of life, evacuations, and the loss of confidence of foreign investors.[15] In 2002, member states of the Association of Southeast Asian Nations ratified the Association of Southeast Asian Nations Agreement on transboundary haze pollution to monitor, prevent, and mitigate transboundary haze through international cooperation.

Singapore is a small, densely-populated island city-state situated in SEA, and experiences periodic large-scale transboundary haze originating from the region. It is hence susceptible to wide day-to-day fluctuations in ambient air pollutant levels over decades. Singapore has robust surveillance capabilities for air pollution and other environmental parameters. These characteristics make Singapore an ideal natural population laboratory to study short-intermediate term health impacts arising from the SEA haze problem.

The objective of this study is to investigate the association between ambient air pollution and AMI occurrence using a time-stratified case-crossover design while adjusting for meteorological parameters and stratifying by individual characteristics. It is hypothesized that exposure to increased Pollutant Standards Index (PSI) is associated with an increase in the number of AMI cases. Other research questions are whether the effect is highest on same day of exposure or after lagged terms of a few days, and whether the risk differs between various subgroups. Findings would inform public health policies relating to measures to reduce air pollutants as well as those to mitigate their effect on susceptible subgroups of the population.

Methods

Data, methods used in the analysis, and materials used to conduct the research available will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Exposure data are available to the public from the respective agency's website, and disease data are owned by National Registry of Diseases Office and data sharing is limited by their policies.

Setting

Singapore is a heavily urbanized island city-state in Southeast Asia with a population of 5.5 million over a land area of 719.1 square kilometers.[16] Singapore has a gross domestic

product of 295.7 billion dollars and a life expectancy of 82.1 years.[17] Singapore lies 1.5° north of the equator and is located at the end of the Malayan Peninsula. Its climate has been classified as tropical rainforest (Köppen-Geiger classification system). As a result of its geographical location and maritime exposure, its climate is characterized by uniform temperature and pressure, high humidity, abundant rainfall, and no true distinct seasons. Tertiary health care was delivered by 7 public general hospitals and several private hospitals, of which 5 provided around-the-clock emergency PCI service.[18]

From prior studies, the age-standardized incidence rate of STEMI in Singapore was 56.6 per 100 000 population from 2010 to 2012.[19] Median first medical contact-to-door time was 33.5 minutes[20] while median door-to-balloon time was 64 minutes.[19] Around 50% of STEMI cases in Singapore presented to the hospitals via ambulances.[19]

Study Population and Outcome Data—The Singapore Myocardial Infarction Registry

The SMIR (Singapore Myocardial Infarction Registry) is a nationwide registry managed and funded by the National Registry of Diseases Office, Ministry of Health Singapore,[21] and collects epidemiological and clinical data on AMI cases diagnosed in all public and private sector hospitals and a small number of out-of-hospital AMI deaths certified by medical practitioners in Singapore. AMI is a disease whose notification to the registry has been mandated by the National Registry of Diseases Act enacted in 2012. Public sector cases comprise 98% of the registered cases.

Registry data were received from various sources on a monthly basis and were processed monthly to obtain unique cases. The sources of data included patient medical claim listings, hospital in-patient discharge summaries, cardiac biomarker listings from hospital laboratories and the national death registry. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code 410 was used to identify AMI cases diagnosed from 2010 to 2011 while *ICD-10* (*Australian Modification*) codes I21 and I22 were used for AMI cases diagnosed in 2012. The differentiation between ST-segment–elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) was based on presenting symptoms, cardiac biomarkers and ECG assessment, and aligned with clinician's diagnosis documented in the physical case notes and electronic medical records. STEMI was defined as follows: typical chest pain of 30 minutes and significant ST segment elevation (0.1 or 0.2 mV on 2 adjacent limb or precordial leads, respectively, or new left bundle-branch block) and confirmed subsequently by a rise in biomarkers. All ECGs were interpreted, and all diagnoses were adjudicated centrally at the National Registry of Diseases Office. The multinational monitoring of trends and determinants in cardiovascular disease (MONICA) criteria[22] were used for defining episodes.

Detailed patient data were extracted from clinical medical records including ambulance records, Emergency department notes, clinical charts, and discharge summaries, by dedicated registry coordinators from the SMIR. Yearly audits on data collected were done to ensure data accuracy and inter-rater reliability of at least 95%.

The primary outcome variable of our study is the occurrence of an AMI. We considered all cases of AMI in Singapore from 2010 to 2015. Recurrence of AMI after 28 days of a recorded AMI episode was considered a separate episode.

The event date was taken to be the date of onset as we included both inpatient and outpatient AMI. Although the date of onset may be subjected to recall bias by patient, it was checked against the start of acute symptoms, serial changes in ECG, elevation in cardiac biomarkers, and fatal collapse, whichever was earliest.

