New perspectives in epidemiological studies on health effects of atmospheric particles:
Time lag, duration and intensity of exposure

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ABSTRACT

Ambient particulate matter (PM) has been associated with adverse health effects. Epidemiological studies on short-term exposure to ambient PM have been investigating time lags to examine whether which lag is a better predictor to the health outcome at current time. The evidence has been showing strong association between ambient PM and health effects, but some aspects should be considered further in a more comprehensive way – time lag, duration and intensity. Time lags have generally shown significant effects in short lags, but lags of hourly unit have not been addressed much, perhaps due to limitation of data availability. Besides time lag, it is essential to investigate duration and intensity of exposure. This information could be useful especially in extreme air pollution events. This thesis aimed to investigate acute effects of ambient particulate matter in view of time lag, duration and intensity. The first study (*Study I*) investigated the acute effects of ambient $PM_{2.5}$ on all-cause and cause specific EAD. The study included 8 cities of Japan. Pooled estimates showed that there were significant increased all-cause [Percent change of EAD: 1.24% (95% confidence interval (CI): 0.92, 1.56)], respiratory [1.88% (95% CI: 1.00, 2.76)] and neuropsychological [1.48% (0.69, 2.28)] EAD on lag 0 day. While these effects were shorter in all-cause and neuropsychological EAD (highest risk on current day lag), respiratory EAD demonstrated some prolonged delay (effects persisted up to 5 days lag). The second study (*Study II*) investigated hourly lags from exposure to disease onset. Further examining acute effects as continuity to findings from the first study, this study investigated the hourly lag pattern of EAD due to ambient SPM for the first 24-hour period upon exposure. City-specific effect estimates of one city from each of 46 prefectures in Japan were pooled using meta-analysis. In unconstrained distributed lag structure, significant increased EAD was observed at different hours at different cities. Meanwhile in the average lag structure, highest risks were observed at first 6 hours average lags. Lag 0-1 hours to lag 0-5 hours lags showed a plateau pattern prior to continuous decline but remained significant even at the 24th hour. The third study (*Study III*) investigated mortality among children of age under 5 years (U5Y mortality) due to haze considering duration and intensity of exposure using a new simple and comprehensive matrix. A new matrix of haze definition, accounted for time lag, duration and intensity, was applied to estimate the odds of U5Y mortality due to haze compared to that of non-haze. Weak association was observed for pooled estimated, with some significant higher risks of U5Y mortality in some cities. Meanwhile, lag pattern showed higher ORs in during haze with longer duration compared to the pattern in shorter duration. In brief, this thesis concluded that health effects of ambient PM were acute. Highest risk was observed during the first 6 hours lags. The application of exposure index incorporating the concept of time lag, duration and intensity could provide insightful information for elucidation of health effects of ambient PM, and may assist future policy decision and public health.

DEDICATION

This thesis is dedicated to
my family,
and my teachers.

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LIST OF SYMBOLS AND ABBREVIATIONS

SYMBOLS

α	Alpha
β	Beta
$\square$	Degree Celcius
γ	Gamma
$\bar{\text{x}}$	Mean
$\mu g/m^3$	Microgram per cubic meter
μm	Micrometer
%	Percent
$\pm$	Plus or minus

ABBREVIATIONS

AIC	Akaike Information Criteria
ANOVA	Analysis of variance
ANS	Autonomic nervous system
API	Air Pollutant Index of Malaysia (*Air Quality Index*)
BBB	Blood Brain Barrier
CI	Confidence interval
df	Degree of freedom
EAD	Emergency ambulance dispatches
GLM	Generalized linear model
ICD	International Statistical Classification of Diseases and Related Health Problems
IL	Interleukin

I^2	Amount of heterogeneity (I-squared)
NO_2	Nitrogen Dioxide
OR	Odds ratio
O_x	Photochemical Oxidant
PM	Particulate matter
$PM_{2.5}$	Particulate matter with aerodynamic diameter less than 2.5 µm
PM_{10}	Particulate matter with aerodynamic diameter less than 10 µm
RH	Relative humidity
RMSE	Root mean squared error
RR	Relative risk
SD	Standard deviation
SO_2	Sulfur Dioxide
SPM	Suspended particulate matter
TNF-α	Tumor Necrosis Factor-alpha
U5Y	Children with age under 5 years old
WHO	World Health Organization

EXECUTIVE SUMMARY

In air pollution and health studies, temporality has been widely explored to elucidate the disease pathway and to quantify the health risks via toxicological and epidemiological approaches. Designs of epidemiological studies ranged from long-term cohorts, panel studies, to short-term case-crossover and time series designs, to evaluate health effects considering different duration of exposures. Focusing on short-term exposure alone, attempts to elucidate adverse health effects by time component include the commonly investigated lag pattern, duration of exposure index, and windows of exposure for studies during extreme air pollution events (i.e. haze). Examining the lag pattern could show possible delayed onset of health effects after the time of exposure. While the concept of time is important in elucidating pathways of disease, the commonly used daily term in lag structures may not be adequate. Evidence on the health effects demonstrated by hourly lag pattern, however, is limited. Besides, more studies on wildfire haze is needed in order to examine health effects during extremely high levels of air pollutants. In the Southeast Asia (SEA) region, haze occurs almost every year due to biomass burning, especially fire in the peat soil areas apart from agricultural activities. Annual hot and humid weather, intensified by prolonged drought due to *El-Nino's Southern Oscillation* (ENSO) phenomenon, has led to several severe haze episodes covering the region including Singapore, Malaysia and Thailand with thick smoke. A regional response of haze – ASEAN Agreement on Transboundary Haze Pollution (AATHP) was initiated in 2002 but only ratified by all members in 2014. Due to geographical location, Malaysia faces the problem of transboundary haze especially during southwest monsoon season. Sometimes, the level of haze reaches alarming level, whereby Haze Emergency is declared to reduce all activities (including work and school) of the public. In addition, there are several studies which examined health effects due to haze, but studies on health effects of haze on susceptible population is scarce. Children of younger age (i.e. age under 5 years) may be highly susceptible due to their immature physiological and immune system. In addition, inconsistent definitions of haze used for reporting of its health effects may lead to confusion among the general public and difficult to be interpreted for policy decisions.

This thesis aimed to investigate acute effects of ambient particulate matter in view of time lags, temporal and intensity. The first study aimed to investigate the association between short-term exposure to ambient $PM_{2.5}$ (particulate matter of size less than 2.5 μm) and emergency ambulance dispatches (EAD) among different types of diagnoses in Japan. The second study aimed to investigate hourly lags from exposure to disease onset. Meanwhile, the third study aimed to investigate mortality among children of age under 5 years due to haze considering intensity and duration of exposure.

In Chapter 1, I introduced about the particulate matter and the health effects, as well as the reason why time lag, duration and intensity should be considered for in investigating the health effects of ambient particulate matter. This includes the concept of time lags in epidemiological studies and criteria which are essential to pass an association into verdict of causal inference. I included a conceptual diagram (Figure E1) to explain the concept and potential use a new matrix of exposure considering time lag, duration and intensity. Evidence from previous studies and the research gaps to be filled in this thesis were discussed.
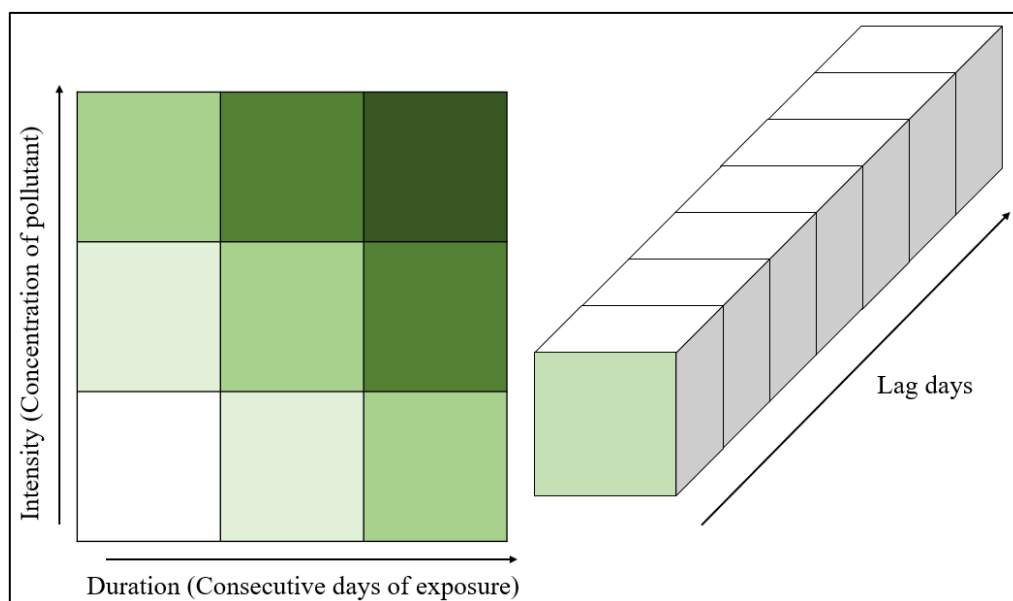
Figure E1. *(Extracted Figure 1.4 from page 11)* Conceptual diagram of expected risk due to exposure by duration and intensity

In Chapter 2, I explained *Study I*, in which I examined the acute effects of ambient $PM_{2.5}$ on all-cause and cause specific emergency ambulance dispatches using "daily" lag structure. Considering that different health indicator may provide insightful information of ambient $PM_{2.5}$ health effects, I investigated the acute effects of ambient $PM_{2.5}$ on all-cause and cause specific EAD in 8 cities of Japan. Duration of exposure may affect the disease pathway and thus different severity or type of disease of health effects. A time series analysis with a generalized linear model was applied to estimate city-specific association between ambient $PM_{2.5}$ and EAD. The city estimates were then pooled using meta-analysis. Pooled estimates showed that there were significant increased all-cause [Percent change of EAD: 1.24% (95% confidence interval (CI): 0.92, 1.56)], respiratory [1.88% (95% CI: 1.00, 2.76)] and neuropsychological [1.48% (0.69, 2.28)] EAD on lag 0 day (current day). While these effects were shorter in all-cause and neuropsychological EAD (highest risk on current day lag), prolonged delay were demonstrated in respiratory EAD (effects persisted up to average 5 days lag). The prolonged effects observed in

respiratory system might be due to wide range of respiratory outcomes, including severe and acute cases such as asthma, to mild and prolonged cases such as upper respiratory tract infections. Meanwhile, the acute effects observed on neuropsychological outcomes may be due to partial harvesting effect from patients with underlying diseases, whereby short-term exposure to ambient $PM_{2.5}$ might have triggered some biological responses such as acute inflammation, microglial activation, oxidative stress and neuronal death as suggested by evidence in experimental studies. Chapter 2 concluded that effects of ambient $PM_{2.5}$ on all-cause EAD and neuropsychological EAD were acute, mainly occurring on the current day lag, while prolonged effects were observed in respiratory EAD.

In Chapter 3, *Study II* examined the hourly variation of ambient suspended particulate matter (SPM) and association with health effects for the first 24 hours. This study responds to the question on appropriateness or representativeness of daily term lag structure in estimation of health risks. Some studies investigated lag pattern using hourly term. The use of daily term in lag structures might have misclassified the outcomes that precede exposure because the health effects at each hour were forced to be assumed occurring at end of the day. Previous studies have suggested that hourly lag structure could provide insightful information on onset of disease, especially on acute illnesses such as myocardial infarction. Examining the hourly lag structure may allow a step forward in compatibility with evidence from toxicological studies to elucidate the biological mechanisms. From *Study I*, it was found that ambient $PM_{2.5}$ effect on EAD were acute, occurring on short lags. Here, hourly exposure to ambient SPM and association with hourly EAD was examined. This study included 46 cities of all prefectures in Japan except for the Tokyo Metropolis, spanning year 2012 to 2015. City specific effect estimates were first obtained from generalized linear model, and then pooled by meta-analysis. In results, hourly distributions of SPM were slightly different among cities but EAD showed strong similar pattern with less EAD during midnight but peaked in the morning at around 9 a.m. In unconstrained distributed lag structure, significant increased EAD was observed on different lags in different cities. Meanwhile in the average lag structure, highest risks were observed at first 6 hours average lags. Lag 0-1 hours to lag 0-5 hours lags showed a plateau pattern prior to continuous decline but remained significant even at the 24th hour (Figure 2). The plateau pattern during first 6 average lags might be time of onset of disease, varying over 6 hours within the day. Some pathological responses during the first 6 hours upon exposure may include pulmonary and systemic inflammatory responses, oxidative stress, and autonomic nervous system imbalance as suggested by evidence from experimental studies. Though, it might be due to behavioral factors of the people in using EAD service. Findings from this study suggested evidence on possible biological response within hours from time of exposure, which could not be explained using daily lag structure.
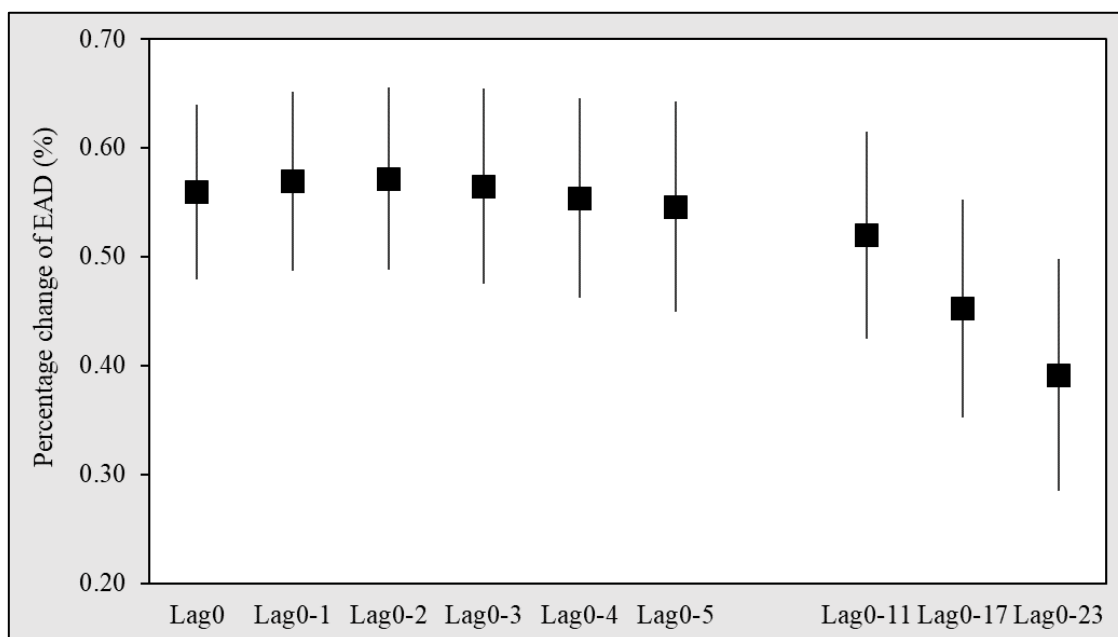
Figure E2. (*Extracted Figure 3.5 from page 44)* Pooled percent change of all-cause EAD associated with each 10 µg/m^3 increase in ambient SPM (average hour lag model).
Note: Each lag is represented by average lag-hour. Values were based on 95% confidence interval.

Chapter 4 contains *Study III*, in which instead of only lag structure, I used a haze matrix which I considered different intensity (level of ambient PM$_{10}$ concentration), duration (number of consecutive days which fulfills the baseline concentration) and lag structure. This prepares a simple and comprehensive tool which can communicate both the exposure (intensity and duration) and lag effects. Previous studies have suggested increased mortality, hospital admissions and emergency room visits, including all-cause and cardiopulmonary outcomes due to haze. These studies investigated the health effects of haze by determining the window of exposure during which the concentration of air pollutant was extremely high; while the baseline concentration being determined have been varying among studies. The studies suggested that there were higher risks of health effects during the haze period if compared to non-haze period. However, reporting of results using only lag pattern and their consideration of haze in using different definitions in estimating the health effects, may be difficult to be interpreted by general public. Exposure index considering both intensity and duration concurrently has not been investigated. The term "intensity" was used here to demonstrate the level of intensity of haze, instead of the commonly used "per unit increment of air pollutant" during non-haze period. Meanwhile, the term "duration" was used to demonstrate the consecutive days of haze. Applying the concept as shown in Figure 1, this study examined the effects of haze considering intensity and duration concurrently as the

exposure index, and time lag to demonstrate the health effects. *Study III* included all 16 states of Malaysia spanning year 2014. A case-crossover analysis was performed to compare the odds of mortality among children of age under 5 years (U5Y mortality) during haze to that during non-haze. Lag pattern was examined for each "definition of haze". There was weak association observed, with some significant higher odds of U5Y mortality during haze in some cities. From the lag pattern, it was observed that in definition with longer duration, the lag pattern showed more acute effects. This suggests that duration and intensity might affect the type of health outcome or specific disease. Though not statistically significant, it is noteworthy to observe that elucidation of health effects using this matrix may assist future policy decision or public health. This study demonstrated application of a new simple and comprehensive tool in estimating health effects of haze accounted for duration, intensity and time lag.

In conclusion, short-term exposure to ambient PM was associated with acute effects on health. High increments in EAD were observed during the first six hours lags at a consistent level. Information from the lag structures may be useful in elucidation of disease pathway or biological mechanism. Finally, haze events defined by different duration and intensity showed weak association on U5Y-mortality, but at haze definition with longer duration, the highest odds ratio was observed on current day (lag 0). The information may assist future policy decision and public communication regarding air pollution events. Furthermore, the haze matrix considered intensity, duration and time lags may provide a simple and direct comprehensive information to the public, as compared to merely reporting of lag effects or varying baseline concentration for haze definition.

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CHAPTER 1: INTRODUCTION

Particulate matter and health effects

Particulate matter (PM) consist of solid particles and liquid droplets suspended in the air. They are mainly sourced from both natural events, including sea spray and volcanic activities, and anthropogenic activities, such as agricultural, manufacturing, vehicle emissions and fossil fuel combustion. PM are usually categorized via their aerodynamic diameters. PM of smaller size, particularly those less than 10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$) are the most concerned PM which could affect human health due to their deposition in the respiratory tract. In addition, $PM_{2.5}$ could deposit deeper in the respiratory tract and penetrate to the circulatory system.

PM is one of the leading factors to health risks. This include its attribution to 4.2 million premature deaths globally in 2015 (Cohen *et al.*, 2017). A few major studies, such as the *Public Health and Air Pollution in Asia* (PAPA) study in Asian countries (Wong *et al.*, 2008) and *Air Pollution and Health: A Combined European and North American Approach* (APHENA) study (Samoli *et al.*, 2008), have reported observed association between ambient PM and mortality. Both these studies have shown that increase in ambient PM_{10} (Wong *et al.*, 2008) and $PM_{2.5}$ (Samoli *et al.*, 2008) increases the risks of death, with similar estimates between the Asian and Western region (Wong et al. 2008). Atkinson et al. (2014) revealed that an increase of 10 μg/m^3

in $PM_{2.5}$ is associated with 1.04% increase in premature deaths via a systematic review (Atkinson *et al.*, 2014).

On the other hand, other studies have shown the health effects of PM using morbidity indicators. Some commonly used morbidity indicators in air pollution studies include hospital admissions (Dominici *et al.*, 2006; Bell *et al.*, 2008; Stafoggia *et al.*, 2013; Zanobetti *et al.*, 2014; Bravo *et al.*, 2017), emergency department (ED) visits (Metzger *et al.*, 2004) and emergency ambulance dispatches (EAD) (Sajani *et al.*, 2014; Michikawa *et al.*, 2015; Ichiki *et al.*, 2016; Tasmin *et al.*, 2016; Liu *et al.*, 2017; Salimi *et al.*, 2017). It is important to realize that mortality alone is not adequate to demonstrate the adverse health effects of ambient PM. In Zanobetti et al.'s (2014) study, they pointed out that ambient PM are associated not only with the life-threatening or acute cardiopulmonary diseases, but also other systemic diseases such as diabetes and neurological disorders. They observed increased risks for diabetes and neurological disorders hospitalizations, and all-cause deaths, but not modified effects on deaths among these hospitalized cases (Zanobetti *et al.*, 2014).

Role of time in air pollution studies

Time is an essential component to consider in elucidating the association between ambient PM and adverse health effects. We need to acknowledge that exposure shall always precede outcome, and the process takes time. The delayed effect is known as "lagged effects.

Lag refers to the duration between the point of exposure and point of adverse health outcomes. In studies on short-term exposure to air pollutants, lag in "daily" term is commonly used. It is common to observe the lag pattern ranging from lag-0 to lag-2 days (i.e. current day to 2 days before) (Dominici *et al.*, 2006; Wong *et al.*, 2008; Zanobetti *et al.*, 2014). This can be interpreted that from the time of exposure, it takes about 2 days for the body to become "sick" or "dead". However, it might be difficult to accept the *"after inhaling a sudden increased level of air pollutant, we die (or sick)"* concept, and whether is this even plausible, remains a question.

The "harvesting" hypothesis was raised in around the 2000's, whether that the increased mortality or morbidity along with air pollution was contributed by the fragile population – the persons who would die or hospitalized in the consequent few days even without air pollution. "Harvesting" is also known as "displacement" (i.e. mortality displacement, or morbidity displacement). A few studies demonstrated that increase in adverse health effects from air pollution is not merely due to the harvesting effects   (Zeger, Dominici and Samet, 1999;

Schwartz, 2000, 2001; Zanobetti and Schwartz, 2008).

Attempts to clarify these time-related issues have shown the importance of time component in air pollution studies. Elucidating the time-related issues might provide important insights into passing an association into the verdict of causal inference.

Time component in Hill's criteria of causal association

In 1965, Sir Austin Bradford Hill pointed out 9 criteria as a guideline for scientists in interpreting an association as causal (Lucas and McMichael, 2005; Fedak *et al.*, 2015). These include *strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy*. Until today, these criteria remain as fundamental thoughts in investigating causal association of an exposure and disease. I will discuss here a few criteria which are related to time in air pollution studies.

Exposure must precede onset of a disease – this is *temporality*. In epidemiology, this criterion is illustrated via natural history of disease. Figure 1.1 shows the natural history of disease timeline. Over time, there are different stages – from healthy, susceptible, exposure, onset of disease, to finally recovery, disability or death.

Natural history of disease

USUAL TIME
OF DIAGNOSIS

PATHOLOGIC   ONSET OF
EXPOSURE   CHANGES   SYMPTOMS

STAGE OF | STAGE OF | STAGE OF | STAGE OF RECOVERY,
SUSCEPTIBILITY | SUBCLINICAL DISEASE | CLINICAL DISEASE | DISABILITY OR DEATH
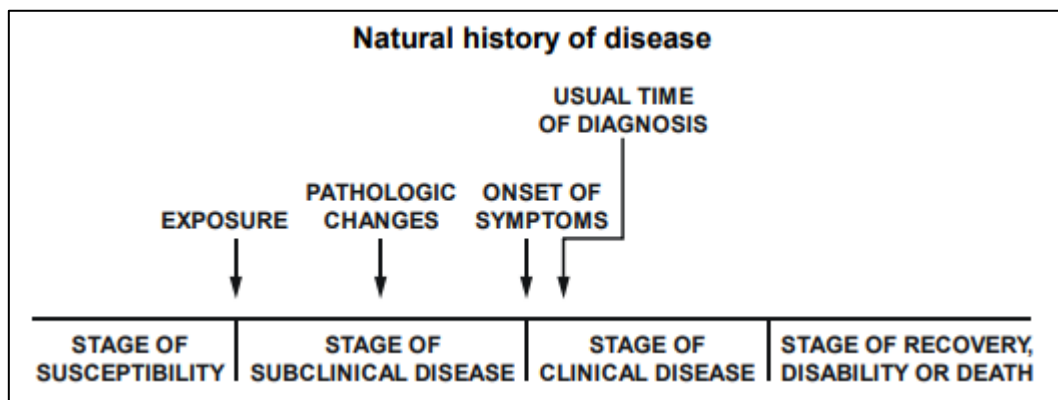
Figure 1.1. Natural history of disease timeline

Adopted from *Centers for Disease Control and Prevention (1992*)

Integration of data from various fields is essential in order to understand the natural history of a disease. In epidemiological studies, lag pattern is examined to clarify two points, (i) examine whether there is harvesting effect, and (ii) how much delayed was the disease (Zanobetti *et al.*, 2000). Such information could contribute to illustrating the natural history of disease for categorization of stages. Next criterion which contributes to this is *coherence*. Toxicological studies are necessary as a complementary to epidemiological studies in causal inferencing. As a cause should be specific (*specificity*) to the outcome, the next criterion could assist researchers to determine the association – *experiment*. If we had removed the exposure, and observed that there is no occurrence of disease, then this might be the cause of the disease.

Evidence from toxicological studies have suggested that exposure to PM could trigger biological mechanisms which lead to pulmonary and cardiovascular diseases by 3 intermediary

pathways (Brook *et al.*, 2010). First, fine sized PM and/or its chemical components translocated

to blood stream and circulated systemically. Second, release of proinflammatory mediators due

to pulmonary oxidative stress and inflammation into blood stream. The systemic oxidative stress

and inflammation are demonstrated by cellular inflammatory response (activation of white blood

cells and myeloperoxidase) and expression of cytokines (interleukin-1-beta (IL-1β), IL-6 and

tumor necrosis factor-alpha (TNF-α)). Third, activation of lung ANS reflex arcs leading

imbalance in autonomic nervous system. These responses could occur within hours from exposure.

The *harvesting* hypothesizes similar process as the natural history of disease. In the

harvesting mechanism, an exposure (i.e. air pollution) leads general population into pool of

susceptibility, and from this stage to onset of disease and/or death (Figure 1.2). Through various

biological mechanisms in the human body, one may revert to general population (i.e. the healthy

stage).
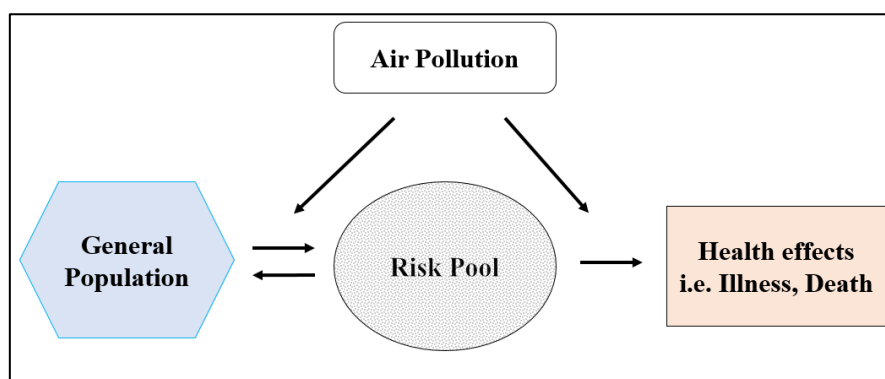
Figure 1.2. Harvesting mechanism
Adopted and modified from *Zanobetti et al. 2000*

Quantifying *harvesting* effects has enabled us to observe that adverse health outcomes do not attribute to only the current day's exposure to air pollution but also from previous days. Short lag pattern (lag-0 to lag-2 or -3) has been commonly observed in previous studies (Dominici *et al.*, 2006; Wong *et al.*, 2008; Zanobetti *et al.*, 2014; Liu *et al.*, 2017). This enables easier examination of *coherence* over different research fields.