Environmental Data

The primary exposure was 24-hour average PSI. PSI is an air quality index used to indicate the level of pollutants in the air. This was based on a scale devised by the United States Environmental Protection Agency to provide a way for news agencies to report daily air quality. PSI has been used in several countries including the United States, Brunei Darussalam, and Singapore. The National Environment Agency in Singapore classifies 24-hour PSI into ranges of good (0–50), moderate (51–100), unhealthy (101–200), very unhealthy (201–300), and hazardous (>300).[23]

PSI is computed based on 6 air pollutants: fine particulate matter with aerodynamic dynamic smaller than 2.5 μm ($PM_{2.5}$), PM_{10}, sulfur dioxide (SO_2), carbon monoxide (CO), ozone (O_3), and nitrogen dioxide (NO_2). For each pollutant, a sub-index is calculated from a segmented linear function that transforms ambient concentrations onto a scale extending from 0 through 500.[24] PSI is then computed to be the maximum of the 6 sub-indices. $PM_{2.5}$ is the major pollutant released by forest fires,[25] and the World Health Organization guideline level for 24-hour mean $PM_{2.5}$ is 25 $\mu g/m^3$.[26]

In Singapore, ambient pollutant levels are continuously monitored at >20 telemetric air quality monitoring stations across the island.[27] Exposure data were retrieved from local government websites. The data were those that are made publicly available by the government agencies but required the authors to write a script to aggregate the data into a usable format. Historical 24-hour PSI data were obtained from www.haze.gov.sg which is maintained by the National Environment Agency. Meteorological parameters were obtained

from www.weather.gov.sg which is maintained by the Meteorological Service Singapore, and included total daily rainfall, daily highest rainfall (over 30-, 60- and 120-minute intervals), daily temperature (mean, maximum, minimum) and daily wind speed (mean, maximum). Data from 5 meteorological stations (Jurong West, Khatib, Simei, Kampong Bahru, and Upper Thomson) scattered across Singapore were obtained.

Ethics Approval

The Centralized Institutional Review Board and Domain Specific Review Board granted approval for this study with a waiver of patient consent (CIRB reference number: 2017/2380).

Statistical Analysis

Data analysis was performed using Stata version 13.[28] Categorical and continuous data were presented as frequency with percentage and median with interquartile range (IQR), respectively. Statistical significance was set at $P<0.05$.

This study used a time-stratified design to control for time trend and other short-term varying confounders like ambient temperature since it compares exposure levels between same weekdays within each month of each year.[29] Exposure on days where AMI occurred (case days) were compared with the exposure on days where AMI did not occur (control days). Control days were chosen on the same day of the week earlier and later in the same month in the same year. Daily AMI counts approximately followed Poisson distribution.

We fitted a conditional Poisson regression model to daily AMI incidence that included 24-hour average PSI and potential confounders such as daily average temperature, total rainfall, and average wind speed. All models were adjusted for over-dispersion and autocorrelation, except for a sensitivity analyses without adjustment for over-dispersion and autocorrelation. Based on National Environment Agency's recommended range, PSI was categorized into 3 categories: good, moderate, and unhealthy (cutoffs previously stated). We assessed the relationship between AMI incidence and PSI range in the entire cohort and in subgroups of demographic and clinical characteristics, which were determined a priori. The subgroups are chosen to allow identification of susceptible subpopulations.

We also investigated percent excess risk of AMI associated with each 30-unit increase in PSI values on the day of incidence (lag 0 day) and subsequent days before the incidence, until there was no further persistent lag effect. The results were presented as incidence risk ratio (IRR) and 95% CI for PSI range and percent excess risk in AMI per 30-unit increase in PSI values using the formula (risk ratio − 1) $\times$ 100.

Table 1. Characteristics of Patients With Myocardial Infarction (n=53 948 Cases)

	n (%)
Age, y; median (IQR)	68.9 (58.0–79.6)
Male	35 133 (65.1)
Ethnicity	
Chinese	35 791 (66.3)
Malay	10 530 (19.5)
Indian	6826 (12.7)
Subtype	
STEMI	13 509 (25.0)
NSTEMI	34 662 (64.3)
History of MI/CABG/PCI	17 342 (32.8)
History of diabetes mellitus	24 524 (46.4)
History of hypertension	38 693 (73.2)
History of hyperlipidemia	33 596 (63.6)
Current/former smoker	24 027 (46.4)
Inpatient MI	12 998 (24.1)
Survived to hospital discharge	44 038 (81.6)

CABG indicates coronary artery bypass grafting; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

Results

Study Population

There were 53 948 cases of AMI between 2010 and 2015 qualified for analysis. The median age was 68.9 years (IQR 58.0–79.6) and 65.1% were male. There were 64.3% were non–ST-segment–elevation myocardial infarction (NSTEMI) while 25.0% were STEMI, 24.1% occurred while inpatient, and 81.6% survived to hospital discharge. The characteristics of included cases are further described in Table 1.