How short is short?

Short-term exposure is considered as exposure within days and not longer than 2 weeks. Most studies have been examining how changes in air pollutant levels affect human health, and these were observed via lag patterns. Various lag structures have been examined – from individual lags (exposure only from each individual day), distributed lags (exposure from each day after adjusting for day-to-day correlation), cumulative lags (cumulated exposure over days), and average lags (averaged exposure level over days).

Indeed, within a day, air pollutant levels vary from time to time. Using daily average concentration as the exposure index might fail to detect the effect of short-term temporal variation (Ono *et al.*, 2007; Yorifuji *et al.*, 2014). The conventional usage of daily exposure on daily health outcomes lay on the assumption that all health outcomes occur at the end of the day (Lokken *et al.*, 2009). Figure 1.3 demonstrates an illustrative diagram on the use of daily hourly terms in

examining association between air pollution and health.
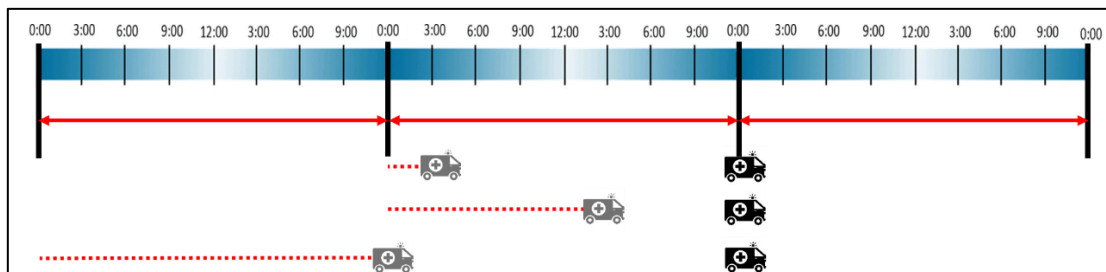
Figure 1.3. Illustrative diagram on difference in the use of daily term and hourly term. Note: Blue bar indicates time, by hours of the day. Red solid line indicates exposure using daily (24-hour average) concentration of air pollutant. Red dotted line indicates actual time taken from exposure to onset of health outcome. Black ambulance figure (🚑) indicates the onset of health outcome assumed to be at the end of the day. Grey ambulance figure (🚑) indicates actual onset of health outcome.

Ono et al. (2007) demonstrated that hourly index could deter estimated effects to 1-day lag (Ono *et al.*, 2007). The usage of hourly exposure index might be able to enlighten the acute health effects such as asthma. For example, increase in coarse PM for lag-1-6-hour and lag-7-12-hour was reported to increase asthma exacerbation (Kim *et al.*, 2015). Such acute effects might not be observed if the hourly variation is averaged into daily context. Elucidating the hourly variations might help to contribute to *coherence* with underlying biological mechanisms. Table 1.1 shows some previous studies which investigated using hourly exposure index.

Table 1.1. Previous studies examining hourly variation

Author (Year)	Exposure	Health outcome	Main findings
Murakami & Ono (2006)	SPM	Myocardial infarction mortality	Rate ratio of each category (low, intermediate, high) against reference category (0-99 µg/m^3): *1 hour*: *Low:* 1.13 (95% CI: 1.07, 1.20) *Intermediate:* 1.17 to 1.24 *High:* 1.40 (95% CI: 1.00, 1.97) *6-hour average:* 1.17 in highest category.
Ono *et al.* (2007)	SPM	Mortality	Relative risk on lag 0 day: New index weighted for hourly outcome: 1.0065. Midnight-to-midnight 24-hour average: 1.0049.
Lanki *et al.* (2008)	PM$_{2.5}$	ST segment depression	Odds ratio per 10 µg/m^3 increase in PM$_{2.5}$ *Lag 1 hour:* 3.26 (95% CI: 1.07, 9.99) *Lag 4 hour average:* 2.47 (95% CI: 1.05, 5.85)
Bhaskaran *et al.* (2009)	PM$_{10}$	Myocardial infarction hospital admission	Excess risk per 10 µg/m^3 increase in PM$_{10}$ *Lag 1-6 hour:* 1.2% (95% CI: 0.3%, 2.1%)
Yamazaki *et al.* (2011)	PM$_{2.5}$	Peak expiratory flow (PEF) in hospitalized children	Changes in PEF associated with 10 µg/m^3 increase in PM$_{2.5}$. *1-hour 10 µg/m^3(Morning and evening):* PEF decreased about 3 litre/minute.
Yorifuji *et al.* (2014)	SPM	CVD emergency room visit by ambulance	Odds ratio: *Lag 0-6 hour:* Cardiovascular 1.04 (95% CI: 1.01, 1.06) Cerebrovascular 1.04 (95% CI: 1.00, 1.08) *Lag 48-72 hour:* Hemorrhagic stroke 1.08 (95% CI: 1.00, 1.16)

Exposure assessment of air pollution considering duration and intensity

Lag structure has been commonly used to examine the temporality of health effects of environmental factors such as air pollutants and temperature. Examining the lag pattern could provide us not only information on the delayed time for onset of disease from time of exposure to the environmental factors, but also whether there is harvesting effect. However, demonstrating adverse health effects of ambient PM via lagged pattern might be difficult to be understood by general public. Studies focusing on the duration and intensity of environmental factors is scarce. One study investigated rate of death attributable to myocardial infarction by comparing different categories of SPM, and at different length of exposure window (Murakami and Ono, 2006). Another study considered time component by lag pattern and intensity by defining a high exposure window (Rappold *et al.*, 2011). They reported increased several respiratory and cardiovascular -related diseases associated with 5-days cumulative lag for high exposure window. Considering linear association assumed for health effects of air pollutants, Figure 1.4 shows an illustrated conceptual diagram of expected health risk due to exposure to air pollutant considering duration and intensity. The y-axis represents increasing concentration of pollutant (intensity), while x-axis represents consecutive number of days for each level of intensity. Association of health effects based on a combination of each duration and each intensity as displayed in Figure 1.4 might be a better way to provide a simple and direct information for general public. Most

studies may represent the health effects in one horizontal layer (one level of intensity) as lag

pattern was examined for a fixed unit increment in air pollutant but fail to demonstrate the results

in a comprehensive way as shown in Figure 1.4.
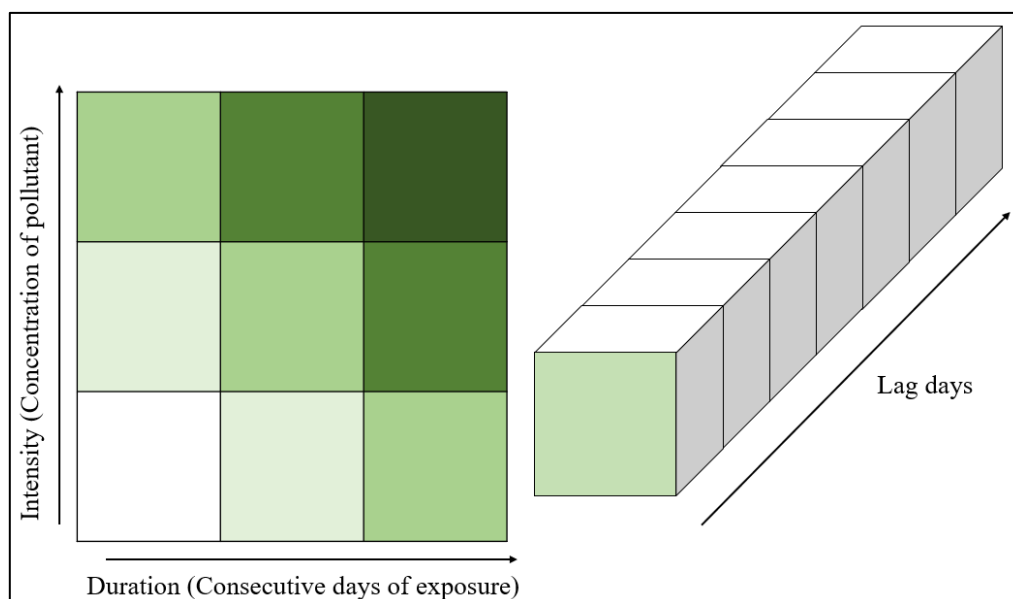
Figure 1.4. Conceptual diagram of expected risk due to exposure by duration and intensity.

In examining health effects of haze, haze is usually modeled as a binary variable,

indicating whether there is an exposure to haze or not. To define haze, some parameters which

are commonly used include visibility, humidity, PM concentration, and air quality index. In

Malaysia, air quality information is disseminated to the public by using air quality index (API).

The API is categorized into "good", "moderate", "unhealthy", "very unhealthy", and "hazardous"

5 status of air quality. Categorization of API consist of a few stages of calculations. Concentration

of each criteria pollutant (sulfur dioxide, ozone, nitrogen dioxide, carbon monoxide, $PM_{2.5}$ and PM_{10}) is first calculated to obtain each respective index. Then, maximum index among these six is used to define API. During poor air quality days, such as when API is unhealthy, the information would be highlighted to alert the public. The shortcoming of using API to define haze is that, it is not possible to conclude the attributable pollutant and thus the pathological pathway. Previous studies defined haze day by determining a baseline concentration of PM_{10} (Sahani *et al.*, 2014) and $PM_{2.5}$ (Morgan *et al.*, 2010; Rappold *et al.*, 2011). Sometimes, the association is investigated by comparing health effects on haze day to health effects on non-haze day (Rappold *et al.*, 2011; Othman *et al.*, 2014; Sahani *et al.*, 2014), increment of PM during haze period (Morgan *et al.*, 2010; Tinling *et al.*, 2016). Other times, lag pattern is also examined (Morgan *et al.*, 2010; Rappold *et al.*, 2011; Sahani *et al.*, 2014). Although haze event may occur for some days consecutively, these studies had not considered duration and intensity of exposure concurrently.

Haze in Malaysia

Malaysia is a tropical country with hot and humid weather throughout the year. In between, there are months of dry weather, from May to October, due to its geographical location and affected by monsoon season. Haze events in Malaysia may be attributed to local activities

such as biomass burning and agricultural activities and transboundary wildfire pollutants which may be brought about from neighboring countries by southwesterly monsoon wind (Afroz, Hassan and Akma, 2003; Sulong *et al.*, 2017). Source apportionment conducted in a study has shown that wildfires in Sumatra, Indonesia contributed to high level of pollutant during haze period (Sulong *et al.*, 2017). The residents are being exposed not only to local air pollutants but also transboundary haze. In some of previous haze episodes, haze had reached a level whereby the authority declared Haze Emergency for the whole country (Kanniah *et al.*, 2016). When the Haze Emergency is declared, all outdoor activities, and public and private workplace shall be ordered to stop. It is usually issued if the air quality index (API) breach 500. The situation may be exacerbated due to the *El-Nino* Southern Oscillation (ENSO) which may prolong the dry season (Islam *et al.*, 2016; Kanniah *et al.*, 2016). The transboundary haze problem has initiated a regional agreement among the Southeast Asia countries (ASEAN) – ASEAN Agreement on Transboundary Haze Pollution (AATHP) in 2002, which was ratified by all members in 2014.

Wildfire haze has been suggested to contribute to increased adverse health effects, including mortality (Sahani *et al.*, 2014), hospital admissions (Mott *et al.*, 2005; Othman *et al.*, 2014), emergency room visits (Rappold *et al.*, 2011), out-of-hospital cardiac arrests (Dennekamp *et al.*, 2015), and physical and psychological stress (Ho *et al.*, 2014). Hospital admission alone would cost about MYR 273,000 (USD 65,000) per year due to haze (Othman *et al.*, 2014). In the

1997 haze episode, it was estimated that total cost of health damage in Malaysia was about MYR

129 million (USD 30 million) (Islam *et al.*, 2016). It was suggested that the effects were not only

attributed to increased level of pollutants during haze but also the toxicity of components (Sulong

et al., 2017).

Rationale

Association between short-term exposure to ambient particulate matter (PM) and health effects

have been commonly investigated using daily exposure and daily health outcomes. Most of the

studies suggested that short-term exposure to air pollutants impose acute effect – most effects

were observed for exposure on current day (lag 0) or the previous day (lag 1). Finer time lag

considering hourly variation may provide insightful information on the biological response upon

exposure to ambient PM rather than merely the association. In addition, investigation on the

association accounting for time lag, duration and intensity is not common. Applying an exposure

index considering duration and intensity may enlighten new direction in future air pollution

studies, as well as assist future policy decision and public health.

Objectives

General objective:

To investigate acute effects of ambient particulate matter in view of time lags, duration and intensity.

Specific objectives:

1   To investigate the association between short-term exposure to ambient $PM_{2.5}$ on EAD among different types of diagnoses in Japan.

2   To investigate hourly lags from exposure to disease onset.

3   To investigate mortality among children of age under 5 years due to haze considering intensity and duration of exposure.

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CHAPTER 2: *Study I (Acute effects of ambient PM$_{2.5}$ on all-cause and cause-specific emergency ambulance dispatches in Japan)*

This chapter discusses about my first study on investigating the acute effects of PM$_{2.5}$ using emergency ambulance dispatches (EAD) as the morbidity health indicator. This study aimed to investigate the association between short-term exposure to ambient PM$_{2.5}$ on EAD among different types of diagnoses. Lag pattern of all-cause and cause specific EAD were examined.

As discussed in Chapter 1, numerous studies have demonstrated how ambient PM is associated with various diseases. These studies mainly used health indicators such as mortality, hospitalization and emergency department visits. The usage of EAD as health indicator in air pollution studies, however, was rare. EAD system in Japan could be different to that of many countries. EAD in Japan is managed by the local fire departments. The public could utilize the EAD service by calling the emergency number "119". Both EAD service and call are free of charge. Paramedics of dispatched ambulance would send the patients to either the nearest available hospital (after confirming with the hospital staffs), or to the patient's regularly visited hospital. Such system allows the data to include general population, wide range of disease categories, age, and severity of disease, and acute effects nearer to the onset of symptoms if compared to mortality or inpatient data.

Method

- *Study settings*

This study included data from 8 cities of Japan, spanning from year 2007 to 2011. The cities are located distinctly across northern to southern regions over the country. Figure 2.1 shows the location of each city included.
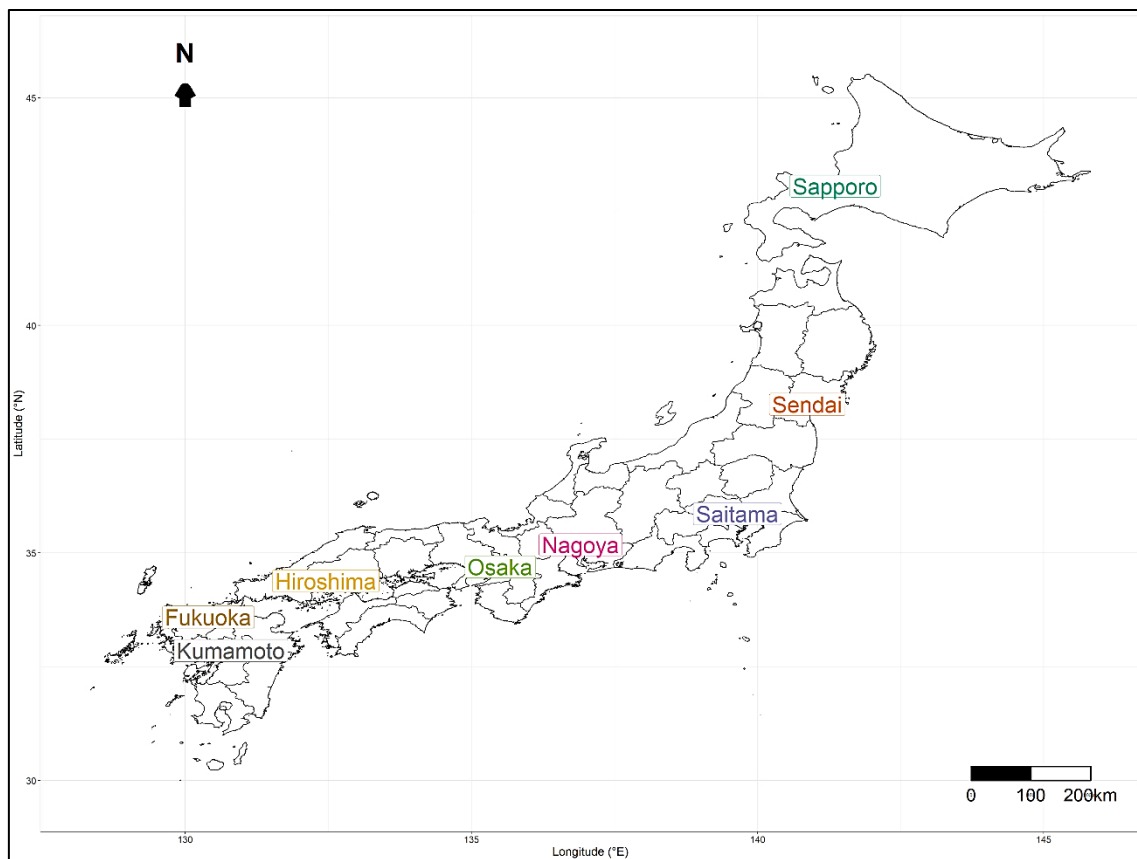
Figure 2.1 Map of Japan indicating the 8 cities included in the study

- *Health data*

Data on daily EAD were obtained from the Fire and Disaster Management Agency of the Ministry of Internal Affairs and Communications of Japan. The data for Kumamoto city were obtained from the Kumamoto city office.

The EAD data contained information on sex, age category, cause of dispatch, type of diagnoses and severity of the patient's condition. For the purpose of this study, I excluded all but the category "acute illness". This is to avoid including health outcomes that are irrelevant to the main exposure (for example, EAD due to drowning). For specific types of diagnoses, I extracted the data from "acute illness" by category – cardiovascular (ICD-10: I10-I15, I20-I25, I01-I02.0, I05-I09, I27, I30-I52), respiratory (ICD-10: J00-J99), cerebrovascular (ICD-10: I63, I69.3, I60-I62, I64-I68, I69.0-I69.2, I69.4-I69.8) and neuropsychological (ICD-10: F00-F99, G00-G99, H00-H59, H60-H95).

- *Exposure data*

Exposure data include air pollutant, temperature, relative humidity and influenza epidemics data. While ambient $PM_{2.5}$ was modelled as the main exposure variable, other exposure data were used to adjust for confounding effects.

(1) Air pollutant data

Air pollutant data were obtained from the National Institute for Environmental Studies (NIES), while ambient $PM_{2.5}$ data for Saitama were obtained from the Center for Environmental Science in Saitama. The data include hourly concentrations of ambient $PM_{2.5}$ and gaseous pollutants (nitrogen dioxide, photochemical oxidants, and sulfur dioxide). Daily 24-hour average concentration was calculated for each pollutant. We also excluded the days which consisted of more than 4 missing hourly concentrations of $PM_{2.5}$.

(2) Meteorological data

Data on ambient temperature and relative humidity were obtained from the Japan Meteorological Agency. Daily mean temperature and relative humidity were treated as continuous variables and adjusted for confounding effects in the model.

(3) Influenza epidemics data

Data on influenza epidemics were obtained from the Japan National Institute of Infectious Diseases. A week was defined as an influenza epidemic week given the condition that the influenza cases within that week were more than 90th percentile of the total distribution throughout the study period. Influenza epidemics data were treated as binary variable in the model.

- *Statistical analyses*

This is a two-stage time series analysis. In the first stage, I analyzed the city-specific association between ambient $PM_{2.5}$ and all-cause EAD (daily EAD for acute illnesses) using a generalized linear model (GLM) based on a Poisson distribution. Seasonal, time trends, and other potential confounders were considered for adjustment in the model (equation 2.1). I applied model simplification approach in selecting covariates to be adjusted in the model, whereby the simpler model would be retained if the *p*-value from the *Chi-square* test of ANOVA was less than 0.05. The following covariates were tested in order: calendar date, daily mean temperature, daily mean relative humidity, public holiday, day-of-week, and influenza epidemic. A natural cubic spline was applied to calendar time to allow smooth modelling for long-term and seasonal patterns, with 7 degrees of freedom (df) per year, as well as to temperature (moving average from the current day to 3 days before) with 3 df. Public holidays and day-of-week were adjusted for all cities as indicator variables. Relative humidity and influenza epidemics, however, were only adjusted in models for Sapporo and Osaka. *Chi-square* test of ANOVA had shown no significant difference between models with or without these variables, and thus the simpler model was determined for these 2 cities.

$$Y_t \sim Poisson$$

$$\log E(Y)_t = \alpha + \beta X_t + ns(date, df = 7 \ per \ year) + ns(Temp_{02}, df = 3)$$

$$+ ns(RH_{02}, df = 3) + HOL_t + DOW_t + FLU_t$$

$$(2.1)$$

Whereby $E(Y)_t$ denotes expected number of EAD at day t;

α is intercept;

X_t: PM$_{2.5}$ concentration at day t;

$date_t$: Natural cubic spline function applied for calendar time (*7 df* per year);

$Temp_{02}$: Natural cubic spline function applied for moving average 0-2 days temperature (*3 df*);

RH_{02}: Natural cubic spline function applied for moving average 0-2 days relative humidity (*3 df*);

HOL_t: Indicator variable for public holiday at day t;

DOW_t: Indicator variable for day of week at day t;

FLU_t: Indicator variable for influenza epidemics at day t.

In the second stage, a random-effects meta-analysis was performed to pool the city-specific effect estimates. An I^2 statistic was used to examine the amount of heterogeneity, while applying the *Chi-square* test from *Cochran's Q* statistic to test the significance of heterogeneity.

Lagged effect of ambient PM$_{2.5}$ was examined using 2 lag structures. First, an unconstrained-distributed lag structure, with an extension of 7 days (lag 0 to lag 7), to observe the estimates over different days. Secondly, average lag structure (average of PM$_{2.5}$ over days: lag 0-1, lag 0-3, lag 0-5, and lag 0-7) to account for the partially displaced risks.

In order to test for robustness of the association, some sensitivity tests were applied. Two-pollutant models by including each gaseous pollutant into the main model one at a time. The

main model with was tested with various df for calendar time (df ranged from 3 to 13) and

temperature (df ranged from 4 to 8), and stratification by age category. An additional analysis was

performed with bootstrapping, utilizing 10,000 simulations to obtain the empirical estimates and

confidence intervals of our results, using the estimates of all-cause EAD at average lag 0-1.

All analyses were performed using R (version 3.1.1, The R Foundation for Statistical

Computing, Vienna, Austria) and the packages *splines* and *metafor* (Viechtbauer, 2010). All

results were presented as percent change of EAD with 95% confidence interval (95% CI) per 10

$\mu g/m^3$ increase in ambient $PM_{2.5}$. Statistical significance was considered when the *p*-value was

less than 0.05.

- *Ethical review*

This study was approved by the Ethics Committee of the Kyoto University Graduate School of

Engineering (No. 201410).

Results

During the study period, there were 1,114,515 cases of EAD for acute illnesses in the 8

cities. Table 2.1 shows the daily average number of EAD in each city. The lowest EAD was in

Kumamoto ($\bar{x}$ =43) while highest was in Osaka ($\bar{x}$ =305). Generally, most of the EAD consist of

adults and elderly, while a balanced distribution was observed between male and females.

Information on exposure variables is shown in Table 2.2. Daily mean $PM_{2.5}$ concentration ranged

from 11.3 µg/m³ (Sapporo) to 20.8 µg/m³ (Hiroshima). Meanwhile, the daily mean temperature

was lowest in Sapporo (8.4 □), and ranged from 12.2 □ (Sendai) to 18.3 □ (Kumamoto).

Table 2.1. Daily emergency ambulance dispatches (EAD) in each city during the study period.

Characteristics	Sapporo	Sendai	Saitama	Nagoya	Osaka	Hiroshima	Fukuoka	Kumamoto
Study period	1 January 2007–31 March 2010	1 January 2007–31 March 2010	1 April 2009–31 March 2011	1 January 2008–31 December 2011	1 January 2008–31 December 2011	1 April 2010–31 December 2011	1 January 2009–31 December 2011	1 April 2010–31 December 2011
Population *	1,913,545	1,045,986	1,222,434	2,263,894	2,665,314	1,173,843	1,463,743	734,474
Sex								
Male	53 (9)	28 (6)	46 (9)	NA	NA	NA	46 (8)	21 (5)
Female	58 (9)	27 (6)	41 (8)	NA	NA	NA	47 (8)	22 (5)
Age								
Children	8 (4)	4 (2)	8 (4)	9 (5)	21 (7)	6 (3)	7 (3)	3 (2)
Adult	53 (9)	24 (5)	37 (8)	66 (12)	142 (18)	31 (7)	43 (8)	18 (4)
Elderly	51 (8)	27 (6)	41 (9)	84 (15)	142 (19)	38 (7)	43 (8)	23 (5)
Diagnosis type								
All acute illness	111 (14)	55 (9)	86 (14)	159 (22)	305 (33)	74 (11)	93 (13)	43 (8)
Cardiovascular	14 (4)	4 (2)	4 (2)	15 (4)	31 (6)	10 (3)	9 (3)	3 (2)
Respiratory	12 (5)	5 (2)	5 (2)	18 (5)	32 (7)	10 (3)	12 (4)	3 (1)
Cerebrovascular	18 (6)	5 (2)	5 (2)	11 (4)	25 (5)	12 (4)	24 (5)	3 (2)
Neuropsychology	12 (4)	5 (2)	6 (3)	14 (4)	53 (9)	10 (3)	5 (2)	3 (2)

* Population based on Japanese census in 2010. Values are shown as the daily mean (standard deviation). Note: Data on the sex category were not available in Nagoya, Osaka, nor Hiroshima.

Table 2.2. Daily average number of emergency ambulance dispatches (EAD) in each city during the study period.

Environmental Variable	Sapporo	Sendai	Saitama	Nagoya	Osaka	Hiroshima	Fukuoka	Kumamoto
$PM_{2.5}$ ($\mu g/m^3$)	11.27 (5.71)	12.41 (6.59)	17.86 (11.76)	16.00 (8.42)	18.58 (9.90)	20.84 (12.32)	18.14 (10.31)	18.73 (12.96)
SO_2 (ppb)	2.27 (1.57)	0.59 (0.58)	1.33 (0.62)	1.83 (1.18)	5.22 (2.97)	1.24 (0.86)	1.77 (1.19)	3.41 (1.56)
NO_2 (ppb)	15.53 (9.78)	13.83 (6.09)	18.78 (7.58)	20.83 (7.72)	20.23 (9.09)	13.82 (6.44)	13.46 (7.35)	9.77 (4.92)
O_x (ppb)	27.58 (11.15)	29.17 (11.62)	28.47 (13.34)	24.70 (12.86)	29.00 (13.21)	27.60 (12.98)	29.45 (13.44)	26.37 (12.15)
Temperature (°C)	8.64 (9.31)	12.19 (8.00)	15.52 (8.62)	16.43 (8.56)	17.08 (8.35)	17.69 (8.57)	17.35 (8.05)	18.34 (8.31)
Relative humidity (%)	67.92 (10.23)	71.48 (13.00)	65.06 (13.84)	63.50 (12.35)	62.76 (10.98)	64.53 (10.33)	65.58 (11.96)	69.33 (10.84)

Values are shown as daily mean (standard deviation).

Figure 2.2 shows the city-specific percent change of all-cause EAD associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ from the unconstrained distributed lag (daily) model. Generally, the highest risk of all-cause EAD were observed for exposure from the current day (lag 0). In some large cities (i.e. Saitama, Nagoya and Osaka), increased EAD was obviously higher on lag 0, followed by stable estimates for other lags. After pooling the effect estimates, the highest increment of EAD remained highest at lag 0 [1.24% (95% CI: 0.92, 1.56)], followed by a decline at lag 1 [-0.47% (95% CI: -0.80, -0.14)] (Figure 2.2). As for average lags, the increase in EAD was observed at average lag 0-1 [0.64% (95% CI: 0.23, 1.06)], and followed by continuous decrease at latter lags (Figure 2.3).
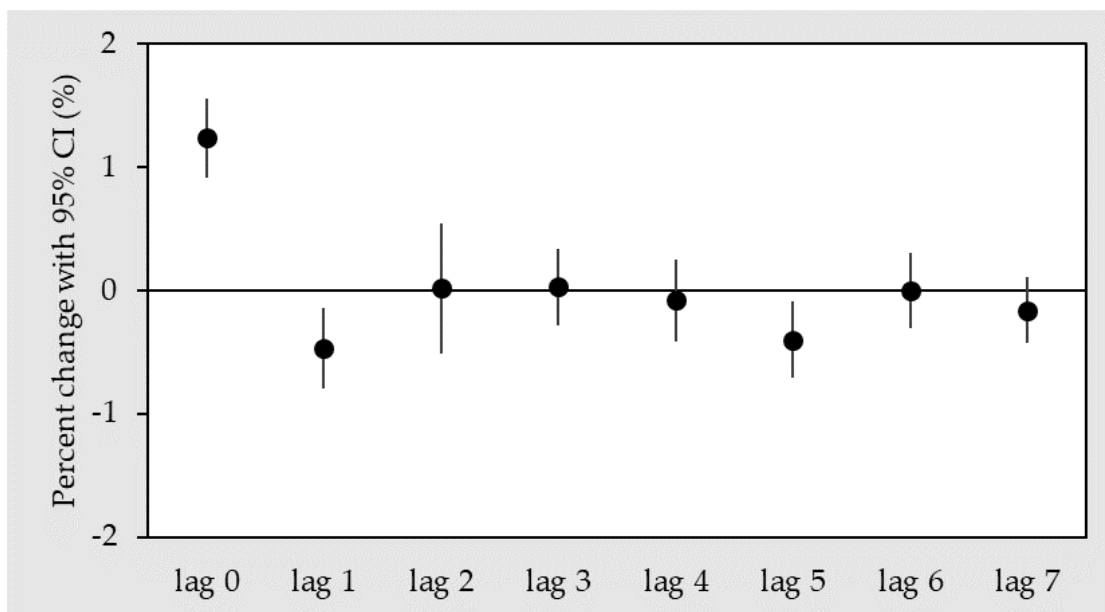
Figure 2.2. Pooled percent change of all-cause EAD for each 10 μg/m^3 increase in ambient PM$_{2.5}$ in unconstrained, distributed lag (daily) model.

Note: Each lag is represented in day-lag unit.

Figure 2.3. Pooled percent change of all-cause EAD for each 10 μg/m^3 increase in ambient PM$_{2.5}$ in average lag (daily) model.

Note: Each lag is represented in day-lag unit.

Cause-specific EAD outcomes showed similar lag pattern as those of all-cause EAD outcomes (Figure 2.4). Significant increased EAD were observed on lag 0 for all-cause, respiratory, and neuropsychological EAD. When examined for average lag structure, highest risk remained on lag 0 for cardiovascular, cerebrovascular and neuropsychological EAD, though only respiratory EAD and neuropsychological EAD were increased with statistical significance. On the other hand, the respiratory risk was higher at longer lags [average lag 0-3: 2.79% (95% CI: 1.31, 4.29)], extending up to 5 days.

Figure 2.4. Pooled percent change of cause specific EAD for each 10 µg/m^3 increase in ambient PM$_{2.5}$ in unconstrained distributed lag (daily) model.
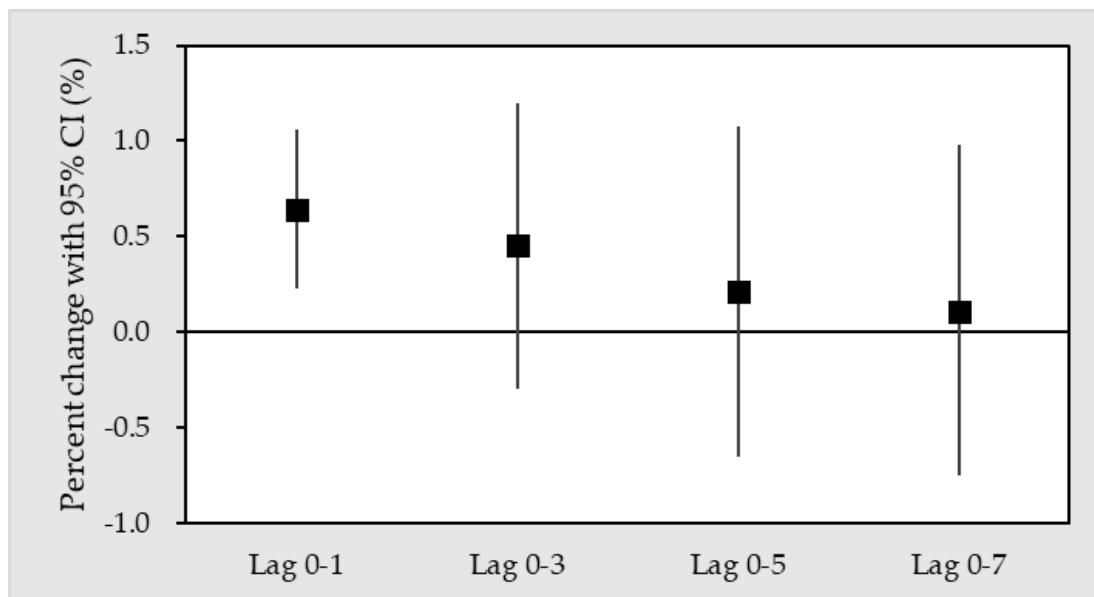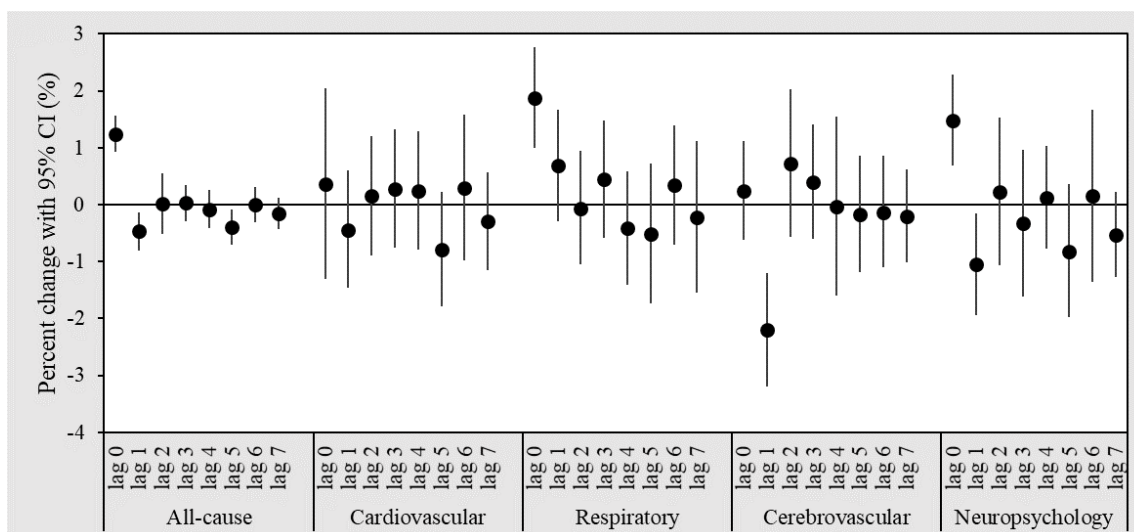
Note: Each lag is represented in day-lag unit.

Table 2.3. Pooled effect of ambient PM$_{2.5}$ on cause-specific EAD outcomes.

Lag structure	Cardiovascular	Respiratory	Cerebrovascular	Neuropsychology
Lag 0 [a]	0.36 (-1.30, 2.05)	**1.88 (1.00, 2.76)**	0.24 (-0.62, 1.11)	**1.48 (0.69, 2.28)**
Average Lags				
Lag 0-1	-0.10 (-0.92, 0.73)	**2.47 (1.69, 3.26)**	**-1.76 (-2.80, -0.72)**	0.59 (-1.09, 2.30)
Lag 0-3	-0.19 (-1.47, 1.11)	**2.79 (1.31, 4.29)**	**-1.27 (-2.22, -0.32)**	1.03 (-1.71, 3.84)
Lag 0-5	-0.20 (-1.37, 0.98)	**1.86 (0.23, 3.51)**	**-1.13 (-2.23, -0.02)**	0.06 (-2.50, 2.68)
Lag 0-7	-0.60, (-1.90, 0.72)	1.53 (-0.07, 3.16)	-1.05 (-2.29, 0.19)	-0.30 (-2.71, 2.17)

Values are shown as percent change (95% CI). [a] Lag 0 is based on unconstrained distributed lag (daily) model. Bolded values are of statistical significance at $p < 0.05$.

The lag pattern did not alter even after stratifying EAD outcomes by age categories (Table 2.4). The highest risk remained at lag 0 [children: 1.24% (95% CI: 0.21, 2.27); adults: 1.29% (95% CI: 0.87, 1.71); elderly: 1.19% (95% CI: 0.75, 1.62)]. For averaged lags, significant increase of EAD risk was observed for adults [0.78% (95%: 0.25, 1.32)] and elderly [0.65% (95%

CI: 0.20, 1.11)] at average lag 0-3. The effect estimates of all-cause EAD remained robust in

models using different df on calendar date and temperature, and in two-pollutant model (Figure

2.5). After bootstrapping with 10,000 simulations, the empirical estimates showed that the

association between $PM_{2.5}$ and EAD would always remain positive [all-cause EAD at lag 0-1:

0.49% (95% CI: 0.02, 0.98)].

Table 2.4. Pooled effect of ambient $PM_{2.5}$ on all-cause EAD by age category.

Lag structure	Children (Age below 18 years)	Adult (18-64 years)	Elderly (Age 65 years and above)
Lag 0 [a]	**1.24 (0.21, 2.27)**	**1.29 (0.87, 1.71)**	**1.19 (0.75, 1.62)**
Average Lags			
Lag 0-1	0.89 (-0.09, 1.89)	**0.78 (0.25, 1.32)**	**0.65 (0.20, 1.11)**
Lag 0-3	1.09 (-0.14, 2.32)	0.55 (-0.37, 1.48)	**0.61 (0.16, 1.07)**
Lag 0-5	0.45 (-0.96, 1.88)	0.16 (-0.99, 1.33)	0.34 (-0.36, 1.05)
Lag 0-7	0.03 (-1.53, 1.61)	0.26 (-0.93, 1.47)	0.05 (-0.73, 0.84)

Values are shown as percent change (95% CI). [a] Lag 0 is based on unconstrained distributed lag (daily) model. Bolded values are of statistical significance at $p < 0.05$.
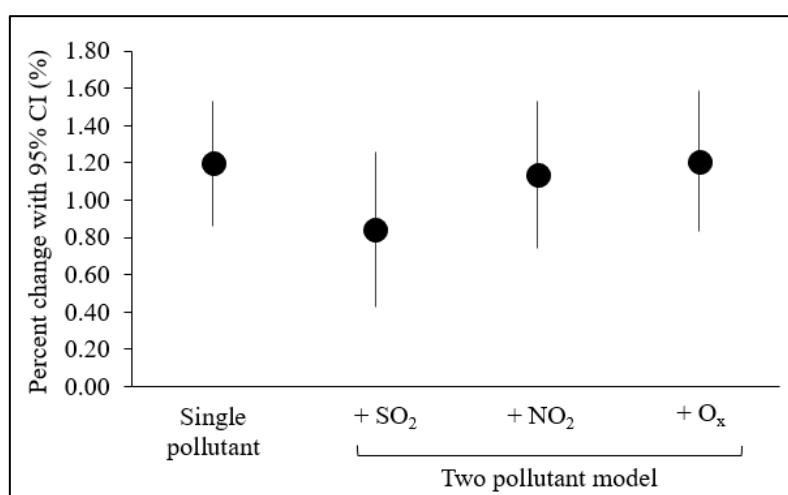

Figure 2.5. Percent change of all-cause EAD at lag 0 when adjusted using two-pollutant models. Each pollutant was included in the model one at a time.

Discussion

The main finding from this study is that short-term exposure to ambient $PM_{2.5}$ was associated with increased all-cause EAD in immediate lags, especially lag 0 for distributed lags and lag 0-1 for averaged lags. Such pattern was similar for models stratified by cause-specific EAD and age category.

The effect of ambient $PM_{2.5}$ was significant in respiratory EAD and neuropsychological EAD, but not cardiovascular EAD. From lag 0, extending to lag 0-5, respiratory EAD was significantly increased for each 10 $\mu g/m^3$ increase in ambient $PM_{2.5}$. Such effects on respiratory outcomes is consistent with previous studies (Dominici *et al.*, 2006; Zanobetti and Schwartz, 2009; Li *et al.*, 2017). Respiratory system is one of the first exposed and injured system when exposed to ambient $PM_{2.5}$. Exposure to ambient $PM_{2.5}$ increases various acute respiratory outpatient visits, including for upper respiratory tract infections, acute bronchitis, community-acquired pneumonia, and acute exacerbation of bronchiectasis (Li *et al.*, 2017). Particulate exposure could lead to cell injury due to oxidative stress (Li *et al.*, 2017), inflammatory responses (Seriani *et al.*, 2016), and imbalanced intracellular calcium homeostasis (Brown *et al.*, 2004). These pro-inflammatory responses could be underlying mechanisms for other diseases, such as cardiovascular and neuropsychological outcomes.

Previous studies have reported air pollutant effects on neuropsychological outcomes. The effects being investigated included both long-term exposure (Chen *et al.*, 2015, 2017; Kioumourtzoglou *et al.*, 2016) and short-term exposure (Szyszkowicz, 2008; Zanobetti *et al.*, 2014; Chen *et al.*, 2015; Lee *et al.*, 2017). Long-term exposure to ambient $PM_{2.5}$ has been associated with increased risks in Alzheimer's disease, Parkinson's disease (Kioumourtzoglou *et al.*, 2016), dementia (Kioumourtzoglou *et al.*, 2016; Chen *et al.*, 2017) and memory loss (Chen *et al.*, 2015), whereas short-term exposure is associated with Parkinson's disease (Zanobetti *et al.*, 2014; Lee *et al.*, 2017), headache (Szyszkowicz, 2008) and migraine (Chen *et al.,* 2015). Inflammatory responses and oxidative stress caused by air pollutant exposure are thought to be the underlying factors to increased neuropsychological outcomes. Several possible pathways to the brain have been suggested: (1) direct transportation of pollutant via circulatory pathway to the brain, passing through the blood brain barrier (BBB); (2) systemic inflammation whereby cytokines are circulated to the brain; and (3) nose-to-brain route that bypasses the protective BBB, whereby pollutants are transported along olfactory nerve to the brain (Lucchini *et al.*, 2012). These mechanisms are speculated to occur following some toxicity mechanisms such as inflammation, microglial activation (Block *et al.*, 2007), oxidative stress, and neuronal death (Heneka *et al.*, 2014). Acute effects were observed for neuropsychological outcomes, but for respiratory outcomes there were prolonged effects observed. This may be due to the possible wide

range of respiratory diseases – acute effects such as asthma, while delayed effects for other symptoms such as upper respiratory tract infections. Meanwhile, acute effects on neuropsychological outcomes may be induced among those with underlying neuropsychological diseases, such as Parkinson's disease.

On the other hand, ambient $PM_{2.5}$ effects on cardiovascular EAD was not significant, while inverse association was observed for cerebrovascular EAD in average lags. This situation might be due to some reasons as follow. First, the effect was too acute, or that the frail population was too weak (perhaps due to some underlying disease or comorbidities). In such situation, the rate of flow from frail pool into endpoint (EAD) pool of population became higher than incidence rate, leading to a low prevalence in the study population (Wilkinson, Milner and Armstrong, 2017). Second, it was a harvesting effect. Wellenius et al. (2012) reported a 12-h lag in $PM_{2.5}$ on stroke onset, instead of a per-day lag (Wellenius *et al.*, 2012). When an acute health outcome occurs within few hours, the use of longer time lag (for example, daily index) might attenuate the effect estimates. However, there was no significant effect observed on lag 0 (Table 2.4). If exposure to ambient $PM_{2.5}$ had harvested (displaced) cerebrovascular EAD, such effects should be observable in shorter lag (e.g. lag 0). Third reason may explain this situation. In studies using mortality as health indicator, double-counting of cases is not a concern. Each count (case) is the one and only (i.e. there will not be 2 mortality count for the same person). For morbidity (such as hospitalization,

clinic visits, or EAD), such kind of "category displacement" is possible. A cerebrovascular patient could have some complications, such as recurrent stroke, seizure, pain, anxiety depression, or infection (Davenport *et al.*, 1996; Langhorne *et al.*, 2000). This may lead to displacing this patient into other diagnoses.

- *Strengths*

This study has several strengths. First, the multi-city analysis allowed a representative overview of the association between ambient $PM_{2.5}$ and various health outcomes covering wide area of Japan. This study is very limited in Japan. A study had applied multi-city analysis which included over 30 prefectures of Japan (Ichiki *et al.*, 2016), but they only investigated the cardiovascular effect and it is limited to only 9 months study period. Second, I examined lag pattern of all-cause and several cause-specific outcomes. From there it is possible to observe potential harvesting effects in different health outcomes. Third, this study indicated the usefulness of EAD as a health indicator which reflects acute onset of medical conditions. EAD has not been used in air pollution studies until recent years. The EAD in Japan is a relatively representative data that include general population, with a wide range of disease categories and severity. In comparison to data such as mortality, the EAD data here include $PM_{2.5}$ effects ranging from mild symptoms to severe diseases.

-   *Limitations*

There were some limitations for this study. First, there might be some misclassification of diagnosis. Each dispatch is confirmed by a medical doctor upon arrival of the dispatch, but the final confirmed diagnosis might differ after several diagnostic examinations in the hospital. As the data used for this study did not include individual information, it is not possible to detect such misclassification, if any exists. Second, the use of ambient concentration of $PM_{2.5}$ might lead to potential exposure misclassification. This study could not account for individual mobility and behavior, thus their personal exposure. Third, the EAD data contained only general categories of disease, but no information for sub-categories. For example, the category of respiratory EAD could not be distinguished for their sub-categories, such as bronchitis, asthma, or chronic obstructive pulmonary disease. This might contribute to observable effects for respiratory EAD over various lags.

Conclusion

Short-term exposure to ambient $PM_{2.5}$ increased the risk of EAD for all-cause, respiratory, and neuropsychological outcomes. The effects were generally acute, mostly occurring within 1 to 2 days upon exposure to ambient $PM_{2.5}$. Meanwhile, effect extending over longer average lags was observed for respiratory EAD.

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CHAPTER 3: *Study II (Hourly variation on association between ambient SPM and health effects)*

In this chapter I will discuss on my second study on which I examined the hourly variation on particulate matter health effects. In ***Study I***, I found that exposure to ambient $PM_{2.5}$ impose acute EAD outcomes. The distributed lag in ***Study I*** indicated that the highest risk occurred on lag 0. The use of daily term might have misclassified the exposure and outcomes, as outcomes are assumed to occur at the end of the day if daily term is used to examine the association. This is because in a causal association, exposure must precede the outcome. Moreover, the use of daily term might attenuate the effects of some acute diseases if the disease onset is within hours instead of day. In this chapter, I investigated the association of ambient particulate matter and health effects using hourly concentration of suspended particulate matter (SPM) and hourly EAD, instead of the conventional "daily" term. Significant increased EAD due to 10 $\mu g/m^3$ increase in ambient SPM were observed, with highest risk at lags within the first 6 hours.

Method

- *Study settings*

This study included data from 46 cities of each prefecture in Japan. Data for the Tokyo

Metropolis was not available in this study as the EAD system in the Metropolis is slightly different

from all prefectures. The study spanned from year 2012 to 2015.

- *Health data*

Hourly data for EAD were obtained from the Fire and Disaster Management Agency of

the Ministry of Internal Affairs and Communications of Japan. The data included information on

sex, age, and cause of dispatch. I used only EAD due to "acute illness" category, which is the non-

accidental or non-traumatic category. All cases in "acute illness" were included, hereafter referred

to as all-cause EAD. The hour of EAD was extracted from "time of call" because the "time of

onset" was not available.

- *Environmental data*

Environmental data include air pollutant, temperature and relative humidity data. While

ambient SPM was modelled as the main exposure variable, meteorological data were used to

adjust for confounding effects.

(1) Air pollutant data

Air pollutant data were obtained from the National Institute for Environmental Studies (NIES). Hourly concentrations of ambient SPM were obtained by averaging the all monitoring stations for each prefecture were averaged. In Japan, ambient SPM level has been monitored since 1970s. SPM are particles which pass through filter of 100% cut-off particles with diameter of larger than 10 μm (>10 μm). SPM can be considered as PM_7, approximately.

(2) Meteorological data

Data on ambient temperature and relative humidity were obtained from the Japan Meteorological Agency. Daily mean temperature and relative humidity were treated as continuous variables and adjusted for confounding effects in the model.

- *Statistical analyses*

This study consisted two stages. In the first stage, I applied a generalized linear model (GLM) to analyze the city-specific association between ambient SPM and all-cause EAD. As from ***Study I***, highest risks were often observed on lag 0 (day). Here, I examined the lags within

the current day (lag 0 day), applying for hourly variables (within first 24 hours). I checked AIC

values, adjusted-R^2 values, and root-mean-squared-error (RMSE) values to determine the best

model. The final model is shown as in equation 3.1. A natural cubic spline was applied to calendar

date to allow smooth modelling for long-term and seasonal patterns, with 7 *df* per year,

temperature (for current day) with 3 *df*, relative humidity (for current day) with 3 *df*, hour-of-day

and day-of-week.

$$Y_t \sim Poisson$$
$$\log E(Y)_{ti} = \alpha + \beta X_{ti} + ns(date, df = 7 \ per \ year) + ns(Temp_i, df = 3)$$
$$+ ns(RH_i, df = 3) + HOD_i + DOW_i$$

<div align="right">(3.1)</div>

Whereby $E(Y)_{ti}$ denotes expected number of EAD at hour t at day i;

α is intercept;

X_{ti}: SPM concentration at hour t of day i;

$date$: Natural cubic spline function applied for calendar time (*7 df* per year);

$Temp_i$: Natural cubic spline function applied for current day temperature (*3 df*);

RH_i: Natural cubic spline function applied for current day relative humidity (*3 df*);

HOD_i: Indicator variable for hour of day during day i;

DOW_i: Indicator variable for day of week at day i.

In the second stage, a random effects meta-analysis was performed to pool the city-

specific effect estimates. An I^2 statistic was used to examine the amount of heterogeneity, while

applying the *Chi-square* test from *Cochran's Q* statistic to test the significance of heterogeneity.

Lagged effect of ambient SPM was examined using 2 lag structures. First, an

unconstrained-distributed lag structure, with an extension for 24 hours. Second, average lag

structure (average lag 0-1 to lag 0-5, and then every 6 hours which follows).

All analyses were performed using R (version 3.4.3, The R Foundation for Statistical Computing, Vienna, Austria) and the packages *splines* and *metafor* (Viechtbauer, 2010). All results were presented as percent change of EAD with 95% confidence interval (95% CI) per 10 $\mu g/m^3$ increase in ambient SPM. Statistical significance was considered when the *p*-value was less than 0.05.

- *Ethical review*

This study was approved by the Ethics Committee of the Kyoto University Graduate School of Engineering (No. 201410).

Results

There were 3,639,881 cases of EAD for acute illnesses in the 46 cities of Japan during the study period. This accounted for about 10% of total population for all cities included in this study. Table 3.1 shows information on all-cause EAD for each city included in this study. The information on population was based on the Japan population census 2015. Japan population

census is updated every 5 years. In general, incidence rate were ranged around 2,000 to 3,000

EAD per 100,000 person-year. The maximum was observed in Osaka (around 4,000 EAD per

100,000 person-year). In general, hourly mean SPM concentration ranged around 20 µg/m^3. Table

3.2 shows information on environmental variables. The lowest hourly mean SPM concentration

was observed in Sapporo city (11.65 µg/m^3) while the highest was in Kumamoto city (25.17

µg/m^3). Hourly mean temperature ranged from 9.6 □ (Sapporo) to 23.2 □ (Naha), while relative

humidity ranged around 60-70% in overall.

Hourly distribution of ambient SPM and EAD for Osaka city are shown (as example) in

Figure 3.1. The distribution of ambient SPM in Osaka city showed a weak wavy pattern over the

24 hours, but the variation was not clear. In contrast, the distribution of EAD showed clear

variation over the 24 hours. The EAD was low during the midnight and increased to peak at

around 9 a.m. before returning to a rather plateau state after that. Some cities showed varying

pattern of ambient SPM, but the pattern for EAD was consistent over all cities (Figure A1).

Table 3.1. Information on all-cause EAD for each city included in this study during 2012-2015.