Description of Exposure Data

Summary characteristics of air pollution and meteorological parameters are shown in Table 2. During the study period,

Table 2. Characteristics of Environmental Indicators (Daily Average Among the Regions in Singapore, n=2191 Days)

	Median (Interquartile Range)
Rainfall, mm	1.8 (0.0–9.6)
Rainfall, mm among the days that rained	4.7 (1.0–12.8)
Temperature, °C	27.7 (26.9–28.4)
Wind speed, km/h	7.0 (6.0–8.5)
Pollutant Standards Index	32.8 (25.7–47.0)

median daily 24-hour average PSI was 32.8 (IQR 25.7–47.0). Median daily total rainfall on the days that rained was 4.7 mm (IQR 1.0–12.8). Median daily average temperature was 27.7°C (IQR 26.9–28.4). Median daily average wind speed was 7.0 km/h (IQR 6.0–8.5).

Association of 30-Unit Increments in Pollutant Standards Index With Occurrence of AMI

Figure shows the distribution of 3-weekly AMI incidence with weekly average measure of 24-hour PSI. Smoothing of data included 1 lagged term, 1 forward term, and the current observation in the time-series moving average filter.

When considering PSI in terms of 30-unit increments, after adjusting for temperature, rainfall, and wind speed, PSI was significantly associated with increased AMI occurrence, with each 30-unit increment in PSI being associated with IRR of 1.04 (95% CI 1.03–1.06) in the entire cohort (Table 3).

In subgroup analyses of demographic and clinical characteristics, the association remained generally significantly positive, except in the subgroup of STEMI (IRR 1.00, 95% CI 0.98–1.03). In addition, even though the association between PSI and AMI were significant in both subgroups of inpatient and outpatient AMI, the strength of association was higher in the inpatient subgroup compared with the outpatient subgroup, with IRR 1.13 (95% CI 1.09–1.16) and IRR 1.02 (95% CI 1.00–1.04), respectively.

Besides STEMI versus NSTEMI and inpatient versus outpatient, there were no significantly increased susceptibility observed in other subgroups of age, sex, ethnicity, history of

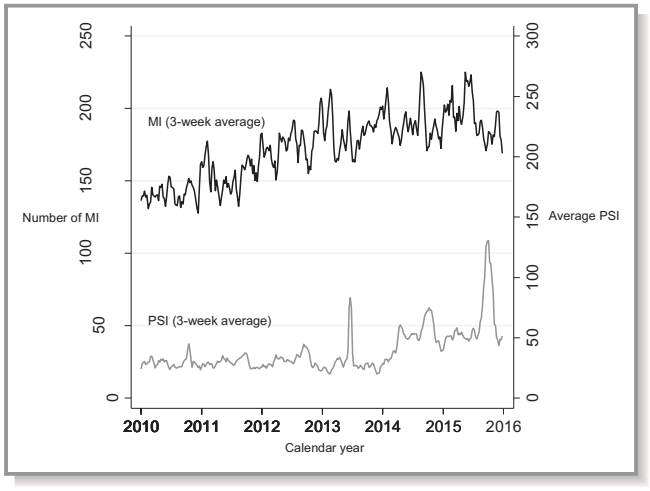

Figure. Distribution of weekly occurrence of myocardial infarction with Pollutant Standards Index. Smoothing of data included 1 lagged term, 1 forward term, and the current observation in the time-series moving average filter. MI indicates myocardial infarction; PSI, Pollutant Standards Index.

Table 3. Estimated Incidence Rate Ratio of Myocardial Infarction for Each 30-Unit Increment in Pollutant Standards Index for the Entire Study Cohort and by Subgroups of Demographic and Clinical Characteristics (n=2191 Days)

	Incidence Rate Ratio (95% CI)	*P* Value
Entire cohort	1.04 (1.03–1.06)	<0.001
Without overdispersion and autocorrelation	1.04 (1.03–1.06)	<0.001
Subgroups		
Age		
<65 y	1.04 (1.02–1.07)	<0.001
≥65 y	1.05 (1.03–1.07)	<0.001
Sex		
Male	1.06 (1.04–1.08)	<0.001
Female	1.04 (1.01–1.06)	0.005
Ethnicity		
Chinese	1.05 (1.03–1.07)	<0.001
Malay	1.05 (1.02–1.08)	0.002
Indian	1.04 (1.01–1.08)	0.014
Subtype		
STEMI	1.00 (0.98–1.03)	0.940
NSTEMI	1.08 (1.05–1.10)	<0.001
History of MI/CABG/PCI		
Yes	1.05 (1.03–1.08)	<0.001
No	1.05 (1.03–1.07)	<0.001
History of diabetes mellitus		
Yes	1.06 (1.04–1.08)	<0.001
No	1.05 (1.03–1.07)	<0.001
History of hypertension		
Yes	1.05 (1.03–1.07)	<0.001
No	1.06 (1.04–1.09)	<0.001
History of hyperlipidemia		
Yes	1.05 (1.03–1.08)	<0.001
No	1.05 (1.02–1.07)	<0.001
Current/former smoker		
Yes	1.04 (1.02–1.07)	<0.001
No	1.06 (1.04–1.08)	<0.001
Place of MI onset		
Inpatient	1.13 (1.09–1.16)	<0.001
Outpatient	1.02 (1.00–1.04)	0.029

Incidence rate ratios were estimated using conditional poisson regression adjusted for overdispersion and autocorrelation, with average Pollutant Standards Index, rainfall, temperature and wind speed as random effects covariates. CABG indicates coronary artery bypass grafting; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

cardiac disease, diabetes mellitus, hypertension, hyperlipidemia, and smoking history.