City	Population [a]	Total number of EAD during study period	Incidence rate (per 100,000 person-year)	Hourly mean number of EAD (SD)
Sapporo	1,952,356	193,305	2475	6 (3)
Aomori	287,648	11,398	1981	1 (1)
Morioka	297,631	35,968	3021	2 (1)
Sendai	1,082,159	99,518	2299	3 (2)
Akita	315,814	29,131	2306	2 (1)
Yamagata	253,832	25,058	2468	1 (1)
Fukushima	294,247	21,227	2405	2 (1)
Mito	270,783	27,051	2497	1 (1)
Tochigi	159,211	13,179	2069	1 (0)
Maebashi	336,154	33,863	2518	2 (1)
Saitama	1,263,979	135,821	2686	4 (2)
Chiba	971,882	112,334	2890	3 (2)
Yokohama	3,724,844	397,922	2671	11 (5)
Niigata	810,157	78,526	2423	3 (2)
Toyama	418,686	39,725	2372	2 (1)
Kanazawa	465,699	38,097	2045	2 (1)
Fukui	265,904	20,505	1928	1 (1)
Kofu	318,140	33,062	2598	2 (1)
Nagano	377,598	44,894	2972	2 (1)
Gifu	406,735	44,722	2749	2 (1)
Shizuoka	704,989	60,221	2847	3 (2)
Nagoya	2,295,638	275,625	3002	8 (4)
Tsu	279,886	31,437	2808	2 (1)
Otsu	340,973	38,495	2822	2 (1)
Kyoto	1,475,183	190,488	3228	6 (3)
Osaka	2,691,185	474,288	4406	14 (5)
Kobe	1,537,272	169,307	2753	5 (3)
Nara	360,310	39,106	2713	2 (1)
Wakayama	364,154	45,254	3107	2 (1)
Tottori	193,717	22,783	2940	1 (1)
Matsue	206,230	18,986	2302	1 (1)
Okayama	719,474	69,610	2419	2 (1)

… (table continued).

City	Population [a]	Total number of EAD during study period	Incidence rate (per 100,000 person-year)	Hourly mean number of EAD (SD)
Hiroshima	1,194,034	115,223	2412	3 (2)
Yamaguchi	197,422	17,277	2188	1 (1)
Tokushima	258,554	24,023	2323	1 (1)
Takamatsu	420,748	47,521	2824	2 (1)
Matsuyama	514,865	54,032	2624	2 (1)
Kochi	337,190	35,733	2649	2 (1)
Fukuoka	1,538,681	157,456	2558	5 (2)
Saga	236,372	29,381	3107	2 (1)
Nagasaki	429,508	49,599	2887	2 (1)
Kumamoto	740,822	74,905	2528	2 (1)
Oita	478,146	37,178	1944	2 (1)
Miyasaki	401,138	31,162	1942	2 (1)
Kagoshima	599,814	57,276	2387	2 (1)
Naha	319,435	38,209	2990	2 (1)

Note: Population [a] is total population in the city based on Japan population census 2015. EAD indicates emergency ambulance dispatch. SD indicates standard deviation.

$$\text{Incidence rate} = \frac{Total\ EAD}{Population^a \times Number\ of\ years} \times 1000 \text{ person-year}$$

Table 3.2. Information on environmental variables for each city included in this study during 2012-2015.

City	Hourly mean (SD) SPM (μg/m³)	Hourly mean (SD) temperature (℃)	Hourly mean (SD) relative humidity (%)
Sapporo	11.65 (8.48)	9.6 (10.1)	68.7 (15.5)
Aomori	17.67 (10.45)	12.4 (9.8)	76.2 (14.2)
Morioka	14.65 (10.33)	11.1 (10.3)	73.3 (17.8)
Sendai	16.38 (9.94)	13.1 (9.0)	70.1 (17.7)
Akita	15.46 (10.57)	12.4 (9.8)	71.5 (15.8)
Yamagata	16.32 (11.18)	12.3 (10.4)	71.3 (18.1)
Fukushima	16.80 (9.71)	13.9 (9.8)	67.9 (18.5)
Mito	20.32 (12.68)	14.6 (9.0)	71.1 (19.8)
Tochigi	19.41 (12.89)	14.8 (9.4)	64.4 (20.5)
Maebashi	17.73 (14.50)	15.6 (9.4)	59.1 (19.3)
Saitama	20.77 (13.51)	15.6 (9.2)	63.0 (21.5)
Chiba	19.28 (13.25)	16.5 (8.2)	64.9 (19.4)
Yokohama	23.82 (13.40)	16.3 (8.2)	67.0 (19.6)
Niigata	18.43 (10.13)	14.1 (9.3)	71.8 (14.8)
Toyama	15.41 (11.94)	14.7 (9.6)	72.6 (17.6)
Kanazawa	16.33 (12.09)	15.2 (9.3)	69.6 (15.5)
Fukui	18.64 (12.98)	15.1 (9.7)	72.9 (17.9)
Kofu	19.17 (12.98)	15.4 (9.7)	60.4 (21.1)
Nagano	15.53 (10.67)	12.6 (10.3)	70.9 (17.7)
Gifu	14.67 (11.86)	16.4 (9.3)	64.3 (18.6)
Shizuoka	19.98 (13.01)	17.1 (7.9)	66.2 (18.8)
Nagoya	20.95 (12.78)	16.2 (9.1)	65.4 (18.4)
Tsu	22.58 (13.08)	16.5 (8.8)	66.7 (16.5)
Otsu	19.14 (11.86)	15.6 (9.1)	71.7 (14.2)
Kyoto	16.24 (11.59)	16.2 (9.3)	65.4 (16.4)
Osaka	22.25 (13.74)	16.9 (8.8)	63.7 (16.1)
Kobe	18.65 (12.85)	17.0 (8.5)	63.4 (14.3)
Nara	17.73 (10.92)	15.5 (9.2)	71.7 (18.3)
Wakayama	21.98 (12.71)	17.0 (8.6)	65.3 (15.7)
Tottori	16.01 (14.94)	15.5 (9.4)	71.5 (17.1)
Matsue	16.60 (11.55)	15.5 (8.9)	74.8 (16.1)
Okayama	22.33 (14.45)	16.4 (9.1)	65.5 (17.3)

… (table continued).

City	Hourly mean (SD) SPM (µg/m³)	Hourly mean (SD) temperature (℃)	Hourly mean (SD) relative humidity (%)
Hiroshima	24.44 (13.05)	16.5 (8.9)	66.3 (16.3)
Yamaguchi	15.69 (12.15)	16.0 (9.2)	71.7 (18.1)
Tokushima	20.12 (14.54)	16.8 (8.5)	66.9 (16.1)
Takamatsu	22.97 (15.64)	16.9 (8.9)	65.4 (16.9)
Matsuyama	22.75 (14.30)	16.8 (8.5)	67.2 (16.5)
Kochi	16.73 (12.70)	17.5 (8.3)	67.8 (19.4)
Fukuoka	22.43 (13.83)	17.3 (8.2)	68.4 (16.7)
Saga	19.70 (12.12)	17.0 (8.7)	69.7 (17.3)
Nagasaki	22.91 (13.23)	17.4 (8.0)	71.2 (15.7)
Kumamoto	25.17 (14.42)	17.1 (8.7)	70.2 (17.9)
Oita	18.91 (11.70)	16.8 (8.2)	68.5 (16.3)
Miyasaki	23.25 (11.68)	17.8 (8.0)	73.5 (18.1)
Kagoshima	24.99 (14.80)	18.8 (7.7)	71.5 (15.8)
Naha	17.58 (11.62)	23.2 (5.0)	72.7 (13.1)

Note: Values are shown as mean (standard deviation).
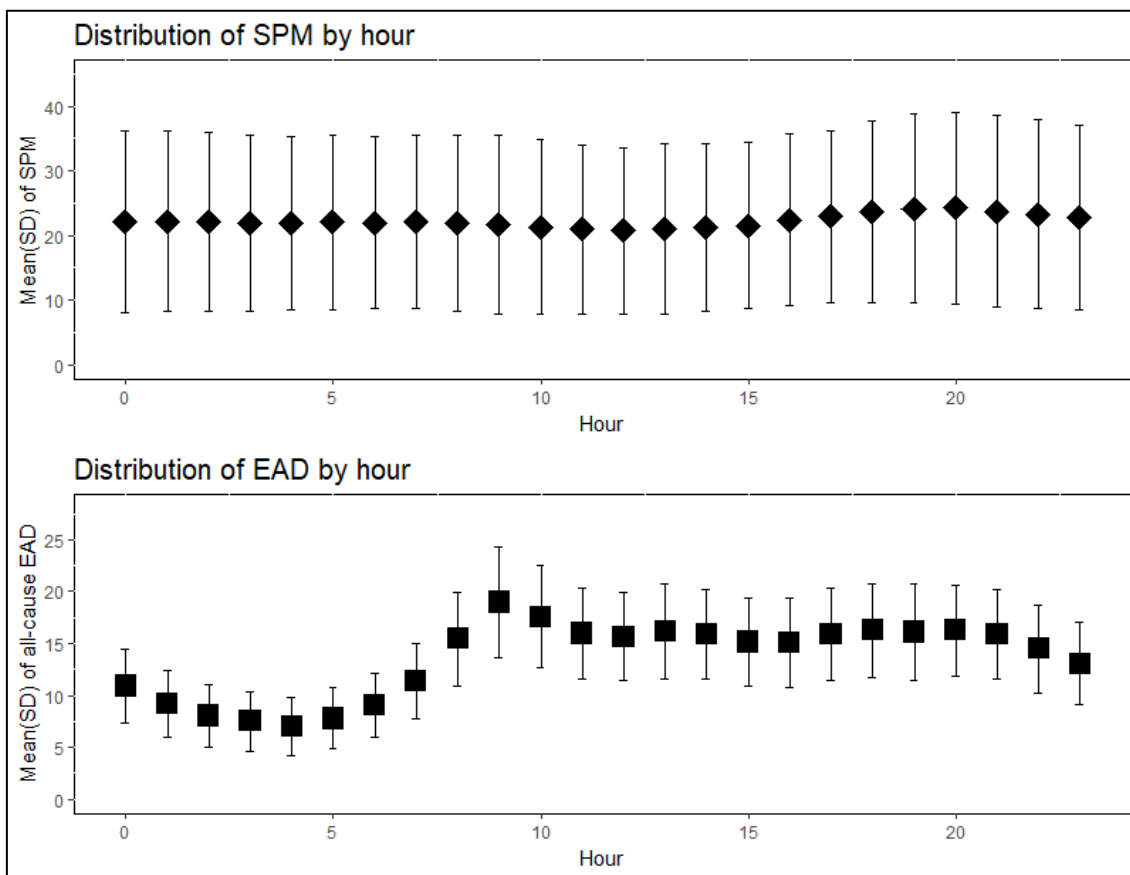
Figure 3.1. A typical pattern of the hourly distribution (mean ± standard deviation (SD)) of ambient SPM (top) and all-cause EAD (bottom).

Note: Figure shows distribution for Osaka city. Distribution for other cities are shown in Appendix A1.

Figure 3.2 shows the hourly lag pattern for all-cause EAD for each 10 μg/m³ increase in ambient SPM. Significant increment of all-cause EAD were observed on lag 0 [0.81 % (95% CI: 0.04, 1.58)] and on lag 14 [1.27 % (0.10, 2.43)]. A significant decrease was also observed on lag 13 [-1.28% (95% CI: -2.45, -0.11)]. In average lag model, the effect remained plateau (about 60 % increased EAD) over average lags of first 6 hours (Figure 3.3). A steady decline followed but remained significant until average lag 0-23 [0.35 % (95% CI: 0.04, 0.67)].
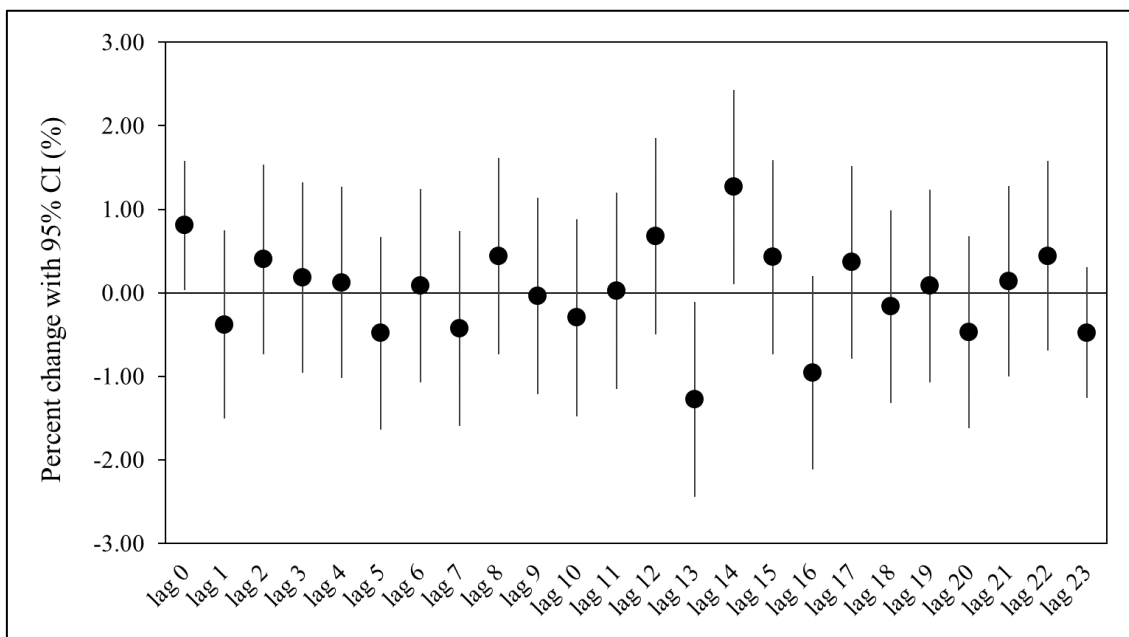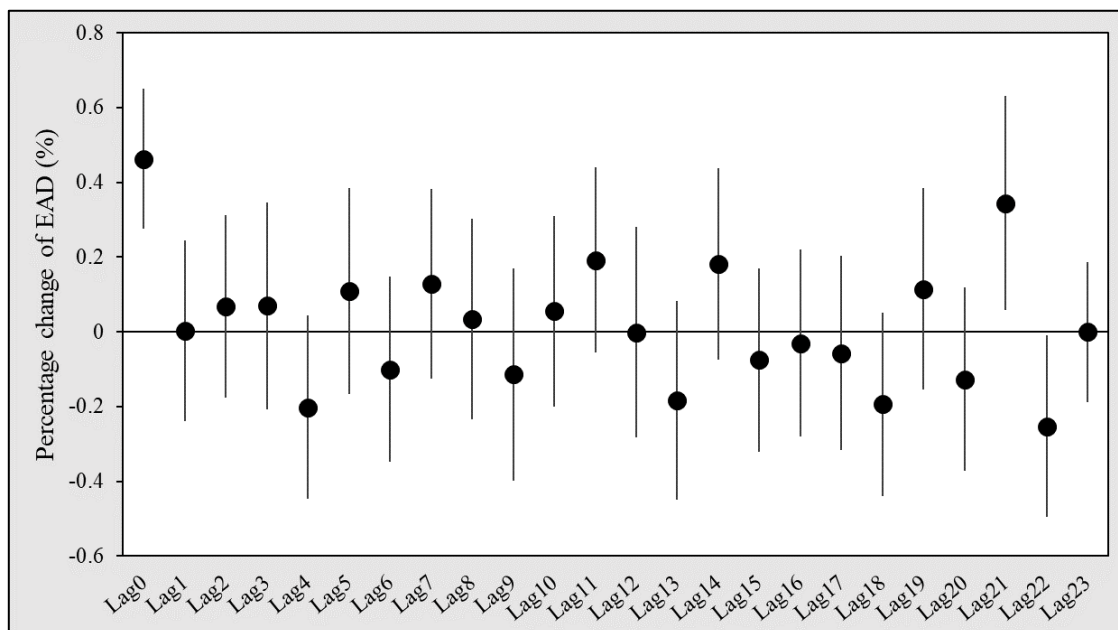
Figure 3.2. An example of the percent change of all-cause EAD associated with each 10 μg/m³ increase in ambient SPM (unconstrained distributed hour lag model) for a single city.

Note: The hourly lag pattern is shown for Osaka city. Lag patterns for other cities are shown in Appendix. Each lag is represented by lag-hour. Values were based on 95% confidence interval.
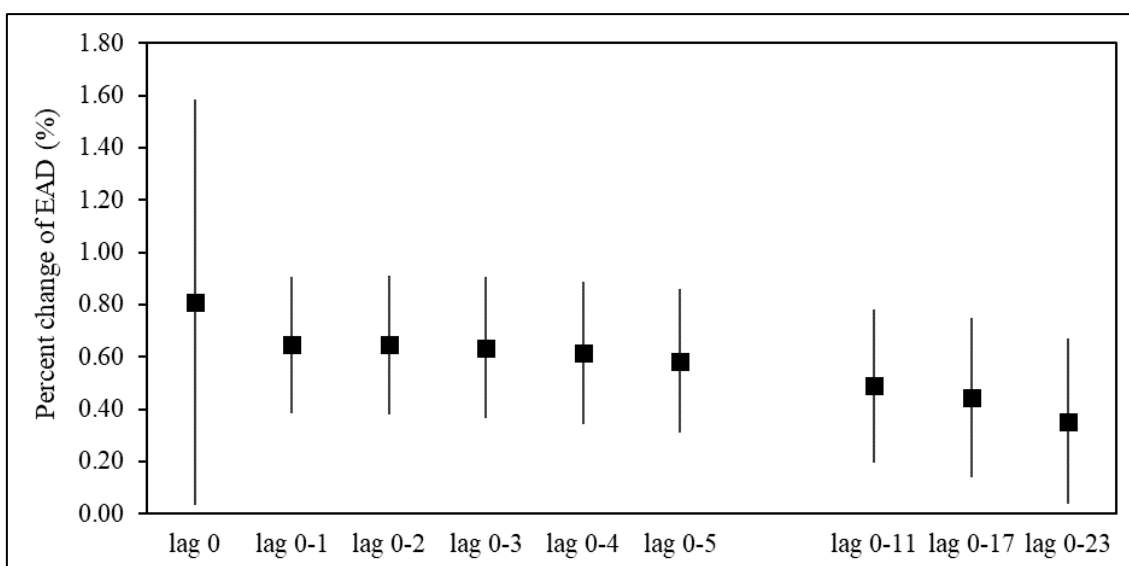
Figure 3.3. A typical pattern of the percent change of all-cause EAD associated with each 10 μg/m³ increase in ambient SPM (average hour lag model) for a single city.

Note: The hourly lag pattern is shown for Osaka city. Lag patterns for other cities are shown in Appendix. Each lag is represented by lag-hour. Values were based on 95% confidence interval. Lag 0 is extracted from the unconstrained distributed hour lag model.

After pooling the city-specific effect estimates, significant increased risk of EAD for each 10 µg/m^3 increase in ambient SPM were observed on lag 0 [0.46 % (95% CI: 0.27, 0.69)] and lag 21 [0.34 % (95% CI: 0.06, 0.63)]. Meanwhile, there was a marginal decrease on lag 22 [-0.25 % (95% CI: -0.50, -0.00)] (Figure 3.4). When examined for the average lag pattern, EAD were significantly increased over all average lags from lag 0-1 to lag 0-23 (Figure 3.5). The pattern of average lags followed that of Osaka city. Effects were similar over the first 6 hours (lag 0 to lag 0-5), remaining at about 0.55 % increased EAD. After the first 6 hours, a declining pattern was observed until lag 0-23. The lowest risk was observed at average lag 0-23 [0.39 % (95% CI: 0.29, 0.50)].

Figure 3.6 shows a forest plot of average lag 0-5. Most of the coefficients were located on the right of the plot, showing positive association. The pooled effect estimate was also significantly positive. Tests for heterogeneity showed that the effects were homogeneous over cities (Table 3.3). Amount of heterogeneity (I^2) were low, whereby the maximum was 23.62%. No significant heterogeneity was observed after examining by *Chi-squared* test of *Cochran's Q*.

Figure 3.4. Pooled percent change of all-cause EAD associated with each 10 µg/m³ increase in ambient SPM (unconstrained distributed hour lag model).

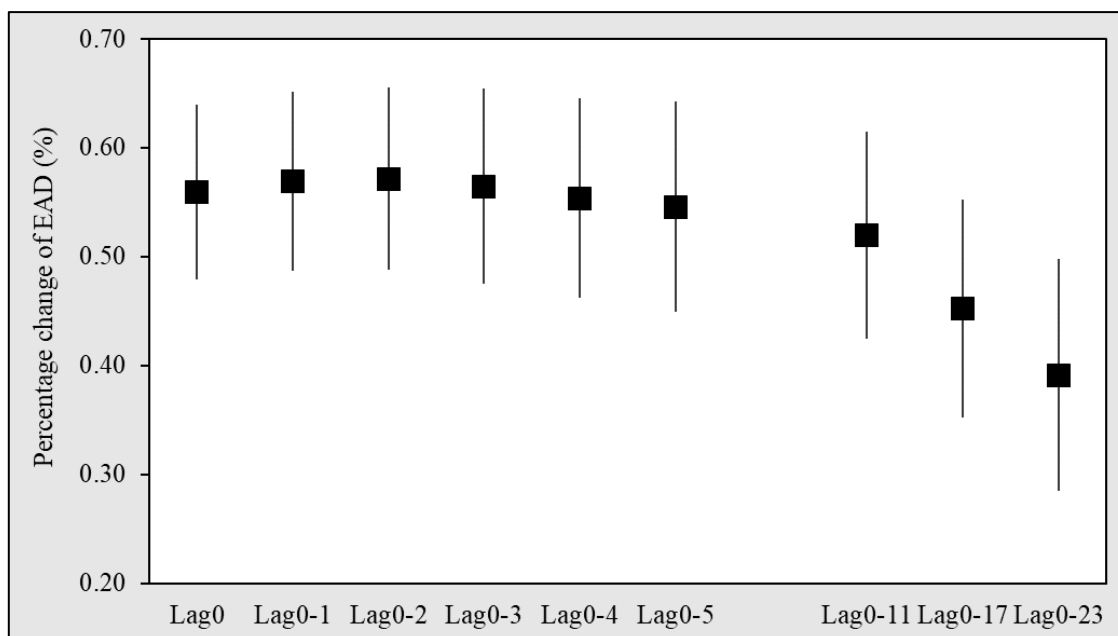Note: Each lag is represented by lag-hour. Values were based on 95% confidence interval.

Figure 3.5. Pooled percent change of all-cause EAD associated with each 10 µg/m³ increase in ambient SPM (average hour lag model).

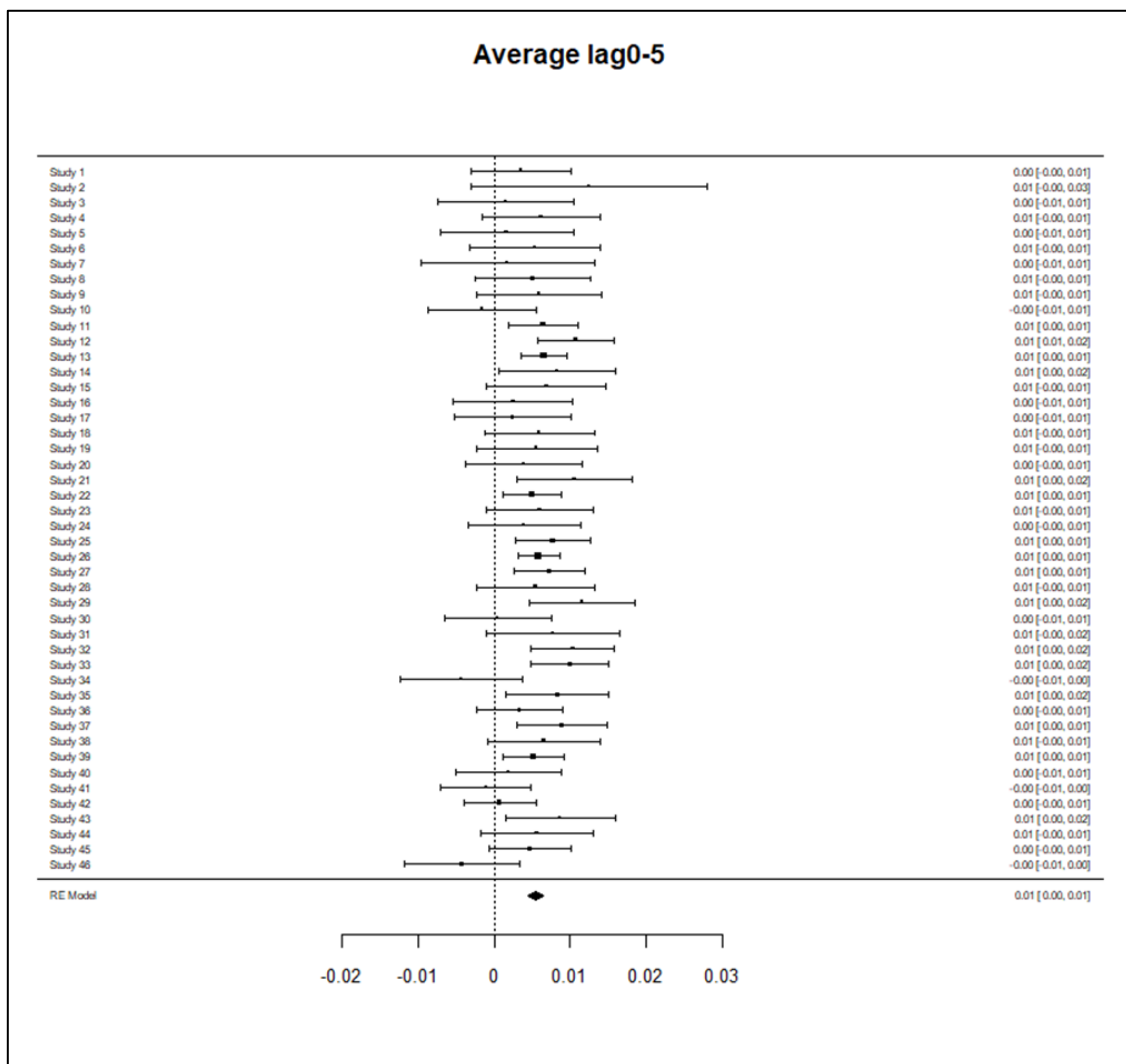Note: Each lag is represented by average lag-hour. Values were based on 95% confidence interval.

Figure 3.6. Forest plot of all-cause EAD for each 10 μg/m^3 increase in ambient SPM (average lag 0-5 hour).

Table 3.3. Hypothesis test for heterogeneity.

Lag	I^2 (%)	Cochran's Q test		Lag	I^2 (%)	Cochran's Q test	
		Q	p-value			Q	p-value
lag 0	0.00	33.52	0.90				
lag 1	0.00	30.40	0.95	lag 0-1	0.00	45.15	0.47
lag 2	0.00	37.57	0.78	lag 0-2	0.00	46.39	0.41
lag 3	19.05	52.60	0.20	lag 0-3	5.75	50.12	0.28
lag 4	0.00	33.12	0.91	lag 0-4	6.98	51.32	0.24
lag 5	17.92	54.73	0.15	lag 0-5	11.44	53.27	0.19
lag 6	1.06	50.68	0.26				
lag 7	4.90	48.84	0.32				
lag 8	13.27	51.33	0.24				
lag 9	21.46	58.44	0.09				
lag 10	5.51	47.37	0.38				
lag 11	1.34	42.94	0.56	lag 0-11	0.56	49.07	0.31
lag 12	20.01	60.28	0.06				
lag 13	12.49	50.72	0.26				
lag 14	6.40	47.53	0.37				
lag 15	0.00	32.02	0.93				
lag 16	3.04	43.56	0.53				
lag 17	9.22	46.74	0.40	lag 0-17	0.00	48.44	0.34
lag 18	0.81	45.18	0.46				
lag 19	15.12	47.93	0.35				
lag 20	0.00	37.87	0.77				
lag 21	23.62	59.35	0.07				
lag 22	0.00	30.75	0.95				
lag 23	0.00	32.04	0.93	lag 0-23	2.34	49.86	0.29

Note: Lags are shown as lag-hour. The left panel shows for unconstrained distributed hour lags while right panel shows for average lags.

Discussion

In this study, it was observed that ambient SPM increased EAD at very short lags. The highest risks were included within the first 6 hours from point of exposure, before declining until the average lag up to the 24th hour.

Hourly distribution of SPM showed weak variation but there was clear variation in EAD through hours of a day. The EAD was low during the midnight but peaked at around 9 a.m. The EAD distributions, instead, showed strong consistency of similar pattern over all the cities. This might be due to management system of EAD or behavioral pattern of the population. In Japan, EAD service is free-of-charge. The public could utilize the system at any time by calling the emergency number 119. However, reception of emergency cases in hospitals is often limited because not all hospitals will accept emergency cases. This is often due to limited available doctor or facilities of the hospital that could handle the emergency case. The person-in-charge of each EAD can either send the patient to the hospital they regularly visit, or to a hospital available for reception (after confirming it with the hospital). Thus, there might be a tendency that the patients have been visiting the hospitals regularly or during some time not long before the EAD. Another reason might be due to possible tendency of the people to wait until the morning before calling for EAD. This could happen if their condition was not too severe. This effect was adjusted in the

model by including hours of the day as indicator variables.

From unconstrained distributed lag model, the highest and significant increased EAD was at lag 0 [0.46 % (95% CI: 0.27, 0.65)]. There was no harvesting effect observed. When the average lag was examined, a plateau pattern was observed for first 6 hours followed by continuous decline until 24 hours. A few studies had investigated hourly lag pattern of ambient air pollutants (Sullivan *et al.*, 2005; Murakami and Ono, 2006; Ono, Omori and Nitta, 2007; Lanki *et al.*, 2008; Bhaskaran *et al.*, 2011; Yamazaki *et al.*, 2011; Yorifuji, Suzuki and Kashima, 2014; Peters *et al.*, 2015). Most of these studies demonstrated similar result to the present study, whereby significant effects were observed at first few hours' lags. However, most studies investigated the pollutant effects on cardiovascular outcomes including hospital admissions (Bhaskaran *et al.*, 2011), emergency room visit (Yorifuji, Suzuki and Kashima, 2014) and mortality (Murakami and Ono, 2006); cerebrovascular outcomes (Yorifuji, Suzuki and Kashima, 2014); and respiratory outcomes (Yamazaki *et al.*, 2011). Findings from the present study showed lower effect estimates than studies in Japan for SPM effects. Yorifuji et al. (2011) reported about 0.5% (95% CI: 0.1, 0.6)] increase of emergency room visit at lag 0-6 hours for cardiovascular and cerebrovascular outcomes (Yorifuji *et al.*, 2011). On the other hand, another study reported 13%, 17%-24%, and 40% increased risk of myocardial infarction mortality in each of the low, intermediate, and high categories of SPM respectively, compared to the reference category (SPM concentration less than

100 µg/m^3) (Murakami and Ono, 2006). The acute effects of ambient SPM as shown in this study may include some pathological responses such as pulmonary and systemic inflammatory responses, oxidative stress and autonomic nervous system imbalance (Brook *et al.*, 2010).

A significant increase of EAD was observed on lag 14 hour for Osaka city, but after pooling the effect estimates for all cities, the significance was not observed on lag 14 hour but on lag 21 hour. I think that this pattern may be due to the typical lag pattern. In typical lag pattern, we can see at beginning of lag a significant increase in risk, followed by a decrease (the so-called harvesting effect) and a second increase in risk before the rest of the lags remain at null.

Besides short lags from exposure to onset of disease, another explanation for the higher risks observed during the first few hours might be due to behavioral factor. The EAD service can be considered as a "convenient" tool for the public to visit the hospital. Firstly, it is free-of-charge. The patient does not need to pay for their transportation fee or service fee. Secondly, the patient does not need find for available hospital. Person-in-charge of the EAD usually checks with the hospital for reception of the case prior sending the patient. For the convenience, patient might call for EAD at convenient time (for example, in the morning). In addition, because midnight is sleeping time for most people, some people might be calling for EAD service only after they wake up, with hope that they could have felt better. These behaviors would lead to some lags from the

time when they felt sick.

The findings from this study suggests a review on the current standards for ambient SPM. At current, the Environmental Quality Standards (for air quality) in Japan is 100 $\mu g/m^3$ (daily 24-hour average) and shall not exceed 200 $\mu g/m^3$ for hourly values. In a previous study, a 10 $\mu g/m^3$ increase in SPM was associated with increased myocardial infarction during the first 6 hours lag (Bhaskaran *et al.*, 2009). The median SPM concentration was observed around 20 (±10) $\mu g/m^3$. While in another study observing hourly mean of 26 (±18) $\mu g/m^3$, a 20 $\mu g/m^3$ increase in SPM was associated with cardiovascular and cerebrovascular hospital visits (Yorifuji, Suzuki and Kashima, 2014). It was reported that 1.13 to 1.40 times higher risk of myocardial infarction deaths when SPM exceeded 100 $\mu g/m^3$ compared to when SPM concentration was less than 100 $\mu g/m^3$, for both 1 hour and 6 hours lags (Murakami and Ono, 2006). I think that the Environmental Quality Standards (for air quality) in Japan shall be revised for the hourly concentration. From this study, a 10 $\mu g/m^3$ increase of ambient SPM increases risk of EAD by about 0.5 %, with a general hourly mean of SPM at about 20 (±10) $\mu g/m^3$ over the cities. This is equivalent to an increase of 18,199 EAD (0.5% of total EAD (3,639,881 cases) in this study). An ambulance dispatch in Japan costs the local authority by about 40,000 Japanese Yen (JPY). That would cost an approximate of 181 million JPY per year. Table 3.4 shows a few suggestions to be considered in future revision on the Environmental Quality Standards (for air quality) in Japan. The

plausibility of the new standard shall be considered carefully prior to implementation.

Table 3.4. Suggested concentrations of ambient SPM for future consideration in the Environmental Quality Standards (for air quality) in Japan.

Standard	Hourly ambient SPM concentration ($\mu g/m^3$)	Basis for the selected level
Suggestion 1	20	Lowest hourly mean concentration observed from this study.
Suggestion 2	50	About 1.5% increase in EAD over Suggestion 1.
Suggestion 3	100	About 4% increase in EAD over Suggestion 1.
Suggestion 4	120	About 5% increase in EAD over Suggestion 1.
Current standard	200	About 9% increase in EAD over Suggestion 1.

- *Strengths*

This study has several strengths. First, the use of hourly terms for both exposure and outcome variables allows clarification on hourly lag pattern for EAD associated with ambient SPM. Availability of such data is a great advantage as evidence on hourly variation in air pollution and health studies is scarce. Most of current literatures were limited due to availability of data. This study added to the literature on the evidence that effects of ambient SPM were higher at the first few hours' lags, and then decline at later lags of the day. Next, this study included 46 cities covering all 46 prefectures of Japan, and the study period were 2012 to 2015 which is quite recent.

This is an additional strength to ***Study I***. Although the slope of the risk may not be significantly altered, the use of more recent data could be more convincing as it might include some information which were related with current situation. Moreover, the use of EAD as health indicator was probably more representative as it included acute health outcomes, which might be different to those of hospitalization or mortality.

- *Limitations*

However, there were some limitations for this study. First, exposure misclassification might occur as air pollution data were obtained from background monitoring stations. The actual personal exposure might vary due to individual behavior and activities. Second, the Tokyo Metropolis was not included in this study. This was due to unavailability of data because the Metropolis has a separate management system of EAD. Third, there might be some unknown delay from the actual time of onset as hour of EAD were extracted using "time of call for EAD".

Conclusion

Ambient SPM increased all-cause EAD at very short lags. The highest risks were observed from average lag 0-1 to lag 0-6, with a plateau pattern. Although the effects declined at following lags, significant effects remained even at the lowest risk at average lag 0-23.

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CHAPTER 4: *Study III (Investigating health effects of haze on children under 5*

years using a simple and comprehensive tool)

In **Study I** and **Study II**, I examined the health effects of ambient PM using both daily

and hourly terms. The conventional use of daily pollutant exposure on daily health outcomes have

been reporting similar findings – short-term exposure to ambient air pollutant is associated with

adverse health outcomes at short lags. **Study II** further demonstrated that within the current day,

the highest risk of ambient PM was at the first 6 hours lags.

In this chapter, I moved on to examining the health effects of haze on children of age

under 5 years (U5Y) in Malaysia by defining "haze days" using definitions considering *duration*

and *intensity*. Aside from the two-dimensional haze matrix, I also examined the lag pattern of

each haze definition following 7 days (Figure 1.3). This study adds to the literature on

demonstrating health effects of haze using a simple matrix which accounts for duration of

exposure, intensity of exposure (concentration) and lagged pattern.

There were higher odds of U5Y mortality due to haze in some state-specific estimates.

However, the pooled effects did not show significant risk. Increasing pattern was observed for 3

conditions: (1) horizontal increasing with *duration* along *level 1*, or (2) vertical increasing with

level along *duration 1*, and (3) diagonal increase of both *definition* and *intensity* concurrently. Lag

pattern was not clear; though there were patterns of higher odds fluctuating in first few lag days,

the effects were not statistically significant.

Method

- *Study settings*

This study included all 13 states [Johor, Melaka, Negeri Sembilan (N.Sembilan),

Terengganu, Pahang, Kelantan, Pulau Pinang (P.Pinang), Perak, Kedah, Perlis, Selangor, Sabah

and Sarawak) and 3 Federal Territories (Wilayah Persekutuan (WP) Kuala Lumpur (KL), WP

Putrajaya (Putrajaya) and WP Labuan (Labuan)) in Malaysia (Figure 4.1). The Federal Territories

will be hereafter referred to as "state". Malaysia, in general, consists of Peninsular Malaysia

(Johor, Melaka, N.Sembilan, Terengganu, Pahang, P.Pinang, Perak, Kedah, Perlis, Selangor, KL

and Putrajaya) and Borneo (Sarawak, Sabah, Labuan) Malaysia, separated by the South China

Sea. This study included U5Y mortality data from all states for year 2014.

Figure 4.1. Map of Malaysia and location of background monitoring stations in each state.
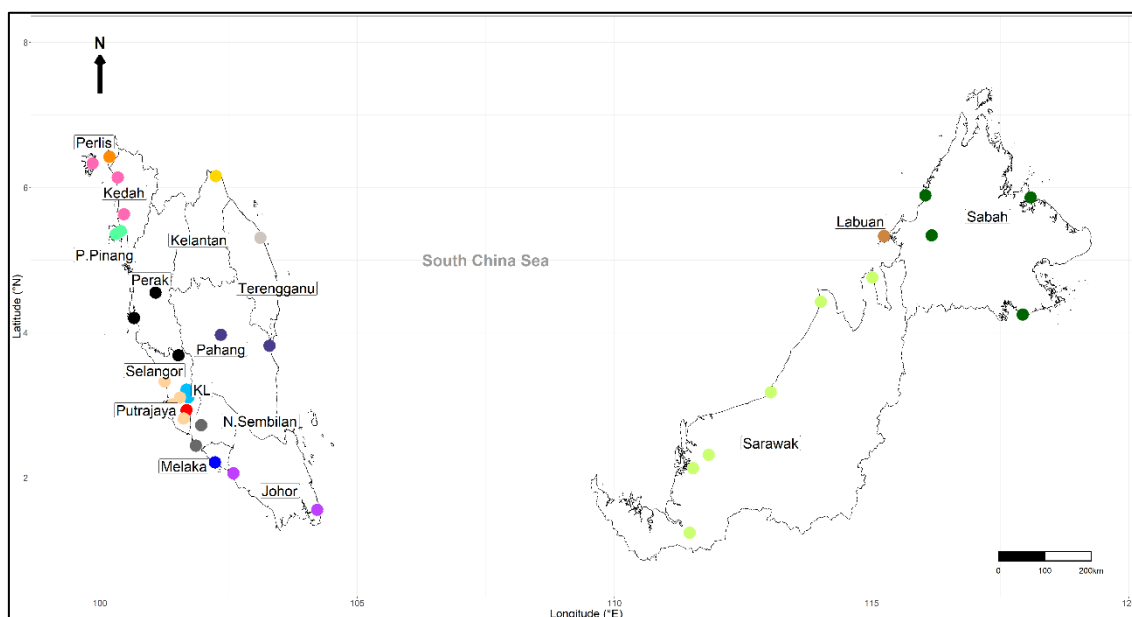
- *Health data*

The main health outcome being investigated in this study was mortality in children of age under 5 years. Secondary data spanning the study period were obtained from the Family Health Division of the Ministry of Health Malaysia. Data for all-cause (natural) mortality were included, except for mortality due to injury and traumatic cases. Data of non-citizen mothers were excluded, to avoid additional unknown factors which might affect the association being investigated. For example, there might be different immunization policies or cultural differences in other countries.

- *Environmental data*

Environmental data were obtained from the Department of Environment Malaysia. The data included ambient PM_{10}, temperature and relative humidity. Data from all background monitoring stations for each state were averaged to obtain daily mean values. Data for days with 4 or more missing hourly values were regarded as missing data. Locations of background monitoring stations for each state were shown in Figure 4.1.

Haze was defined using 3 definitions. Prior to defining haze events, a baseline concentration was determined over entire study period. A day was regarded as "haze day" when the ambient PM_{10} concentration exceeds the baseline concentration. "*Level 1*", "*Level 2*" and "*Level 3*" refers to baseline concentration defined at daily mean PM_{10} concentration exceeding 50 $\mu g/m^3$, 75 $\mu g/m^3$ and 100 $\mu g/m^3$, respectively. For each "*level*", 3 *durations* were determined. "*Duration 1*" refers to days with only 1 day whereby PM_{10} concentration exceeding the concentration of each "definition"; "*Duration 2*" refers to that with 2 consecutive days while "*Duration 3*" refers to that with 3 consecutive days. Considering these criteria, Table 4.1 shows how "haze day" was defined for this study. The baseline concentrations were determined based on ambient air quality standard for daily (24-hour average) PM_{10} [(1) WHO guideline (50 $\mu g/m^3$), and (2) New Malaysia Ambient Air Quality Standard to be implemented in year 2020 (100

$\mu g/m^3$)] and (3) an arbitrary baseline concentration in between the two standards (75 $\mu g/m^3$).

Table 4.1. An example of how haze definition is determined in this study.

Level	Baseline concentration ($\mu g/m^3$)			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
		Concentration of PM$_{10}$ on current day ($\mu g/m^3$):		103.0	78.0	35.0	98.0	88.0	105.0	113.0	65.0
		Duration	**Exceeds baseline**	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
1	50	1		1	1	0	1	1	1	1	0
		2		0	1	0	0	1	1	1	0
		3		0	0	0	0	0	1	1	0
		Duration	**Exceeds baseline**	Yes	Yes	No	Yes	Yes	Yes	Yes	No
2	75	1		1	1	0	1	1	1	1	0
		2		0	1	0	0	1	1	1	0
		3		0	0	0	0	0	1	1	0
		Duration	**Exceeds baseline**	Yes	No	No	No	No	Yes	Yes	No
3	100	1		1	1	0	1	1	1	1	0
		2		0	1	0	0	1	1	1	0
		3		0	0	0	0	0	1	1	0

Note: From left, *Level* refers to level of intensity. *Level 1* represents condition when PM$_{10}$ concentration exceeds 50 $\mu g/m^3$. *Level 2* represents condition when PM$_{10}$ concentration exceeds 75 $\mu g/m^3$. *Level 3* represents condition when PM$_{10}$ concentration exceeds 100 $\mu g/m^3$. The condition is shown by "yes" or "no" indicator whether the current day's PM$_{10}$ concentration (shown on upper row in table) exceeds the baseline concentration. Indication of "1" representing *haze day (for respective duration and level)* if condition is fulfilled, "0" if otherwise. Colors represent a few examples of indicating the current day as "haze day".

Examples: *blue box* – PM$_{10}$ concentration exceeds baseline concentration for 1 day; *orange box* – exceeds baseline concentration for 2 consecutive days; *green box* – exceeds baseline concentration for 3 consecutive days.

- *Statistical analyses*

A conditional logistic model (equation 4.1) was applied as a case-crossover analysis to estimate odds ratios (ORs) with 95% confidence intervals (95% CI), describing the association between haze events (of different duration and intensity) and the risk of U5Y mortality. All models were adjusted for temperature and relative humidity.

$$\text{clogit}(Y_{hi}) = \alpha + \beta X_{hi} + Temp_{hi} + RH_{hi}$$

(4.1)

Whereby Y_{hi}: U5Y mortality on day h in stratum i;

                α: intercept;

                X: Indicator for exposure (haze or non-haze);

                $Temp$: Temperature;

                RH: Relative humidity;

The case-crossover approach allows adjustment for long-term trends and seasonality by design. Each subject serves as its own control by assessing referent exposure at other point in time. The referent period represents the counterfactual exposure experience of the individual. In this study, day-of-week within a stratum of 28 days were matched as controls for each U5Y mortality on haze day (case). The effect estimates were examined for each haze definition as described in Table 4.1.

The model was first applied for each state in Malaysia. Random-effects meta-analysis was then used to pool the state-specific estimates. Heterogeneity was examined using I^2 value and

its significance using *Chi-square test* in *Cochran's Q* statistic. Then, lag pattern was examined for

lag 7 days.

All statistical analyses were performed using R (version 3.4.3, The R Foundation for

Statistical Computing, Vienna, Austria). R packages used in this study include *survival* (Therneau,

2015) and *metafor* (Viechtbauer, 2010).

- *Ethical review*

This study was reviewed and approved by the Medical Research & Ethics Committee

of Ministry of Health Malaysia [Ethics initial approval: NMRR-18-2945-42784 (IIR)].

Results

There were total of 3,487 all-cause mortality among children of age under 5 years (U5Y

mortality) in Malaysia (Table 4.2). The total incidence rate was 14 cases of U5Y mortality per

10,000 person-year among U5Y children. By state, incidence rate ranged from 5 to 19 cases of

U5Y mortality per 10,000 person-year among U5Y children.

Figure 4.2 shows daily trend ambient PM_{10} during study period. In general, ambient

PM_{10} in Malaysia exceeded WHO guideline of 50 µg/m³ during most of the time. Several peaks especially in March, and several peaks over June to October exceeding the current Malaysia air quality standard (120 µg/m³) were observed.

Table 4.2. Information of population and incidence of mortality for children of age under 5 years in each state of Malaysia in 2014.

State	Total population[a] ('000)	Population[b] ('000)	Percentage of population[b] (%)	Total mortality[c]	Incidence rate[c] (per 10,000 person-year)
Perlis	245.1	20.9	8.5	13	6
Kedah	2062.7	181.2	8.8	273	15
P.Pinang	1678.1	113.2	6.7	166	15
Perak	2458.8	177.9	7.2	287	16
Kelantan	1723.4	186.5	10.8	295	16
Terengganu	1140.4	124.2	10.9	160	13
Pahang	1591.7	139.6	8.8	239	17
Selangor	6051.3	518.1	8.6	692	13
KL	1737.4	125.7	7.2	180	14
Putrajaya	80.9	14.4	17.8	26	18
N.Sembilan	1079.6	85	7.9	152	18
Melaka	871.7	68.8	7.9	83	12
Johor	3559.8	289.6	8.1	395	14
Sarawak	2664	209.6	7.9	352	17
Sabah	3669.9	307.5	8.4	157	5
Labuan	93.8	9.1	9.7	17	19
Total	30708.6	2571.3	8.4	3487	14

Note: Information of population is based on Malaysia population census 2014. [a] represents total population in each state. [b] represents population of age < 5 years in each state. [c] represents mortality of children age < 5 years in this study. [d] is Incidence rate $= \frac{Total\ mortality\ (c)}{Population\ (b)\ \times\ Number\ of\ year} \times$ 10,000.
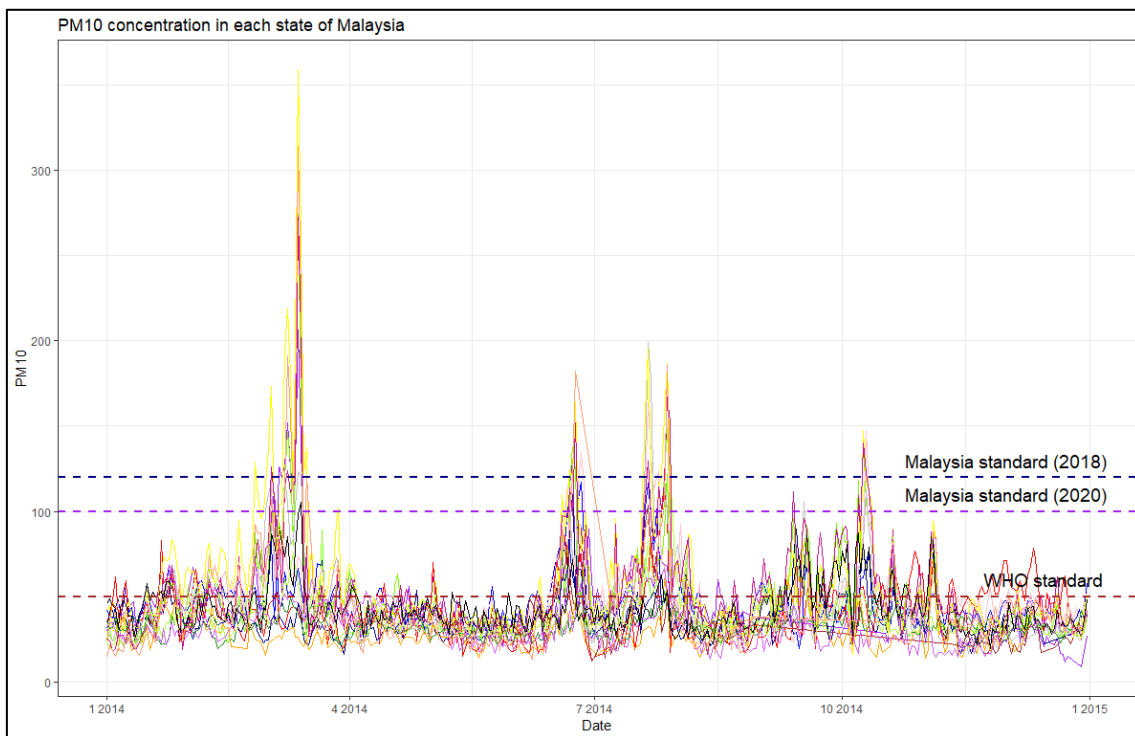
Figure 4.2. Concentration of PM$_{10}$ over time for all states in Malaysia in 2014.
Note: Standards shown with dotted lines for daily (24-hour mean). WHO standard (50 μg/m^3);
Malaysia standard (2018 – current) (120 μg/m^3); Malaysia standard (2020) (100 μg/m^3).