Association of Good, Moderate and Unhealthy Ranges of Pollutant Standards Index With Occurrence of AMI

When considering PSI in terms of categories of good, moderate, and unhealthy ranges, after adjusting for temperature, rainfall and wind speed, taking the good PSI range as a reference, moderate and unhealthy PSI ranges were significantly associated with increased AMI occurrence (Table 4), with IRR 1.08 (95% CI 1.05–1.11) and IRR 1.09 (95% CI 1.01–1.18), respectively.

The associations between moderate and unhealthy ranges of PSI with AMI in the STEMI subgroup were not statistically significant, IRR 1.02 (95% CI 0.98–1.07) and IRR 1.00 (95% CI 0.89–1.14), respectively.

Moderate range of PSI was significantly associated with AMI in all other subgroups analyzed.

Unhealthy range of PSI was only significantly associated with AMI in the subgroups of men (IRR 1.11, 95% CI 1.02–1.21), NSTEMI (IRR 1.11, 95% CI 1.01–1.21), no history of cardiac disease (IRR 1.13, 95% CI 1.04–1.23), no history of diabetes mellitus (IRR 1.11, 95% CI 1.01–1.22), history of hypertension (IRR 1.09, 95% CI 1.00–1.19), no history of hyperlipidemia (IRR 1.14, 95% CI 1.03–1.26), non-smokers (IRR 1.12, 95% CI 1.02–1.24) and inpatient AMI (IRR 1.32, 95% CI 1.15–1.52).

Excess Risk at Different Lag Terms

In addition, after adjusting for temperature, rainfall, and wind speed, each 30-unit increment in PSI values on the same day (lag 0) and previous 1 day up until 2 years and 4 months (not cumulative) was significantly associated with increased risk of AMI incidence (Table 5), presented at intervals of 2 months.

The excess risks from 30-unit increment in PSI for same day exposure was 4.38 (95% CI 2.66–6.12) and for the 427th day after was 4.76 (95% CI 2.34–7.25) (Table 5).

Limitations

There are several limitations to this study. First, the study design does not allow a causative relationship between PSI and AMI to be proven, even though strongly suggested on the basis of plausibility, temporality, and dose-response.

Secondly, there are possible residual confounding factors because the study design did not permit controlling for behavioral changes related to air pollution, as people take different approaches to mitigation based on their beliefs and attitudes. For example, while the elderly can mitigate the haze by staying at home, those who had to work outdoors during the haze period have no such recourse. Also, those with higher socioeconomic status may have access to air-conditioning and respirator masks (which are proven to improve a range of cardiovascular health measures in patients with coronary disease[30]) which would modify their risk. This same effect may explain findings in other studies that the adverse effects from PM2.5 exposure were higher for individuals with lower education level.[31]

Thirdly, PSI, which is a composite air quality index, was used instead of concentrations of individual constituent pollutants. Therefore, we are unable to examine the relative excess risk contributed by each pollutant. On the other hand, PSI is an easily recognizable indicator for the public to understand, monitor, and interpret. The findings of this study are hence easily actionable for health education of the public and to calibrate as public policy. It is also suspected that the individual pollutants may interact in complex ways that may not be accounted for by the statistical methods used. There is therefore value in considering air pollution in phenotypic groups of their origins, such as forest fire or urban exhaust, rather than in their constituent components. This is supported by a study of 6 cities in the United States showing that for the same particle size and concentration, combustion-origin particles are associated with increased mortality, but not crustal-origin particles.[32] We have previously demonstrated correlation of PSI with other health outcomes such as sudden cardiac death and acute ischemic stroke.[33,34]

Fourthly, the small number of events incurring on days with PSI in the unhealthy range (n=41) is small and hence the power to detect significant association is reduced for the comparison of unhealthy PSI versus good PSI ranges.

There is also potential for misclassification of AMI onset date as it is partially affected by recall bias by the patient. Also, some symptoms preceding admission may have been angina episodes and not attributed to the index AMI episode.

Discussion

This study demonstrated that in a population exposed to wide fluctuations in ambient air pollution, exposure to increases in a composite air pollution index was associated with a markedly increased short-intermediate risk of AMI. The excess risk was most pronounced on the day of the exposure, but remained elevated for the next 5 days. This is, to our knowledge, the first study linking the Southeast Asian haze to AMI, other than indirectly, in our previous study of the effect of PSI on out-of-hospital cardiac arrest (currently in press).

The finding of a significant association of exposure to air pollution and occurrence of AMI is generally consistent with previous studies.[6,7,35,36] We have found 8% and 9% excess risk of AMI when PSI is in the moderate and unhealthy range,

Table 4. Estimated Incidence Rate Ratio of MI for Each PSI Group for the Entire Study Cohort and by Subgroups of Demographic and Clinical Characteristics (n=2191 Days)

		Moderate PSI (n=429)		Unhealthy PSI (n=41)	
	Good PSI (n=1721)	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Entire cohort	1.00 (reference)	1.08 (1.05–1.11)	<0.001	1.09 (1.01–1.18)	0.021
Without overdispersion and autocorrelation	1.00 (reference)	1.08 (1.05–1.11)	<0.001	1.09 (1.01–1.18)	0.018
Subgroups					
Age					
<65 years	1.00 (reference)	1.08 (1.04–1.12)	<0.001	1.09 (0.99–1.21)	0.092
≥65 years	1.00 (reference)	1.11 (1.07–1.15)	<0.001	1.10 (1.00–1.21)	0.052
Sex					
Male	1.00 (reference)	1.09 (1.06–1.13)	<0.001	1.11 (1.02–1.21)	0.018
Female	1.00 (reference)	1.11 (1.06–1.16)	<0.001	1.08 (0.96–1.21)	0.228
Ethnicity					
Chinese	1.00 (reference)	1.10 (1.06–1.13)	<0.001	1.08 (0.99–1.19)	0.070
Malay	1.00 (reference)	1.09 (1.03–1.15)	0.001	1.08 (0.93–1.25)	0.306
Indian	1.00 (reference)	1.08 (1.02–1.14)	0.013	1.08 (0.92–1.27)	0.331
Subtype					
STEMI	1.00 (reference)	1.02 (0.98–1.07)	0.363	1.00 (0.89–1.14)	0.939
NSTEMI	1.00 (reference)	1.15 (1.11–1.18)	<0.001	1.11 (1.01–1.21)	0.029
History of MI/CABG/PCI					
Yes	1.00 (reference)	1.10 (1.05–1.14)	<0.001	1.04 (0.92–1.18)	0.488
No	1.00 (reference)	1.10 (1.07–1.14)	<0.001	1.13 (1.04–1.23)	0.005
History of diabetes mellitus					
Yes	1.00 (reference)	1.08 (1.04–1.12)	<0.001	1.10 (0.99–1.22)	0.064
No	1.00 (reference)	1.12 (1.08–1.16)	<0.001	1.11 (1.01–1.22)	0.030
History of hypertension					
Yes	1.00 (reference)	1.08 (1.05–1.11)	<0.001	1.09 (1.00–1.19)	0.046
No	1.00 (reference)	1.14 (1.09–1.19)	<0.001	1.12 (1.00–1.27)	0.057
History of hyperlipidemia					
Yes	1.00 (reference)	1.09 (1.05–1.13)	<0.001	1.08 (0.98–1.19)	0.117
No	1.00 (reference)	1.10 (1.06–1.14)	<0.001	1.14 (1.03–1.26)	0.015
Current/former smoker					
Yes	1.00 (reference)	1.07 (1.03–1.11)	<0.001	1.06 (0.96–1.18)	0.250
No	1.00 (reference)	1.13 (1.09–1.17)	<0.001	1.12 (1.02–1.24)	0.019
Place of MI onset					
Inpatient	1.00 (reference)	1.23 (1.17–1.30)	<0.001	1.32 (1.15–1.52)	<0.001
Outpatient	1.00 (reference)	1.05 (1.02–1.08)	0.002	1.03 (0.95–1.12)	0.522

Incidence rate ratios were estimated using conditional poisson regression adjusted for overdispersion and autocorrelation, with average PSI, rainfall, temperature and wind speed as random effects covariates. CABG indicates coronary artery bypass grafting; IRR, incidence rate ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; PSI, Pollutant Standards Index.

respectively. Furthermore, when considering only NSTEMIs, which seems to be driving the association, the magnitude of the excess risk is greater at 15% and 11%, respectively. Given that practically the entire population is exposed involuntarily to this risk factor, the collective health burden is magnified. Further, the study is designed to examine only the short-

Table 5. Estimated Percent Excess Risk of Myocardial Infarction for Each 30-Unit Increment of Pollutant Standards Index at Different Lag Term (n=2191, d)

Lag, d	Excess Risk in % (95% CI)	*P* Value
0	4.38 (2.66–6.12)	<0.001
61	5.69 (3.98–7.43)	<0.001
122	6.17 (3.86–8.53)	<0.001
183	4.35 (2.02–6.73)	<0.001
244	5.02 (2.70–7.40)	<0.001
305	3.53 (1.16–5.95)	0.003
366	3.70 (1.32–6.14)	0.002
427	4.76 (2.34–7.25)	<0.001
488	2.12 (−0.54 to 4.84)	0.119

Lag 0 refers to same day exposure; lag 61 refer to exposure at 61 days prior. Excess risks were estimated using conditional poisson regression adjusted for overdispersion and autocorrelation, with average Pollutant Standards Index, rainfall, temperature and wind speed as random effects covariates.

intermediate term risk, and would not capture long-term risk. Therefore, the effect of air pollution on AMI is significantly greater than suggested by this risk estimate magnitude alone.