However, regional time-trends showed some different pattern (Figure 4.3). Some region which are least affected by the southwesterly monsoon wind, such as Terengganu and Sabah, showed lower and less dynamic pattern of ambient PM$_{10}$. On the other hand, regions located alongside the west coast of the Peninsular, including Kedah, P. Pinang, Perak, Selangor, KL, Putrajaya, N. Sembilan, Melaka and Johor, showed similar peaks. Sarawak, though located to the southwest of Sabah, showed similar trends to these states but with lower concentration.
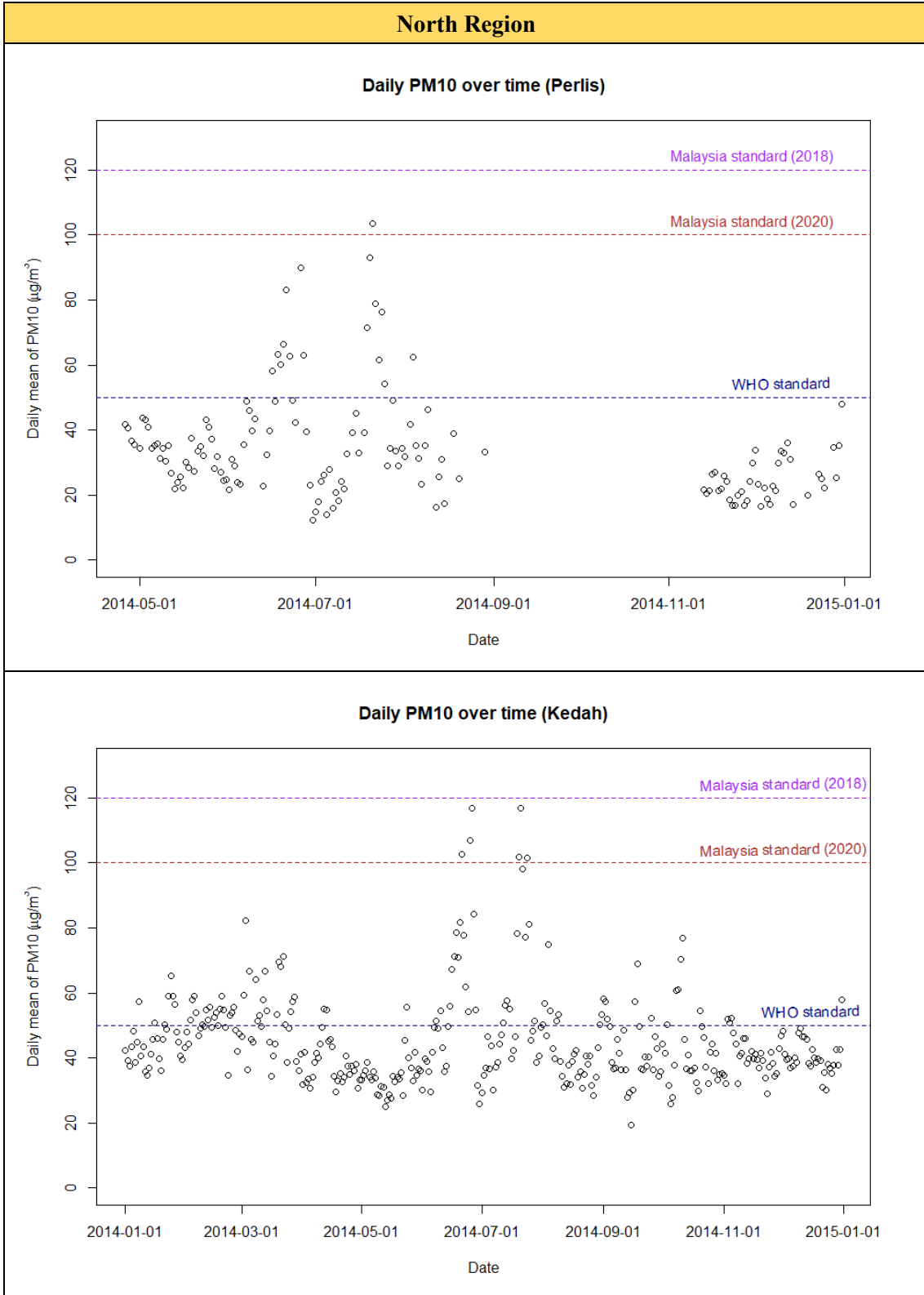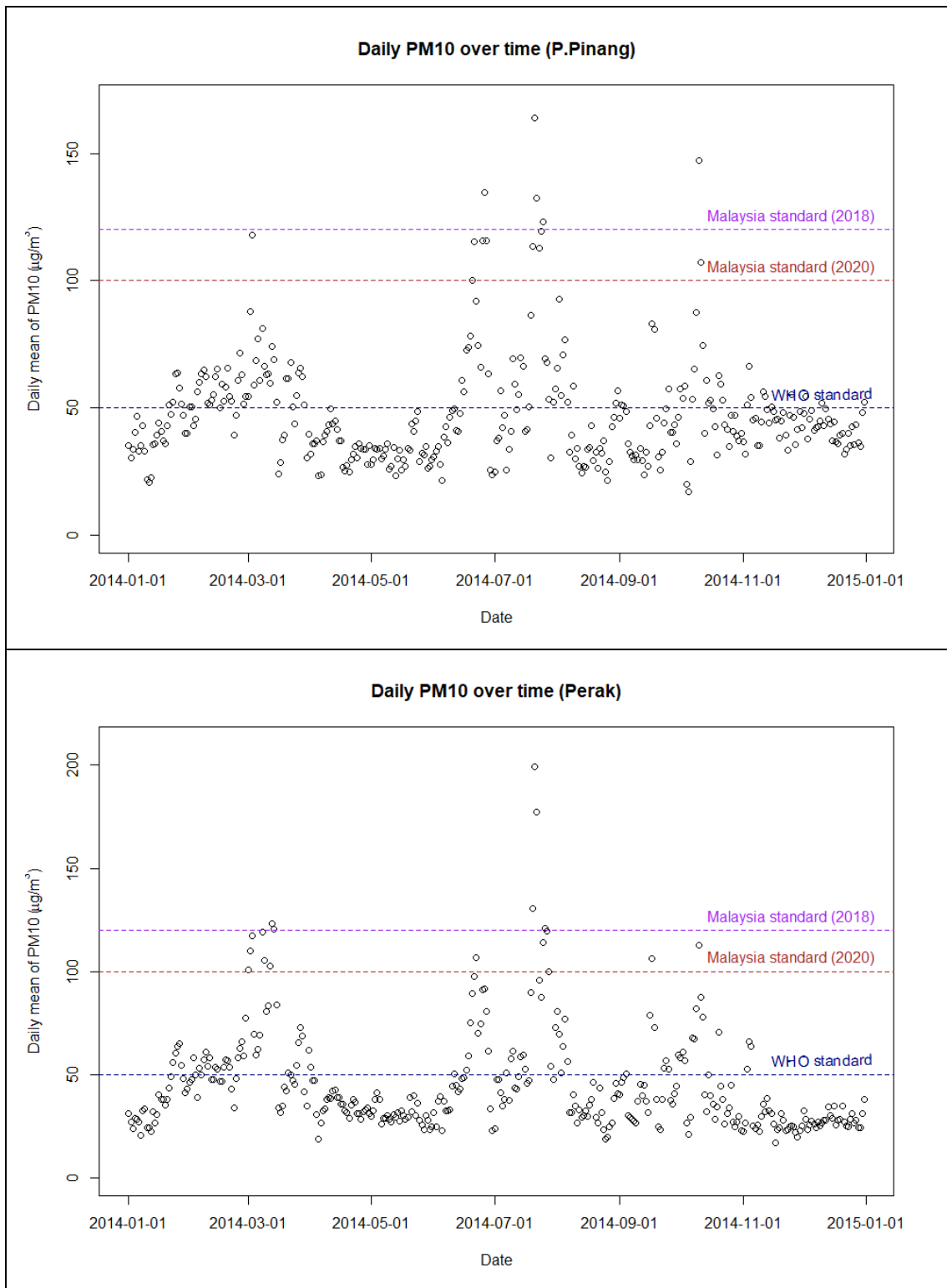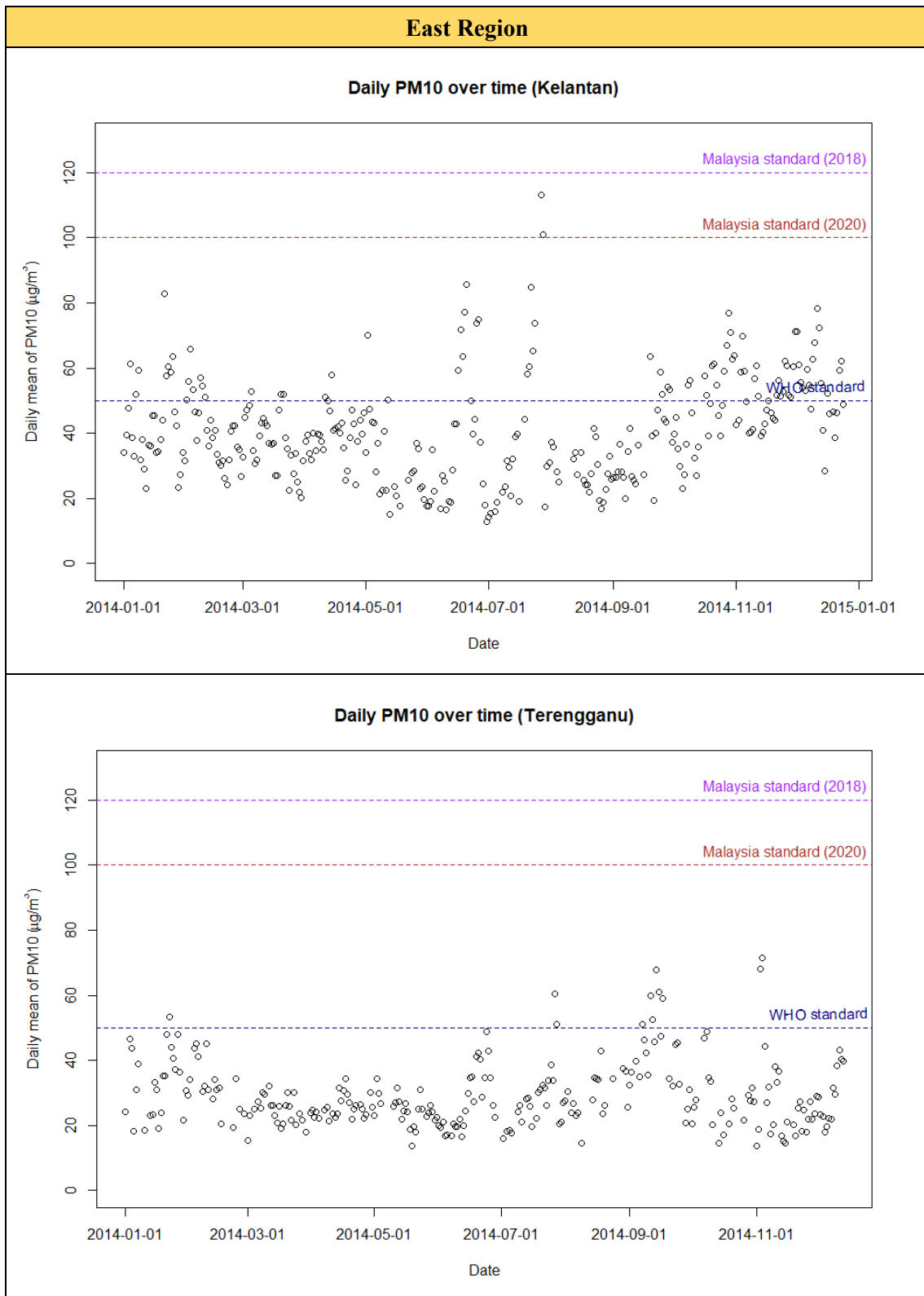
North Region

Daily PM10 over time (Perlis)

Daily PM10 over time (Kedah)

… (figure continued)

Daily PM10 over time (P.Pinang)

Daily PM10 over time (Perak)

… (figure continued)

East Region

Daily PM10 over time (Kelantan)

Daily PM10 over time (Terengganu)

… (figure continued)

Central Region

… (figure continued)

Daily PM10 over time (KL)

Daily PM10 over time (Putrajaya)

… (figure continued)

Daily PM10 over time (N.Sembilan)

South Region

Daily PM10 over time (Melaka)

… (figure continued)

Daily PM10 over time (Johor)

Sarawak Region

Daily PM10 over time (Sarawak)
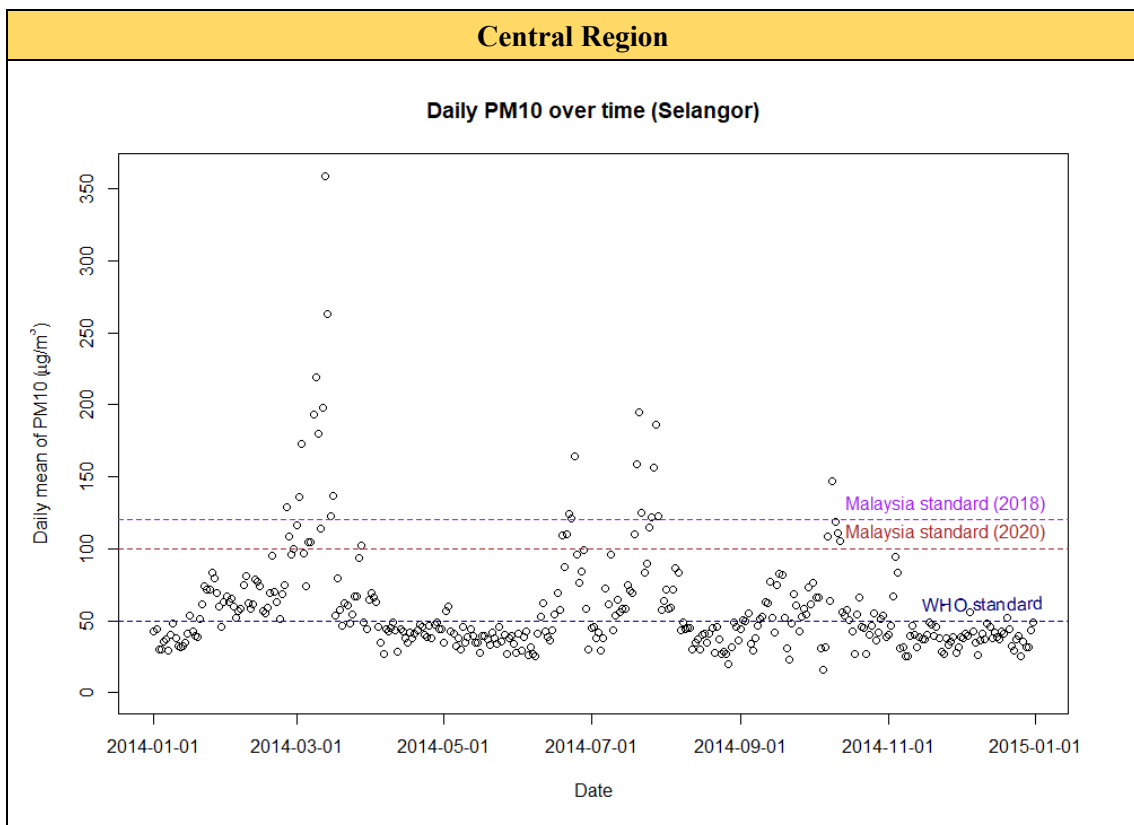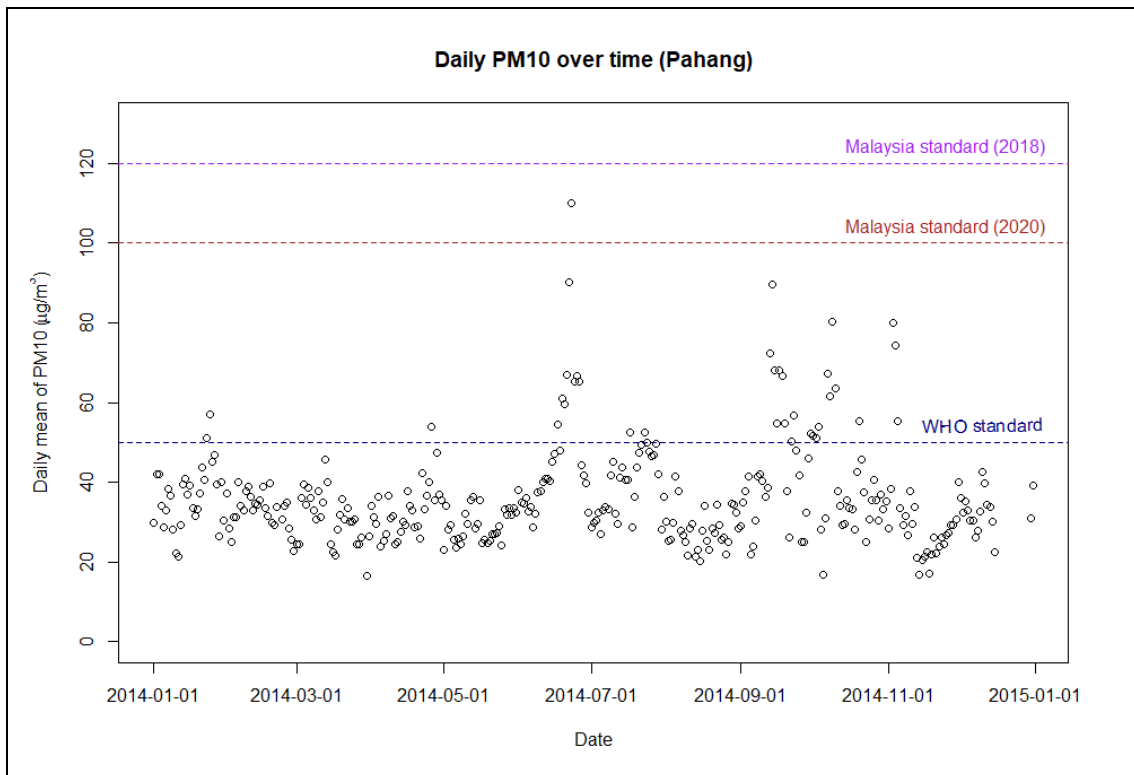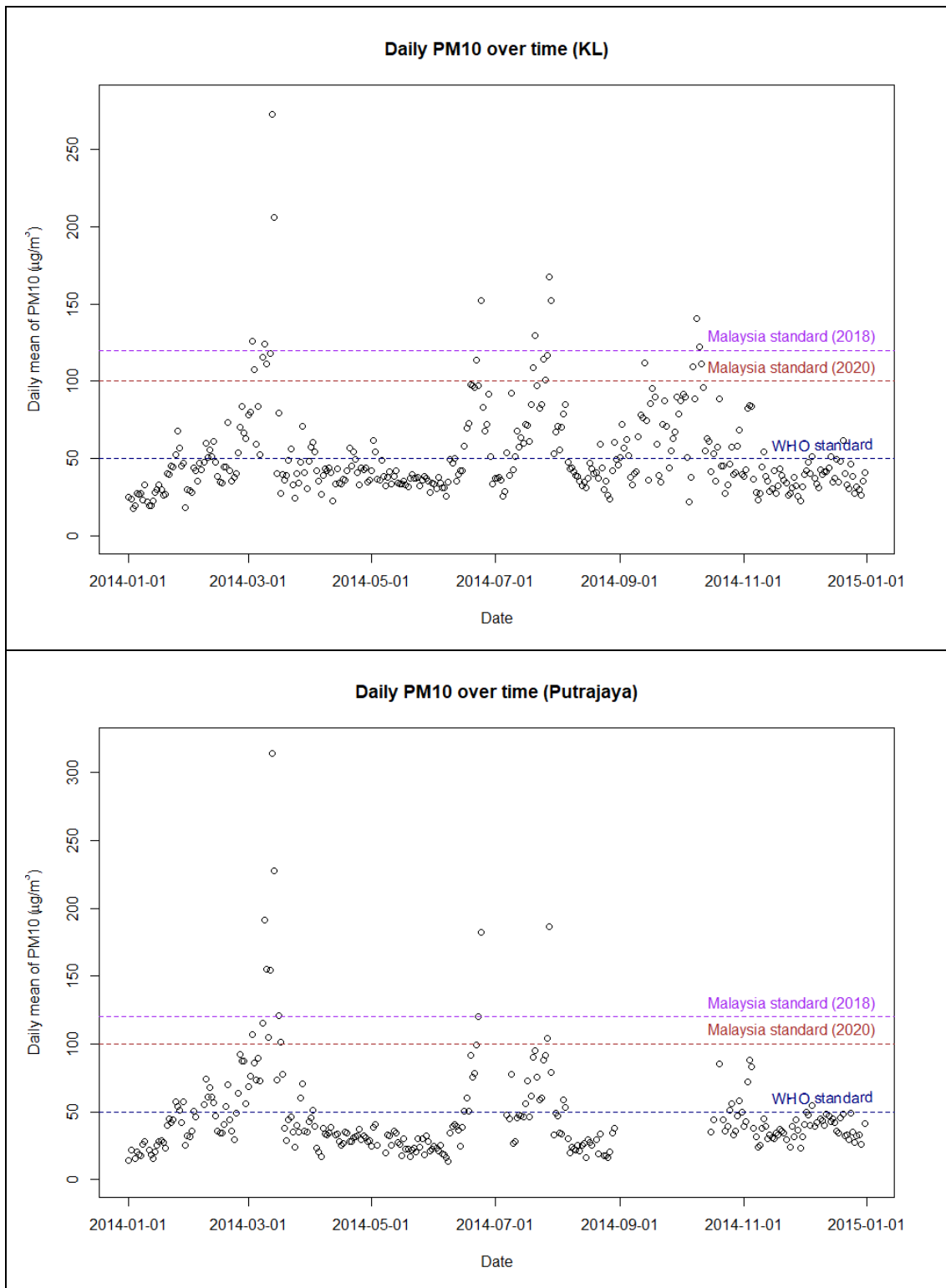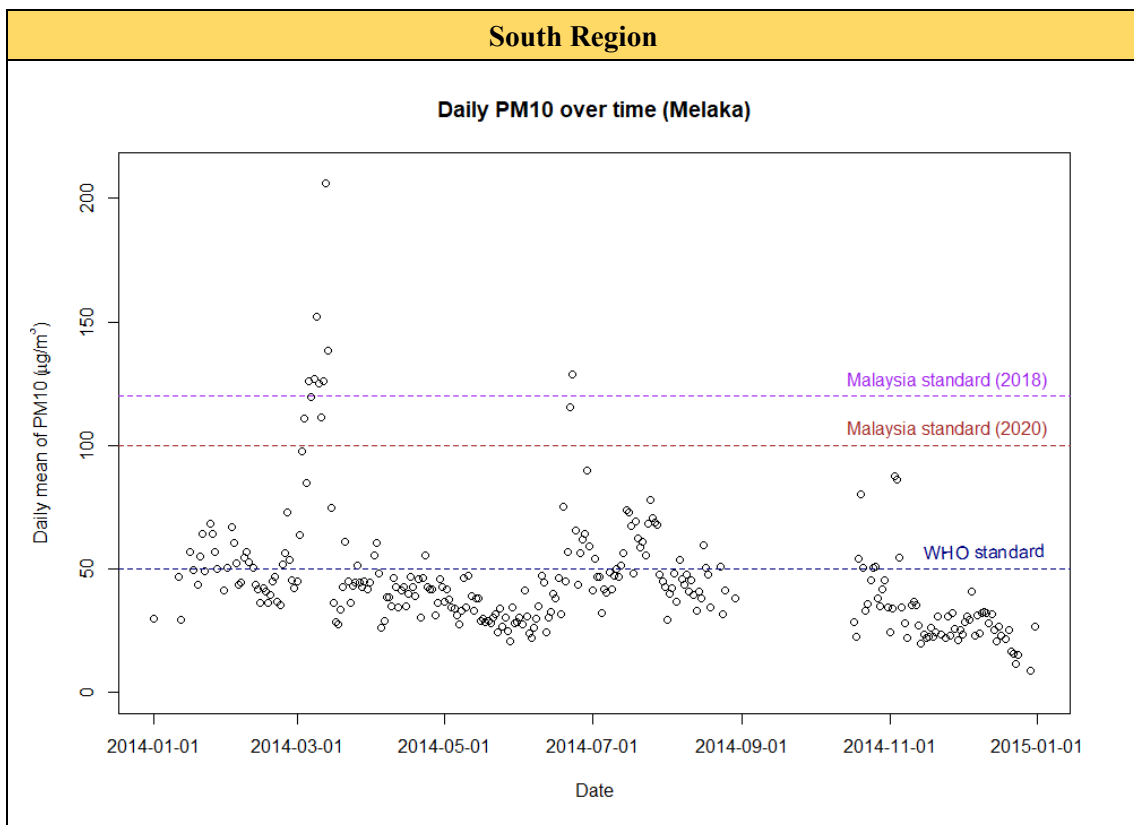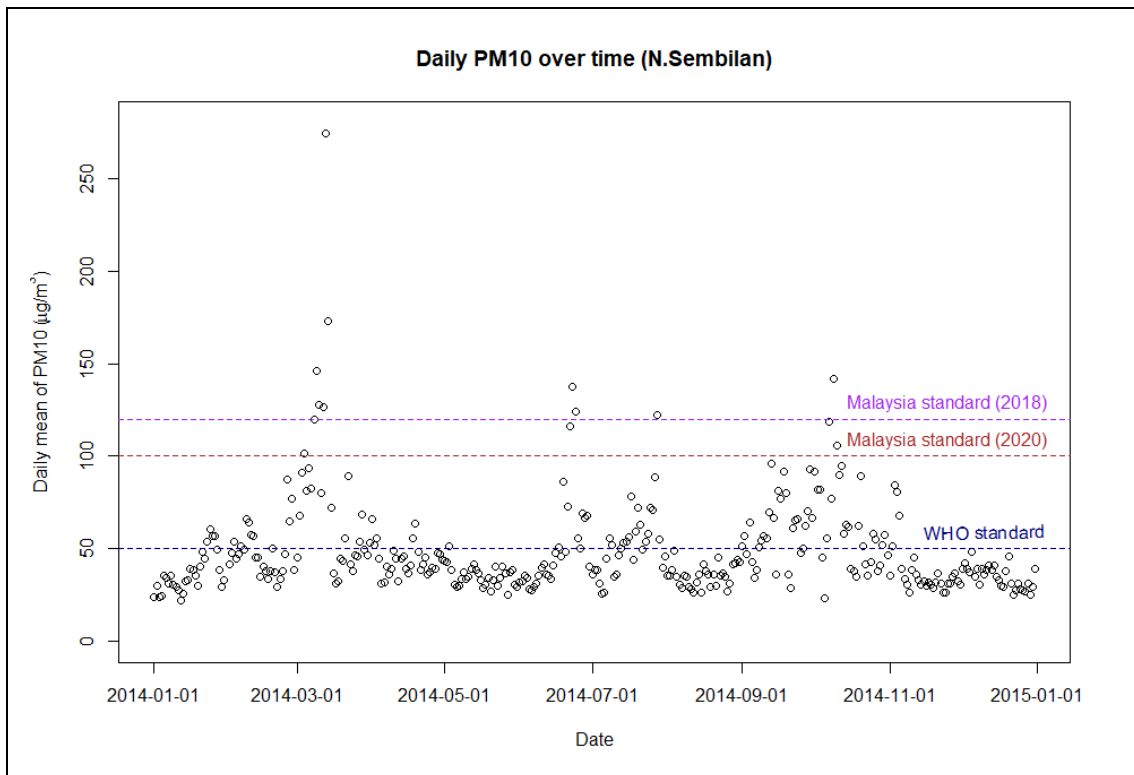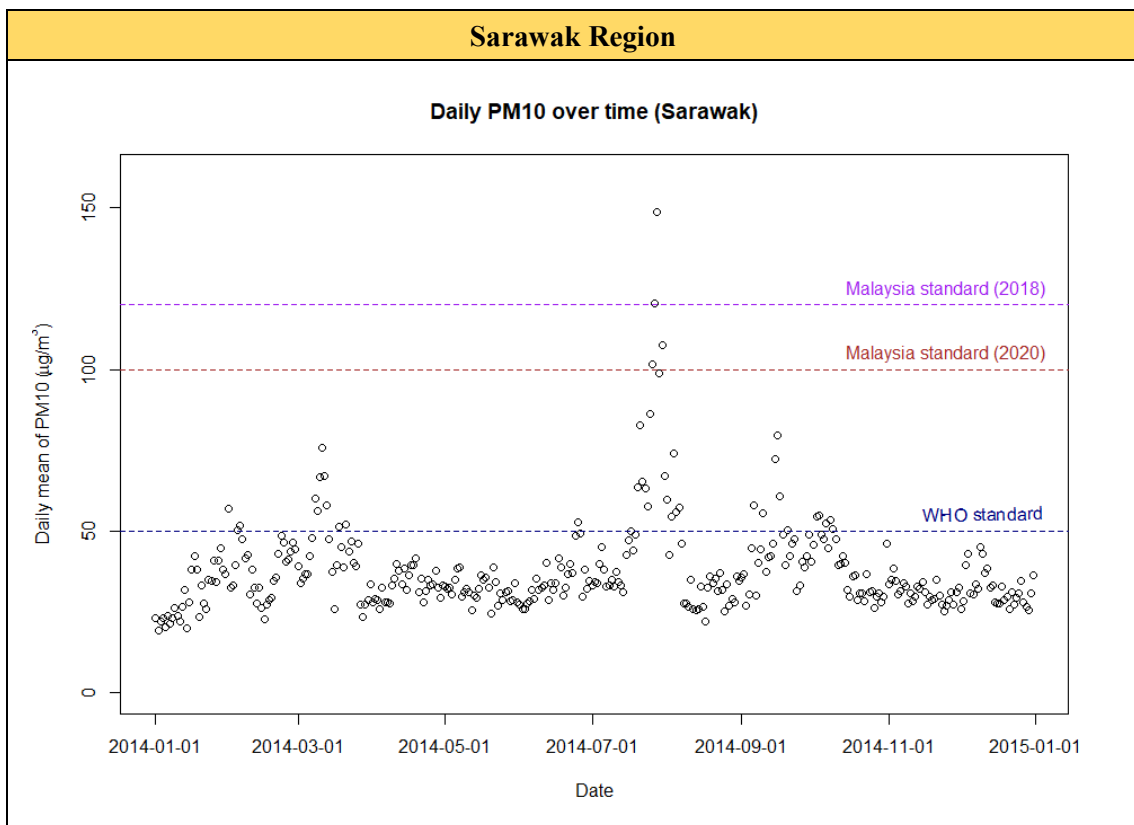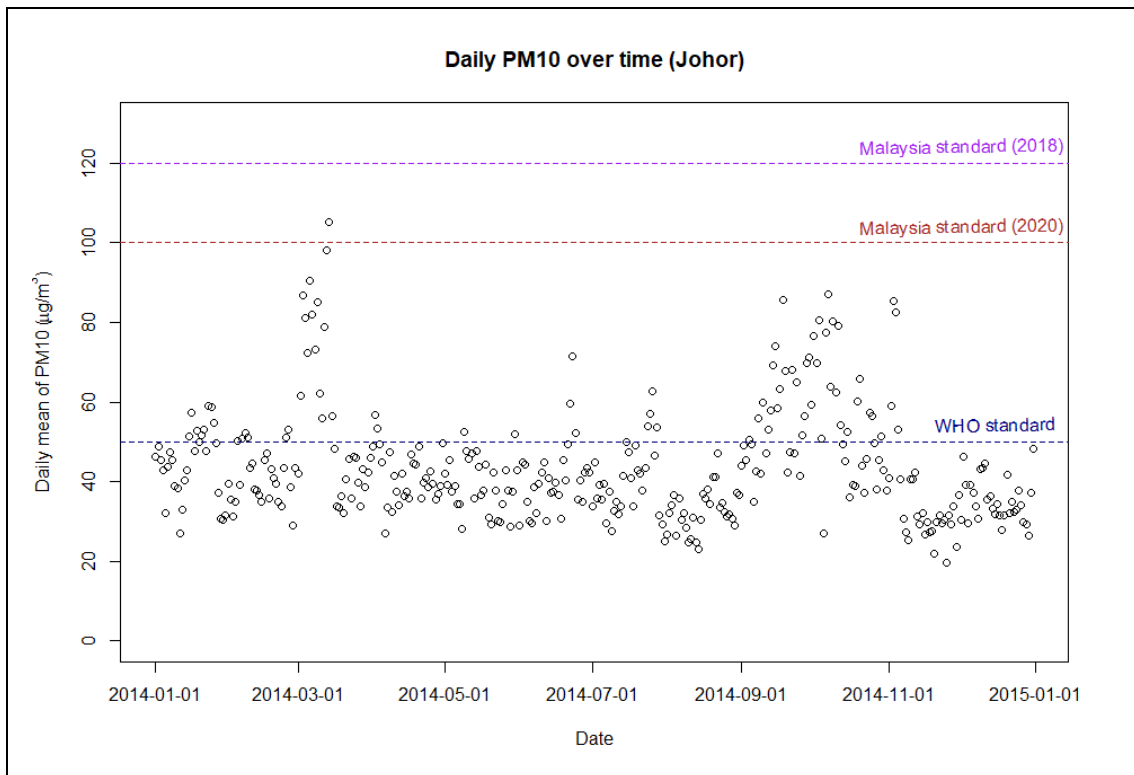
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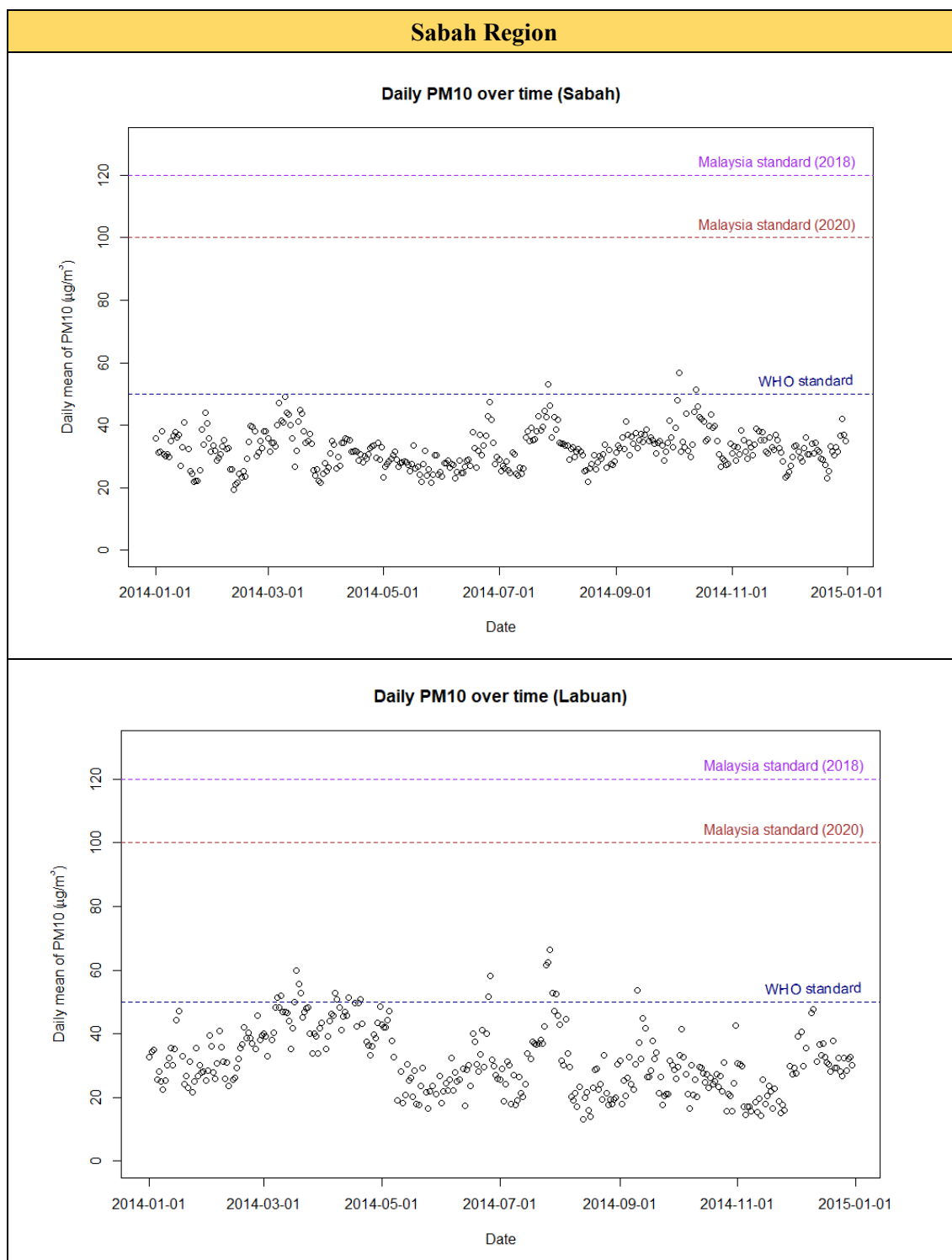
Figure 4.3. Time trend of PM$_{10}$ in each state of Malaysia for year 2014.