The finding that only NSTEMI, but not STEMI is associated with increases in PSI is of interest. A case-crossover study of the England and Wales Myocardial Ischaemia National Audit Project , which was the only other study which examined the differential effect on NSTEMI versus STEMI, showed comparable results. In that study of 202 550 STEMI and 322 198 NSTEMI events, air pollutants were significantly associated with NSTEMI but not STEMI. In addition, taking AMI as a whole cohort (including both NSTEMI and STEMI), the excess risk ceased to remain significant.[37] However, other smaller studies on AMI (not designed specifically to look at the differential effect on NSTEMI and STEMI), do not corroborate these findings, with several finding significantly increased risk for STEMI,[36,38,39] and 1 study showing no increased risk for NSTEMI.[40] Given these mixed findings, it is difficult to postulate the underlying reason for the differential effects on STEMI and NSTEMI, even though knowing that mechanistically, STEMI is more often because of an acute plague rupture than NSTEMI.

Further clues are found in the related finding that excess risk for inpatient AMI is greater than for outpatient AMI. In general, inpatient AMIs more often occur in patients admitted for unrelated diagnoses such as sepsis or surgery and develop AMI as a result of relative myocardial oxygen demand-supply mismatch. This may suggest that the effect of air pollution on AMI is less likely to be mediated through primary plaque rupture processes.

In terms of susceptible sub-populations, we have found no clear evidence of increased susceptibility in elderly patients or patients with cardiac history, diabetes mellitus, hypertension, or hyperlipidemia. This is in general agreement with previous studies.[41] Knowledge of susceptible sub-populations, if any, is important for policy makers in formulating health advisories to target these at-risk populations, and to plan cost-effective interventions.

There is literature supporting a range of possible mechanisms for developing AMI in response to air pollution, and they generally fall into categories of coagulation,[42] inflammation,[42–45] vascular dysfunction,[46] and autonomic dysfunction.[47–50] These include experimental cellular, histological, animal, and healthy volunteer studies. It is likely that multiple mechanisms jointly contribute to the phenomenon.

One strength of this study lies in the high-quality outcome data from a national registry featuring comprehensive case capture. Legislated mandatory reporting of AMI and central adjudication of case qualification contributed to comprehensive and consistent case capture. In addition, we used exposure data that are measured directly by stations located around Singapore, and hence there was less exposure misclassification caused by extrapolating to rural areas via modeling. Additionally, the conditional Poisson regression model used in this study accounted for over-dispersion and autocorrelation in the time-dependent counts data.[29]

Millions of people worldwide are exposed to seasonal high levels of air pollution from forest fires, a modifiable risk factor, making it a tremendous public health issue. Being previously shown to be the risk factor that contributes the highest population attributable fraction to myocardial infarction alone,[9] air pollution presents a high yield disease prevention target for public health administrators. This study adds a Southeast Asian context to the growing body of evidence on the effect of air pollution on health, which as a whole, presents a compelling argument for concerted national efforts and intensified international cooperation to develop sustainable programs to tackle the haze problem in Southeast Asia and worldwide. Also, quantification of the health impact helps guide policy makers in evidence-based policy design and resource allocation. These measures may include issuing health advisories, public N95 respirator distribution programs, school closure policies, city planning from the urban development perspective, emergency medical resources deployment, as well as training doctrines for military training institutes.

Conclusion

During the study period, exposure to higher PSI was associated with an increased short-intermediate term risk of AMI in Singapore. Excess risk remained elevated through the day of exposure and for up to 5 days after exposure. This is, to our knowledge, the first study linking the Southeast Asian

haze problem to AMI. These results have public health implications for the region.

Disclosures

None.

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References

1. Brauer M. Air pollution, stroke, and anxiety. *BMJ*. 2015;350:h1510.
2. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng ATA, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FGR, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD, Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang YH, Khatibzadeh S, Khoo JP, Kok C, Laden F, Lalloo R, Lan Q, Lathlean T, Leasher JL, Leigh J, Li Y, Lin JK, Lipshultz SE, London S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L, Marks R, Martin R, McGale P, McGrath J, Mehta S, Mensah GA, Merriman TR, Micha R, Michaud C, Mishra V, Hanafiah KM, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK, Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CDH, Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope CA, Powles J, Rao M, Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I, Room R, Rosenfeld LC, Roy A, Rushton L, Salomon JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A, Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJC, Steenland K, Stöckl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Van Dingenen R, Van Donkelaar A, Veerman JL, Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray CJL, Ezzati M. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2224–2260.
3. World Health Organization. Burden of disease from ambient and household air pollution. 2014.
4. World Health Organization. The top 10 causes of death. 2017.
5. Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC, Whitsel L, Kaufman JD. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121:2331–2378.
6. Pope CA, Muhlestein JB, May HT, Renlund DG, Anderson JL, Horne BD. Ischemic heart disease events triggered by short-term exposure to fine particulate air pollution. *Circulation*. 2006;114:2443–2448.
7. Peters A, Dockery DW, Muller JE, Mittleman MA. Increase particulate air pollution and the triggering of myocardial infarction. *Circulation*. 2001;103:2810–2815.
8. Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M, Périer M-C, Marijon E, Vernerey D, Empana J-P, Jouven X. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. *JAMA*. 2012;307:713–721.
9. Nawrot TS, Perez L, Künzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet*. 2011;377:732–740.
10. Min Kok L. Haze in Singapore: a problem dating back 40 years. *The Straits Times*. 2015.
11. Vadrevu KP, Lasko K, Giglio L, Justice C. Analysis of Southeast Asian pollution episode during June 2013 using satellite remote sensing datasets. *Environ Pollut*. 2014;195:245–256.
12. ASEAN Haze Action Online. Combating Haze in ASEAN: Frequently Asked Questions. 2017.
13. Jaafar Z, Loh T-L. Linking land, air and sea: potential impacts of biomass burning and the resultant haze on marine ecosystems of Southeast Asia. *Glob Chang Biol*. 2014;20:2701–2707.
14. Dennis RA, Mayer J, Applegate G, Chokkalingam U, Colfer CJP, Kurniawan I, Lachowski H, Maus P, Permana RP, Ruchiat Y, Stolle F, Suyanto, Tomich TP. Fire, people and pixels: linking social science and remote sensing to understand underlying causes and impacts of fires in Indonesia. *Hum Ecol*. 2005;33:465–504.
15. Glover D, Jessup T. *Indonesia's Fires and Haze: The Cost of Catastrophe (With a 2006 Update)*. Ottawa, Canada: International Development Research Centre; 1999.
16. Statistics Singapore—Department of Statistics Singapore. Singapore in Figures 2017. 2017.
17. International Monetary Fund. World Economic Outlook Database; 2014.
18. Ho AFW, Chew D, Wong TH, Ng YY, Pek PP, Lim SH, Anantharaman V, Ong MEH. Prehospital trauma care in Singapore. *Prehosp Emerg Care*. 2015;19:409–415.
19. Ho AFW, Loy EY, Pek PP, Wah W, Tan TXZ, Liu N, Chua TSJ, Koh TH, Chow KY, Ong MEH. Emergency medical services utilization among patients with ST-segment elevation myocardial infarction: observations from the Singapore Myocardial Infarction Registry. *Prehosp Emerg Care*. 2016;3127:1–8.
20. Ho AFW, Pek PP, Fook-Chong S, Wong TH, Ng YY, Wong ASL, Ong MEH. Prehospital system delay in patients with ST-segment elevation myocardial infarction in Singapore. *World J Emerg Med*. 2015;6:277–282.