Note: Standards shown with dotted lines for daily (24-hour mean). WHO standard (50 µg/m^3); Malaysia standard (2018 – current) (120 µg/m^3); Malaysia standard (2020) (100 µg/m^3).

Table 4.3 shows number of haze days (HD) and haze days with U5Y mortality

(HDwUM) in each state of Malaysia. In Sabah and Perlis, there were several HD, but no HDwUM.

The Sabah region and East region were regions least affected by haze. It was observed that in

some states, there were no *haze day* defined neither of these 2 conditions: (1) when baseline

concentration increased considering same duration (i.e. *Level 1 to Level 3, at each duration*); and

(2) when duration was increased for a particular baseline concentration (i.e. *Duration 1 to*

Duration 3, at each level).

State-specific and pooled odds ratio of U5Y mortality due to haze were shown in Table

4.4. At haze on *Level 1*, there were significantly higher odds of U5Y mortality due to haze day

compared to non-haze day in Perak for *Duration 1* [OR: 1.614 (95% CI: 1.129, 2.307)] and

Duration 2 [OR: 1.599 (95% CI: 1.117, 2.289)] , and in Kedah for *Duration 3* [OR: 1.800 (95%

CI: 1.127, 2.874)]. Meanwhile, lower odds were observed in Pahang at *Duration 3* [OR: 0.344

(95% CI: 0.120, 0.987)]. Pooled effects for *Level 1* showed increasing risk of U5Y mortality due

to haze when *duration* increased, though not statistically significant. At haze on *Level 2*,

significant higher odds was observed in Kedah at *Duration 1* [OR: 2.177 (95% CI: 1.128, 4.203)].

Pooled effects for *Level 2* did not show any pattern through *levels*. Whereas at haze on *Level 3*,

significant higher odds were observed in Perak at *Duration 1* [OR: 1.891 (95% CI: 1.075, 3.326)]

and *Duration 3* [OR: 2.478 (95% CI: 1.056, 5.814)], but lower odds were observed in Selangor

at *Duration 3* [OR: 0.621 (95% CI: 0.389, 0.993)]. Pooled results for *Level 3* showed higher odds on *Duration 1* and *Duration 3* without statistical significance.

Figure 4.4. shows the single day lag pattern for odds ratio of U5Y mortality during haze compared to non-haze at each baseline concentration and duration. It was observed that in low intensity and short duration, lag pattern showed similar effects on each lag days. As moving from *Level 1* to *Level 2*, *Level 2* showed a consistent pattern of higher ORs at first few days lag compared to later lags. In *Level 3*, it seems that ORs were higher on current day lag and showed a declining pattern at later lags. On the other hand, when haze had occurred for 3 consecutive days (*duration 3*), ORs were highest observed on lag 0 for *Level 1* and *Level 3*.

Table 4.3. Number of haze days and haze days with U5Y mortality in each state in 2014.

| | | Level 1 (Baseline concentration 50µg/m^3) | | | | | | | | | Level 2 (Baseline concentration 75µg/m^3) | | | | | | | | | Level 3 (Baseline concentration 100µg/m^3) | | | | | | | | |
| | | Duration 1 | | | Duration 2 | | | Duration 3 | | | Duration 1 | | | Duration 2 | | | Duration 3 | | | Duration 1 | | | Duration 2 | | | Duration 3 | | |
Region	State	HD	HDwUM	%	HD	HDwUM	%	HD	HDwUM	%	HD	HDwUM	%	HD	HDwUM	%	HD	HDwUM	%	HD	HDwUM	%	HD	HDwUM	%	HD	HDwUM	%
North	Perlis	16	0	-	11	0	-	8	0	-	6	0	-	2	0	-	1	0	-	1	0	-	0	0	-	0	0	-
	Kedah	96	48	50	62	32	52	41	26	63	16	9	56	10	5	50	7	5	71	6	3	50	2	1	50	0	0	-
	P.Pinang	127	44	35	98	33	34	78	24	31	25	11	44	15	7	47	9	4	44	14	6	43	9	3	33	5	2	40
	Perak	103	63	61	79	47	59	61	36	59	37	24	65	28	17	61	21	13	62	18	13	72	10	7	70	5	4	80
East	Kelantan	85	53	62	58	34	59	39	23	59	8	5	63	2	1	50	0	0	-	2	0	-	1	0	-	0	0	-
	Terengganu	11	7	64	4	2	50	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-
	Pahang	36	17	47	24	8	33	16	4	25	5	1	20	1	0	-	0	0	-	1	0	-	0	0	-	0	0	-
Central	Selangor	160	132	83	136	116	85	118	99	84	64	52	81	46	37	80	34	26	76	36	26	72	26	19	73	19	12	63
	KL	129	44	34	97	35	36	81	29	36	57	23	40	40	17	43	30	12	40	22	10	45	13	5	38	8	3	38
	Putrajaya	73	8	11	54	6	11	43	5	12	35	4	11	24	3	13	16	1	6	14	2	14	9	1	11	5	0	-
South	N. Sembilan	112	37	33	81	23	28	57	20	35	40	10	25	25	7	28	18	5	28	14	4	29	7	2	29	3	1	33
	Melaka	76	22	29	53	17	32	38	14	37	20	7	35	13	5	38	10	5	50	12	5	42	9	4	44	7	3	43
	Johor	78	53	68	51	35	69	36	27	75	17	11	65	6	3	50	1	1	100	1	1	100	0	0	-	0	0	-
Sarawak	Sarawak	41	26	63	25	17	68	18	14	78	9	6	67	5	4	80	4	3	75	4	3	75	2	1	50	1	1	100
Sabah	Sabah	3	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-
	Labuan	18	0	-	8	0	-	4	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-

Note: "Level" indicates different baseline concentration of PM$_{10}$ used to define haze. *Duration 1* indicates haze day for only 1 day. *Duration 2* indicates haze day for 2 consecutive days. *Duration 3* indicates haze day for 3 consecutive days. *HD* indicates haze day. *HDwUM* indicates haze day with U5Y mortality. % indicates percentage HDwUM within HD.

Table 4.4. Odds ratio of U5Y mortality due to haze by each level and duration.

		Duration 1 (Haze for 1 day only)			Duration 2 (Haze for 2 consecutive days)			Duration 3 (Haze for ≥ 3 consecutive days)	
	State	OR	95% CI		OR	95% CI		OR	95% CI	
Level 1 (Baseline concentration 50 µg/m³)	Perlis	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Kedah	0.923	0.644	1.323	1.117	0.743	1.681	**1.800**	**1.127**	**2.874**
	P.Pinang	1.027	0.647	1.630	1.052	0.653	1.693	1.136	0.694	1.862
	Perak	**1.614**	**1.129**	**2.307**	**1.599**	**1.117**	**2.289**	1.465	0.985	2.179
	Kelantan	1.031	0.743	1.432	0.855	0.573	1.275	0.919	0.588	1.435
	Terengganu	0.913	0.353	2.357	0.297	0.035	2.511	NA	NA	NA
	Pahang	0.896	0.522	1.536	0.659	0.324	1.342	**0.344**	**0.120**	**0.987**
	Selangor	0.954	0.765	1.190	1.051	0.848	1.303	0.919	0.737	1.147
	KL	0.864	0.580	1.287	0.889	0.584	1.353	0.861	0.553	1.341
	Putrajaya	0.707	0.232	2.153	0.607	0.177	2.081	0.589	0.173	2.008
	N. Sembilan	0.950	0.615	1.468	0.756	0.466	1.227	1.169	0.707	1.936
	Melaka	1.178	0.628	2.210	1.246	0.639	2.428	1.634	0.778	3.429
	Johor	1.010	0.741	1.375	1.174	0.834	1.653	1.408	0.953	2.078
	Sarawak	0.656	0.425	1.013	0.868	0.520	1.448	1.210	0.672	2.180
	Sabah	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Labuan	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Pooled	*0.987*	*0.869*	*1.104*	*1.029*	*0.899*	*1.160*	*1.124*	*0.952*	*1.296*
	State	OR	95% CI		OR	95% CI		OR	95% CI	
Level 2 (Baseline concentration 75 µg/m³)	Perlis	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Kedah	**2.177**	**1.128**	**4.203**	1.530	0.655	3.570	2.490	0.994	6.240
	P.Pinang	1.461	0.753	2.837	1.393	0.609	3.188	1.171	0.421	3.256
	Perak	1.397	0.886	2.204	1.350	0.828	2.203	1.243	0.720	2.145
	Kelantan	0.867	0.358	2.100	0.787	0.152	4.089	NA	NA	NA
	Terengganu	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Pahang	0.332	0.043	2.585	NA	NA	NA	NA	NA	NA
	Selangor	0.829	0.642	1.071	0.771	0.581	1.023	0.723	0.521	1.005
	KL	1.396	0.849	2.295	1.511	0.865	2.639	1.215	0.654	2.257
	Putrajaya	0.607	0.149	2.478	0.548	0.114	2.641	0.248	0.022	2.752
	N. Sembilan	0.594	0.305	1.157	0.760	0.343	1.686	0.661	0.260	1.681
	Melaka	0.843	0.305	2.328	1.314	0.339	5.087	1.558	0.372	6.517
	Johor	1.284	0.744	2.216	1.005	0.417	2.421	0.969	0.100	9.360
	Sarawak	0.767	0.304	1.933	1.382	0.426	4.478	1.178	0.314	4.414
	Sabah	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Labuan	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Pooled	*1.076*	*0.839*	*1.312*	*1.075*	*0.821*	*1.329*	*1.040*	*0.730*	*1.350*

(… table continued)

	State	Duration 1 (Haze for 1 day only)			Duration 2 (Haze for 2 consecutive days)			Duration 3 (Haze for ≥ 3 consecutive days)		
		OR	95% CI		OR	95% CI		OR	95% CI	
	Perlis	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Kedah	1.299	0.455	3.706	2.818	0.396	20.033	NA	NA	NA
	P.Pinang	1.398	0.578	3.380	1.239	0.394	3.904	2.481	0.587	10.482
	Perak	**1.891**	**1.075**	**3.326**	1.703	0.817	3.553	**2.478**	**1.056**	**5.814**
	Kelantan	NA	NA	NA	NA	NA	NA	NA	NA	NA
Level 3 (Baseline concentration 100 μg/m³)	Terengganu	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Pahang	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Selangor	0.849	0.608	1.183	0.754	0.514	1.105	**0.621**	**0.389**	**0.993**
	KL	1.427	0.732	2.782	1.585	0.594	4.229	1.018	0.271	3.817
	Putrajaya	0.627	0.103	3.820	0.482	0.054	4.333	NA	NA	NA
	N. Sembilan	0.743	0.274	2.015	1.119	0.295	4.252	2.342	0.376	14.594
	Melaka	1.007	0.294	3.450	1.113	0.310	3.998	1.034	0.268	3.996
	Johor	0.969	0.100	9.360	NA	NA	NA	NA	NA	NA
	Sarawak	1.406	0.358	5.524	0.975	0.101	9.427	2.994	0.187	47.888
	Sabah	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Labuan	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Pooled	*1.154*	*0.855*	*1.452*	*1.104*	*0.725*	*1.483*	*1.320*	*0.719*	*1.922*

Note: Bolded values indicates statistical significance level at $p < 0.05$. OR: Odds ratio. CI: Confidence interval.
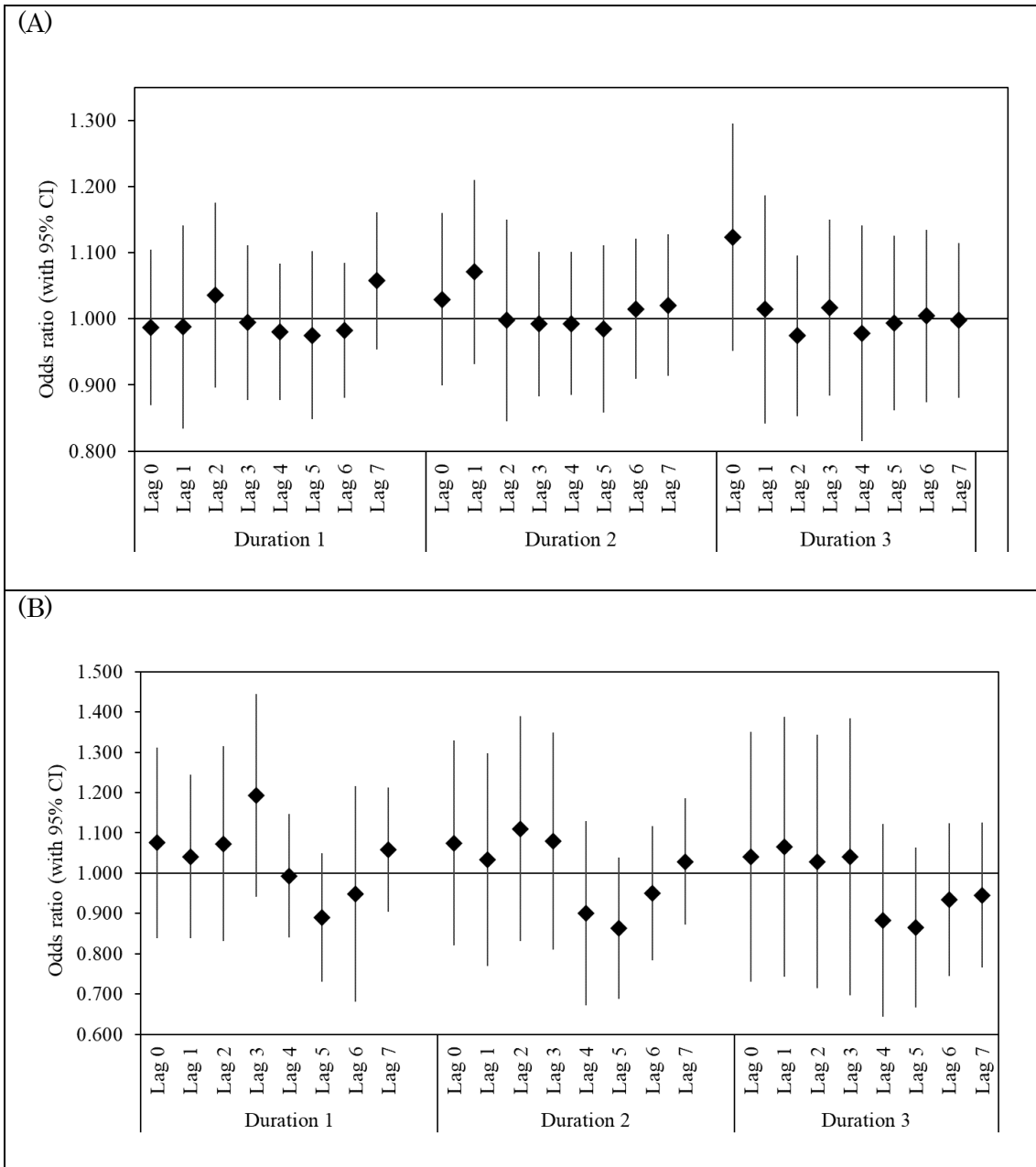
(… figure continued)
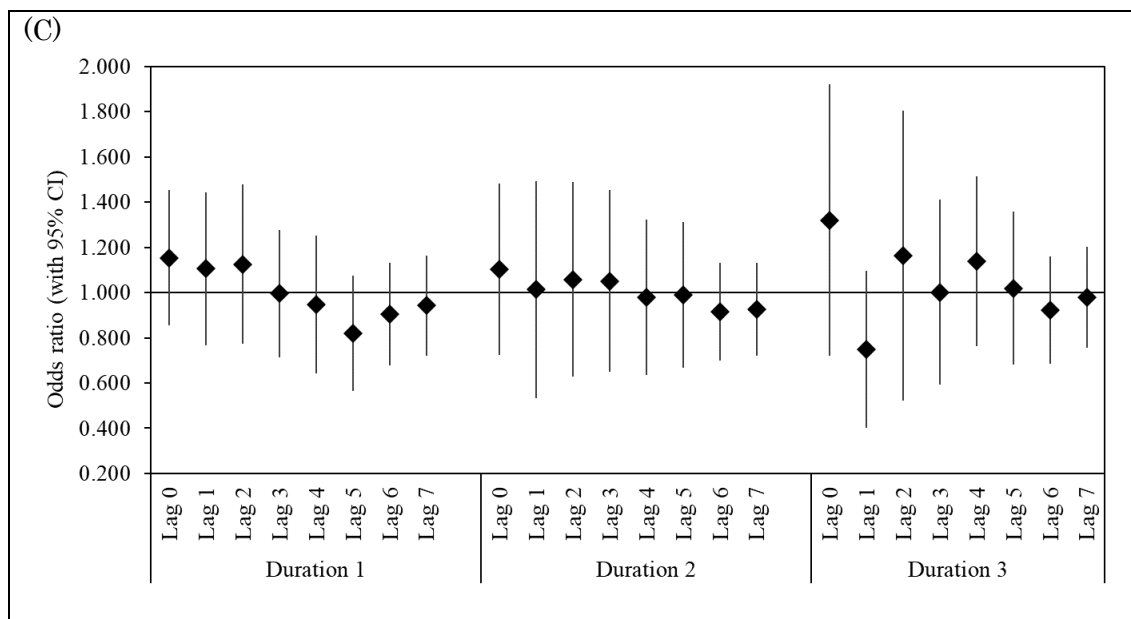
Figure 4.4. Single day lag pattern for odds ratio of U5Y mortality during haze compared to U5Y-mortality during non-haze at each baseline concentration (*level*) and duration:
(A) *Level 1*: 50 μg/m³, (B) *Level 2*: 75 μg/m³, and (C) *Level 3*: 100 μg/m³.

Discussion

There were higher odds of U5Y mortality associated with haze days compared to non-haze days in some cities and at different definitions. In general, though statistically weak, it is worthwhile to note that there was a pattern of increasing risk from haze days defined by: (1) lower baseline concentration to higher baseline concentration, and (2) shorter to longer duration of haze occurrence. The lag pattern showed a tendency that odds of U5Y mortality were more immediate when there were longer consecutive days of haze occurrence.

The baseline concentration used to define *haze day* in this study included the WHO guideline (50 µg/m^3), the New Malaysia Ambient Air Quality Standard (by year 2020 – 100 µg/m^3), and an arbitrary concentration in between the two (75 µg/m^3). The New Malaysia Ambient Air Quality Standard is a revised version of the Malaysia Ambient Air Quality Guideline that has been used since 1989. The new standard is divided into 3 interim targets to improve ambient air quality – interim target 1 (IT-1) in 2015, IT-2 in 2018 and full implementation of the standard in 2020. In addition to existing guideline with 5 air pollutants (PM$_{10}$, sulfur dioxide, nitrogen dioxide, ground level ozone, and carbon monoxide), the new standard included PM$_{2.5}$ as a new parameter (Table 4.5). At present, ground monitoring stations for PM$_{2.5}$ are at installation stage, starting from the capital city (Kuala Lumpur).

Table 4.5. New Malaysia Ambient Air Quality Standard for ambient PM.