21. Singapore Myocardial Infarction Registry Annual Report 2007–2013 National Registry of Diseases Office. 2014.
22. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation*. 1994;90:583–612.
23. National Environment Agency. Health Advisories. 2014.
24. National Environmental Agency Singapore. Computation of the Pollutant Standards Index (PSI). 2015.
25. Reisen F, Meyer CP (Mick), Keywood MD. Impact of biomass burning sources on seasonal aerosol air quality. *Atmos Environ*. 2013;67:437–447.
26. World Health Organization. Fact sheet on: ambient (outdoor) air quality and health. 2016.
27. Is it true that NEA's PSI figures are deliberately under-reported? 2016. Available at: gov.sg. Accessed December 20, 2017.
28. StataCorp. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp Publisher; College Station, TX: 2015.
29. Armstrong BG, Gasparrini A, Tobias A. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. *BMC Med Res Methodol*. 2014;14:122.
30. Langrish JP, Li X, Wang S, Lee MMY, Barnes GD, Miller MR, Cassee FR, Boon NA, Donaldson K, Li J, Li L, Mills NL, Newby DE, Jiang L. Reducing personal exposure to particulate air pollution improves cardiovascular health in patients with coronary heart disease. *Environ Health Perspect*. 2012;120:367–372.
31. Pratt G, Vadali M, Kvale D, Ellickson K. Traffic, air pollution, minority and socio-economic status: addressing inequities in exposure and risk. *Int J Environ Res Public Health*. 2015;12:5355–5372.
32. Laden F, Neas LM, Dockery DW, Schwartz J. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. *Environ Health Perspect*. 2000;108:941–947.
33. Ho AFW, Wah W, Earnest A, Ng YY, Xie Z, Shahidah N, Yap S, Pek PP, Liu N, Lam SSW, Ong MEH. Health impacts of the Southeast Asian haze problem—a time-stratified case crossover study of the relationship between ambient air pollution and sudden cardiac deaths in Singapore. *Int J Cardiol*. 2018;271:352–358.
34. Ho AFW, Zheng H, De Silva DA, Wah W, Earnest A, Pang YH, Xie Z, Pek PP, Liu N, Ng YY, Wong TH, Foo LL, Ong MEH. The relationship between ambient air pollution and acute ischemic stroke: a time-stratified case-crossover study in a city-state with seasonal exposure to the Southeast Asian haze problem. *Ann Emerg Med*. 2018;72:591–601. DOI: 10.1016/j.annemergmed.2018.06.037.
35. Collart P, Dramaix M, Levêque A, Coppieters Y. Short-term effects of air pollution on hospitalization for acute myocardial infarction: age effect on lag pattern. *Int J Environ Health Res*. 2017;27:68–81.
36. Akbarzadeh MA, Khaheshi I, Sharifi A, Yousefi N, Naderian M, Namazi MH, Safi M, Vakili H, Saadat H, Alipour Parsa S, Nickdoost N. The association between exposure to air pollutants including PM10, PM2.5, ozone, carbon monoxide, sulfur dioxide, and nitrogen dioxide concentration and the relative risk of developing STEMI: a case-crossover design. *Environ Res*. 2018;161:299–303.
37. Butland BK, Atkinson RW, Milojevic A, Heal MR, Doherty RM, Armstrong BG, MacKenzie IA, Vieno M, Lin C, Wilkinson P. Myocardial infarction, ST-elevation and non-ST-elevation myocardial infarction and modelled daily pollution concentrations: a case-crossover analysis of MINAP data. *Open Heart*. 2016;3:e000429.
38. Pope CA, Muhlestein JB, Anderson JL, Cannon JB, Hales NM, Meredith KG, Le V, Horne BD. Short-term exposure to fine particulate matter air pollution is preferentially associated with the risk of ST-segment elevation acute coronary events. *J Am Heart Assoc*. 2015;4:e002506. DOI: 10.1161/JAHA.115.002506.
39. Argacha JF, Collart P, Wauters A, Kayaert P, Lochy S, Schoors D, Sonck J, de Vos T, Forton M, Brasseur O, Beauloye C, Gevaert S, Evrard P, Coppieters Y, Sinnaeve P, Claeys MJ. Air pollution and ST-elevation myocardial infarction: a case-crossover study of the Belgian STEMI registry 2009–2013. *Int J Cardiol*. 2016;223:300–305.
40. Gardner B, Ling F, Hopke PK, Frampton MW, Utell MJ, Zareba W, Cameron SJ, Chalupa D, Kane C, Kulandhaisamy S, Topf MC, Rich DQ. Ambient fine particulate air pollution triggers ST-elevation myocardial infarction, but not non-ST elevation myocardial infarction: a case-crossover study. *Part Fibre Toxicol*. 2014;11:1. DOI: 10.1186/1743-8977-11-1.
41. Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Effects of air pollution on the incidence of myocardial infarction. *Heart*. 2009;95:1746–1759.
42. Muller JE, Abela GS, Nesto RW, Tofler GH. Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. *J Am Coll Cardiol*. 1994;23:809–813.
43. Finkelstein JN, Johnston C, Barrett T, Oberdörster G. Particulate-cell interactions and pulmonary cytokine expression. *Environ Health Perspect*. 1997;105(suppl):1179–1182.
44. Driscoll KE, Carter JM, Hassenbein DG, Howard B. Cytokines and particle-induced inflammatory cell recruitment. *Environ Health Perspect*. 1997;105(suppl):1159–1164.
45. van Eeden SF, Tan WC, Suwa T, Mukae H, Terashima T, Fujii T, Qui D, Vincent R, Hogg JC. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM(10)). *Am J Respir Crit Care Med*. 2001;164:826–830.
46. Lucking AJ, Lundback M, Mills NL, Faratian D, Barath SL, Pourazar J, Cassee FR, Donaldson K, Boon NA, Badimon JJ, Sandstrom T, Blomberg A, Newby DE. Diesel exhaust inhalation increases thrombus formation in man. *Eur Heart J*. 2008;29:3043–3051.
47. Pope CA III, Dockery DW, Kanner RE, Villegas GM, Schwartz J. Oxygen saturation, pulse rate, and particulate air pollution: a daily time-series panel study. *Am J Respir Crit Care Med*. 1999;159:365–372.
48. Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. *Environ Health Perspect*. 1999;107:521–525.
49. Pope CA, Verrier RL, Lovett EG, Larson AC, Raizenne ME, Kanner RE, Schwartz J, Villegas GM, Gold DR, Dockery DW. Heart rate variability associated with particulate air pollution. *Am Heart J*. 1999;138:890–899.
50. Peters A, Perz S, Döring A, Stieber J, Koenig W, Wichmann HE. Increases in heart rate during an air pollution episode. *Am J Epidemiol*. 1999;150:1094–1098.