Ambient PM	Averaging time	Concentration ($\mu g/m^3$)		
		IT-1 (2015)	IT-2 (2018)	Standard (2020)
PM_{10}	24-hour	150	120	100
$PM_{2.5}$	24-hour	75	50	35

Note: IT refers to interim target, which is a stage-by-stage implementation of the new standard prior to full implementation in year 2020.

Other definitions of haze used in previous studies include haze defined by visibility (Field *et al.*, 2016), by humidity (Quan *et al.*, 2011), by combination of visibility and humidity (Gu *et al.*, 2017), by Malaysian air quality index within "lower moderate" category (API $\geq$ 76) which is equivalent to PM_{10} concentration exceeding 100 $\mu g/m^3$ (Othman *et al.*, 2014), by PM_{10} concentration exceeding 100 $\mu g/m^3$ (Sahani *et al.*, 2014), or by PM_{10} concentration exceeding the 99th percentile of daily mean PM_{10} concentration (Morgan *et al.*, 2010). Malaysia is a tropical country with hot and humid weather throughout the year. In such weather condition, using visibility as a measure to define haze might misclassify haze days of low concentration of air particles, as this might include days with low visibility attributed to high humidity. Humidification of particles could increase scattering coefficients and thus reduce visibility in the atmosphere (He *et al.*, 2019).

Highest number of haze days were observed in the central region and some states in the northern and southern region which were aligned on western part of the Peninsular Malaysia, alongside the Straits of Malacca adjacent to the Sumatra, Indonesia. Meanwhile, in those states

located on the east part showed lower levels of ambient PM_{10}. Though, similar peaks follow but at relatively low concentration. This might be attributed to transboundary forest fire effect brought along by the southwesterly monsoon wind (Sulong *et al.*, 2017). On the other hand, an extremely high peak was observed in March, which was during northeast monsoon season, in states except for those located at the east coast (Terengganu, Kelantan, and Pahang) of the Peninsular Malaysia adjacent to the South China Sea. In these states, northeasterly monsoon wind brings rainy season (Varikoden *et al.*, 2011), whereby rainfall might have caused wet deposition of the particles, thus low concentration of PM_{10}. The peak in March might be contributed by local pollutant (Sulong *et al.*, 2017, DOE Malaysia 2019). However, further investigation is necessary to distinguish the source of pollutant.

Significant increased ORs of U5Y mortality were observed at some cities, with increasing pattern along either increasing duration or increasing intensity. The pattern, though, was not observed for *Level 2*. Previous study showed increased risk of mortality in children (age 0-14), whereby mortality due to haze were 41% higher than those of non-haze at lag 2-day (Sahani *et al.*, 2014). The study included children of age 0-14 while the current study investigated the health effects among children of age 0-4. The present study found about 60% (Perak) to 80% (Kedah) higher risks of U5Y mortality in haze days than non-haze days. However, the pooled effects were of non-statistical significance. Some studies reported significant effects of PM_{10} on U5Y-children mortality, particularly due to respiratory outcomes (Conceição *et al.*, 2001; Woodruff, Darrow and Parker, 2008; Gouveia *et al.*, 2018). Other studies reported increased hospital admissions due to asthma and chronic obstructive pulmonary disease (COPD) in children

(age 0-14) (Anderson *et al.*, 2001) and reduced lung function in school children (Oftedal et al. 2008) due to ambient PM. These studies demonstrated health effects of ambient PM but not particular on haze events. Meanwhile, a study in Sydney reported that wildfire haze PM_{10} was associated with increased risk of respiratory-related hospital admission in the adults (age 15 and above but not in children, while urban PM_{10} was associated with increased all-cause mortality, and cardiorespiratory hospital admissions (Morgan *et al.*, 2010). $PM_{2.5}$ during urban haze was reported to increase respiratory, cardiovascular and ocular emergency room visits (Liang *et al.*, 2017) and mortality (Gu *et al.*, 2017) over short lags. Another study reported increased cardiorespiratory emergency department visits due to wildfire smoke in rural North Carolina (Rappold *et al.*, 2011). The studies were less focused on children under 5 years old, though some included children aged 0-14 years old.

Studies on health effects of haze have not considered intensity and duration in a way as demonstrated in the present study. Some studies have examined the association using lag terms, considering a possible delayed onset of disease upon point of exposure (Morgan *et al.*, 2010; Rappold *et al.*, 2011; Sahani *et al.*, 2014; Gu *et al.*, 2017; Liang *et al.*, 2017). Reporting of lagged pattern is very important for elucidation of biological mechanism as well as understanding of the development of disease. However, it is difficult to communicate the information to the public as well as policy makers afterwards. Among these studies, Rappold et al. (2011) attempted to consider lag pattern and intensity of pollution. They defined a 3-day window period of high exposure with emergency department visits in a county as *case* and compared the risks with referent counties (counties of which high exposure window period was 1 day or less than 1 day).

Accounting for lagged effects, they estimated the odds by using a cumulative lag over 5 days ahead of the specified window period (Rappold *et al.*, 2011). It is interesting that the unconventional study design itself adjusted for long-term trend and seasonality, between-state variability, and possible lagged effects of wildfire haze. As compared to conventional method of case-crossover design adjusting for several lags, the authors managed to report the health effects in a simpler way with confounders being accounted for by design of their study. In the present study, instead of using lag structure, I examined the health effects of haze whereby haze events were defined considering both intensity and duration. Figure 4.5. shows a graphical summary of my expected outcome and the result from this study. As health effects of ambient PM are assumed linear, I expected continuous increment of risks as intensity or duration increases. However, as observed in the figure, except for these 3 conditions: (1) increasing *duration* for *level 1*, or (2) increasing *intensity (level)* for *duration 1*, and (3) diagonal increase of both *intensity* and *duration* concurrently; the other conditions did not show consistent increment of risk.

Although the present study did not show significant pooled effects, graphical information (as shown in Figure 4.5) would be useful in future development of warning system for haze. At present, the API is a commonly used tool to communicate timely air quality information to the public. It is recalculated every few hours and the latest information would be uploaded in the website or publicized through other media. The shortcoming of API is that, although it provides latest information, it could not deliver information about intensity and duration of exposure to haze. *Level 1* (50 $\mu g/m^3$) is equivalent to "good" category, while *Level 3* (100 $\mu g/m^3$) is equivalent to "lower moderate" category of the Malaysian API. All definitions of

haze used in this study were below "hazardous" category, but there were some significant increased risks at state-specific levels.

The third dimension of the haze matrix is the lag pattern of ORs of U5Y mortality due to haze compared to non-haze (Table 4.5). When conventional definition of haze was used, it is comparable to definition of "*Level 3 – Duration 1*" in this study, whereby baseline concentration of PM_{10} was at 10 µg/m³, and each day with PM_{10} concentration exceeding the baseline concentration is considered as *haze day*. Meanwhile, longer occurrence of haze events demonstrated immediate lagged effects when compared to those in shorter *duration*. This is not commonly observable in studies using conventional method to define haze. By using the haze matrix (Figure 4.5), it became simpler and more effective to have a comprehensive view of health effects considering duration, intensity and lags.
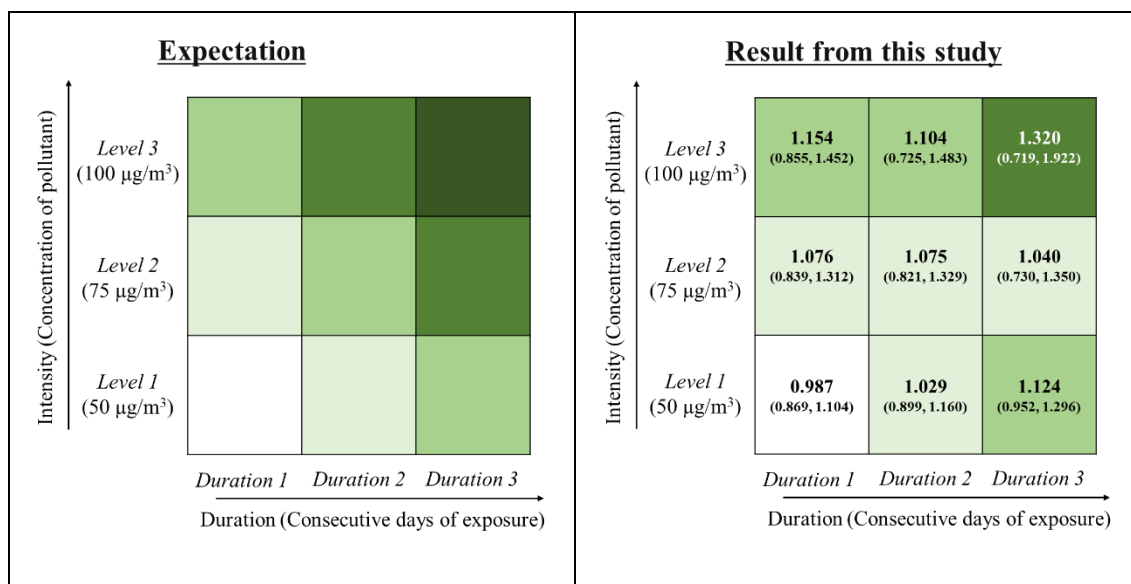
Figure 4.5. Graphical summary of pooled odds ratio of U5Y mortality due to haze days.
Note: Figure on the left shows the expected outcome; figure on the right shows the results from this study. Values shown are the pooled odds ratio with 95% confidence intervals. Color codes

were aligned by categories of odds ratio (each category for 0.100 odds ratio increment).

Children are considered as susceptible population to air pollutants due to some factors, including lung growth and development, time-activity patterns, chronic disease and acute disease (WHO, 2005). At this growth stage, their incomplete metabolic systems and immature host defense increases their vulnerability to air pollutants. A study which examined serum cytokine levels in healthy children reported higher levels of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), while lower levels of IL-8 and gamma interferon (IFN-γ) in children than those in adults (Sack *et al.*, 1998). TNF-α was higher in children of age below 2 years compared to children of older age (Berdat et al. 2003, Decker *et al.*, 2017). PM could induce systemic inflammatory responses and thus associated with circulatory and pathogenesis of cardiopulmonary diseases (van Eeden *et al.*, 2001). Such differences in the inflammatory mediators in children may lead to different responses and mechanism of disease if compared to adults. An animal study supported that exposure to PM_{10} could induce pulmonary inflammation more potently that those from fine PM (Huang *et al.*, 2017). There were increased neutrophils, eosinophils and inflammatory cytokines (TNF-α, IFN-γ, and IL-5) when treated with PM, whereby the effects of PM_{10} were higher than the other smaller sized PM. The weak association observed in this study might be due to relatively small dataset being used as short study period was included.

- *Strengths*

This is the first study which investigated U5Y mortality due to haze events, accounted

for duration and intensity of PM_{10} concentration. Reporting of the health effects of haze with clear information on duration and intensity on simple figure contributes to potential communication tool regarding haze events in the future. In addition, this is the first study which was conducted in Malaysia to investigate the health effects of ambient PM on U5Y-children. Previous study in Klang Valley reported significant increased mortality among children of age under 14 years. Children of younger age might have different health outcomes associated with ambient PM.

- *Limitations*

First limitation of this study is relatively small size of data available. The study period included only one year – year 2014. Though the data was nationwide, covering all regions. Due to this limitation, a case-crossover study design was applied, allowing each case to serve as its own control. Second limitation is possible exposure misclassification. Exposure was assumed using ambient PM measured by monitoring stations. This could not account for actual exposure by individual. Thirdly, the source of haze was unknown. The haze might be attributed to transboundary wildfire or local biomass burning.

Conclusion

There were higher risks of U5Y mortality due to haze in some state-specific estimates. However, the pooled effects did not show significant risk. Increasing pattern was observed under 3 conditions: (1) horizontal increasing by *duration* along *level 1*, or (2) vertical increasing by *intensity* for *duration 1*, and (3) diagonal increase of both *duration* and *intensity* concurrently. In addition, when lag pattern was examined, longer *duration* of haze occurrence demonstrated seemingly higher odds of U5Y mortality due to haze compared to non-haze on immediate lags.

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CHAPTER 5: CONCLUSION

- *Implications of findings*

1. The use of hourly component provides important information in elucidating the mechanism of toxicity of ambient PM. It is difficult to interpret an association as causal when evidence from different fields are not compatible. This thesis added to the epidemiological evidence on short-term health effects of ambient PM which could be potentially compatible to experimental evidence.

2. Elucidating acute effects of ambient PM using hourly component assists for better future policy making in air quality regulations and public communications. Regulating air quality in daily terms may not be as effective in hourly terms if the health effects of air pollutant occur within hours upon exposure.

3. Air pollutant events, such as haze, which occur during certain period in a year should be carefully considered by including the duration and intensity. In fact, the public are exposed to air pollutants continuously over time and such effects could be intensified during haze events.

- *Conclusion*

Acute effects were observed in short-term exposure to ambient PM. Investigation of the association by different lag structure and windows of exposure provided insightful information to understand the health effects of ambient PM. The information may assist future policy decision in improving air quality and public health.

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CHAPTER 6: FUTURE STUDIES

1.	*To investigate health effects of air pollutant using other health indicators.*

Studies using other health indicators should be conducted to examine the consistency of evidence. In Study I and Study II, EAD has been used to examine acute effects of ambient PM. EAD included all severity levels which could represent early stage of disease timeline, unlike hospital admission or mortality data which represent the endpoint of disease timeline. Meanwhile, Study III demonstrated different pattern of U5Y mortality at different levels of intensity and duration. This suggests possible differences of mechanisms at lower intensity with longer duration, or higher intensity with shorter duration.

2.	*To investigate health effects of air pollution events which occur at limited time (e.g. haze) by considering the duration and intensity.*

Exposure to air pollutants is continuous over time. When duration and intensity are considered using simple indicators, the findings could be used for future policy decisions and better way of public communication. The public could understand better regarding the air quality – what is the current level of intensity and for how long has the air quality consisted as such level. In addition, future warning system about haze with clearer and more detailed information would be feasible.

3.	*To investigate the health effects of transboundary haze and local air pollution.*

When haze is defined only by concentration of air pollutant, or other conditions such as visibility or API, it unknown of what source attributes most to the risk. Understanding of source of haze could assist future policy decisions on solving the issue effectively.

4.	*To develop a critical path network diagram for health effects of air pollutant.*

Critical path network diagram is a tool commonly used by project engineers to illustrate an overview of the time need for a project and each activities of the project. The use of this diagram may show how much time at least (shortest) it takes from exposure to air pollutant to the onset of disease, and possible lags. An illustrative diagram as an example is shown in Figure 6.1.
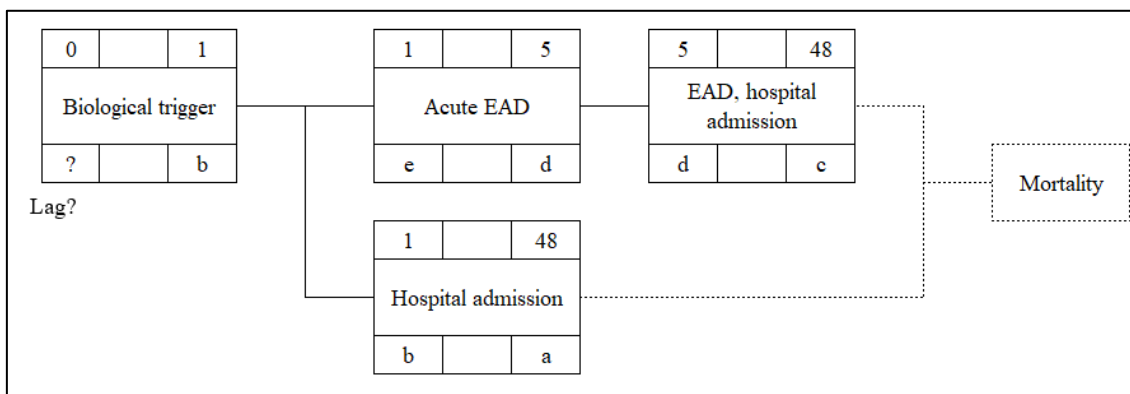
Figure 6.1. Illustrative diagram of critical path network for health effects of air pollutant.
Note: Each box represents a process. Upper columns of each represent the earliest (shortest) time possible for each process. Lower columns of each box represent latest time possible for each process. Middle part of each box is listed for the process. Values are displayed in hour unit.

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APPENDIX

Appendix A1
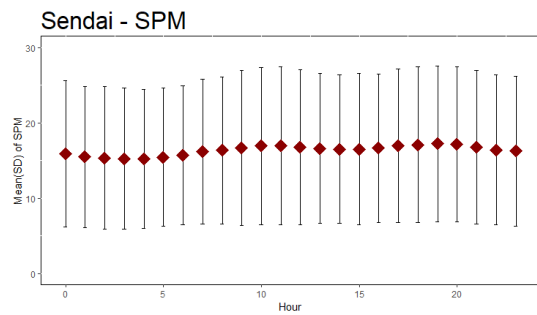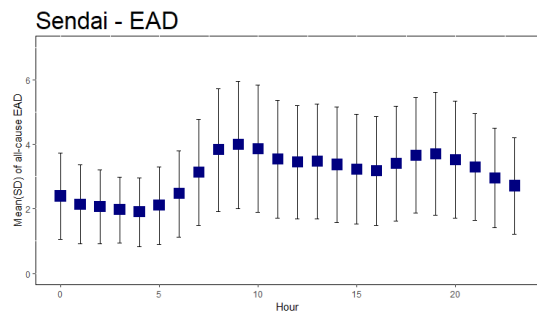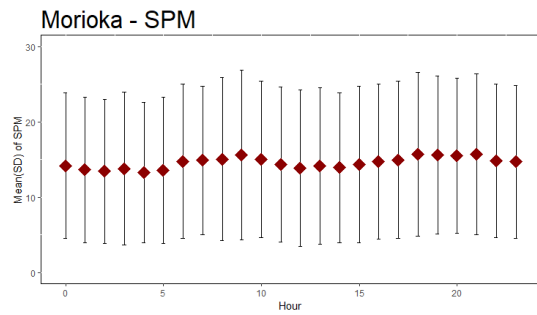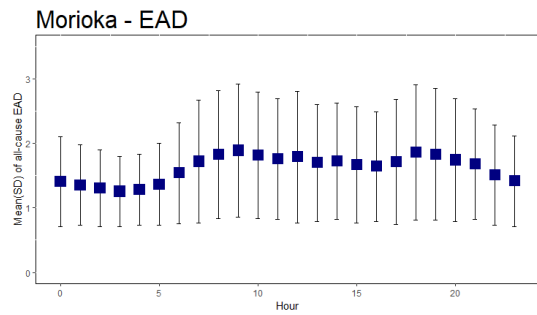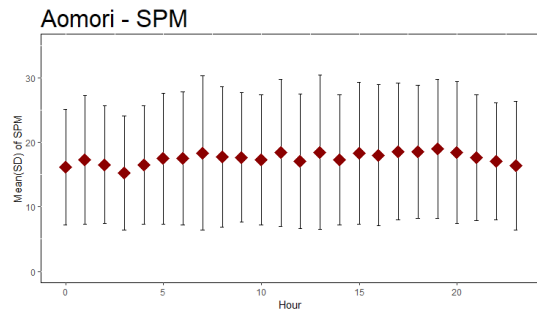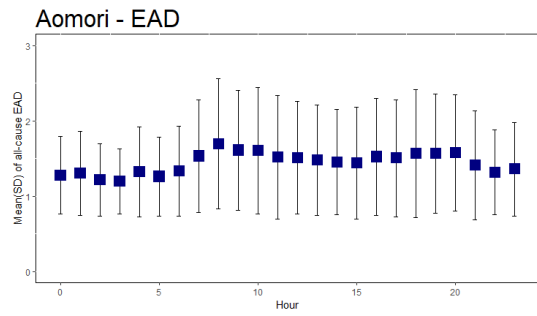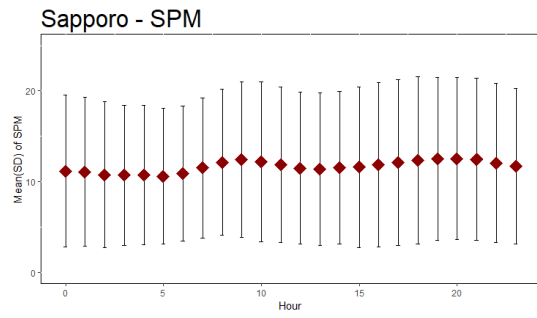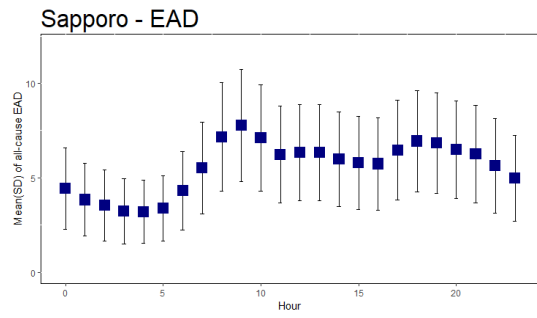
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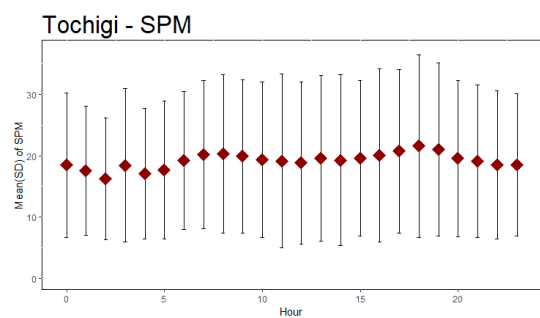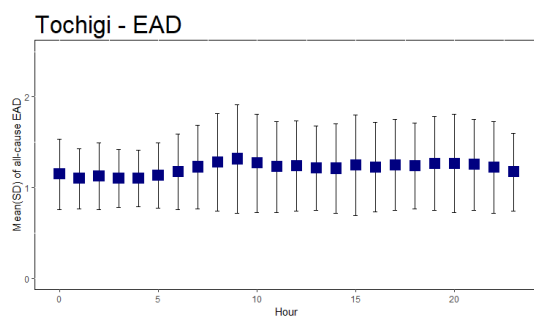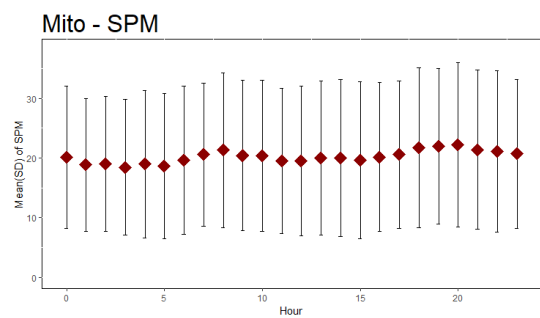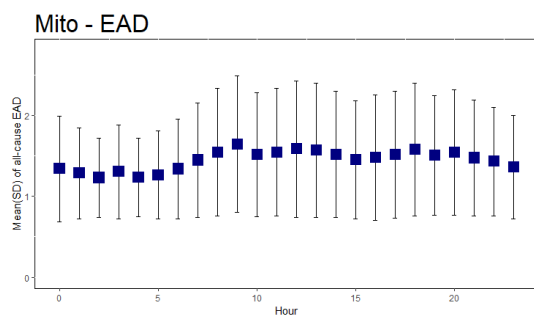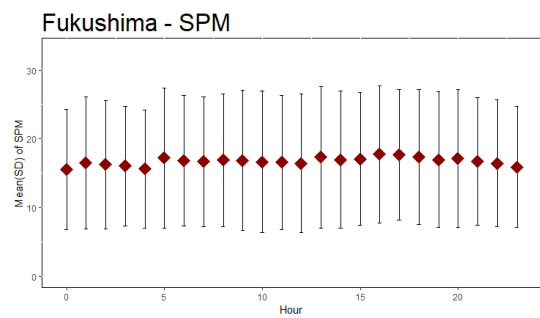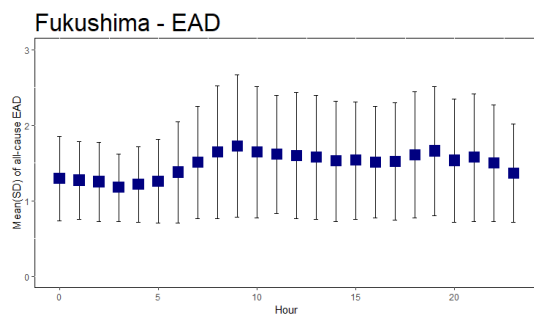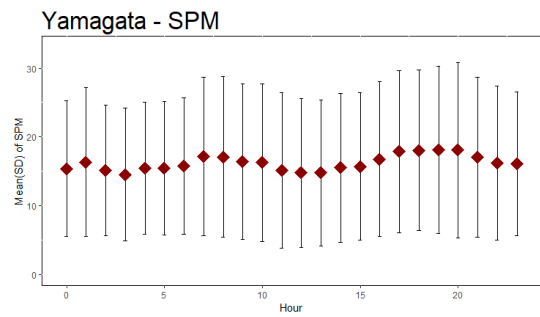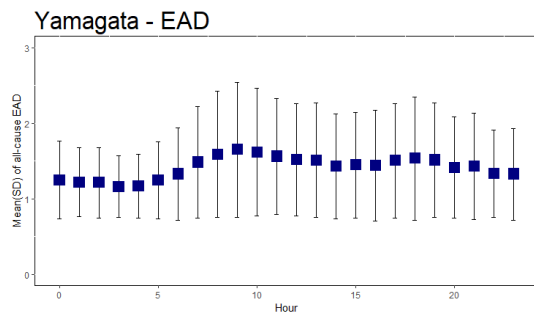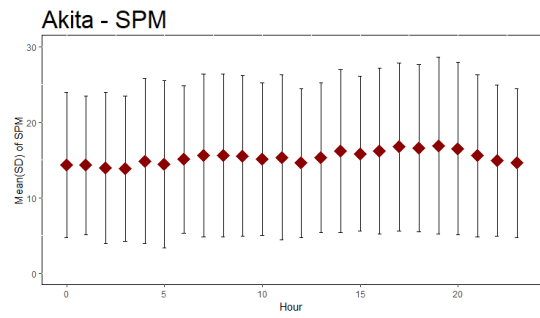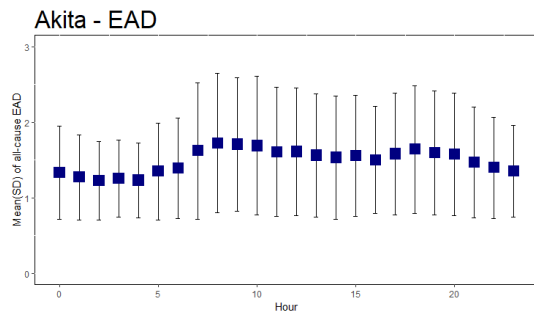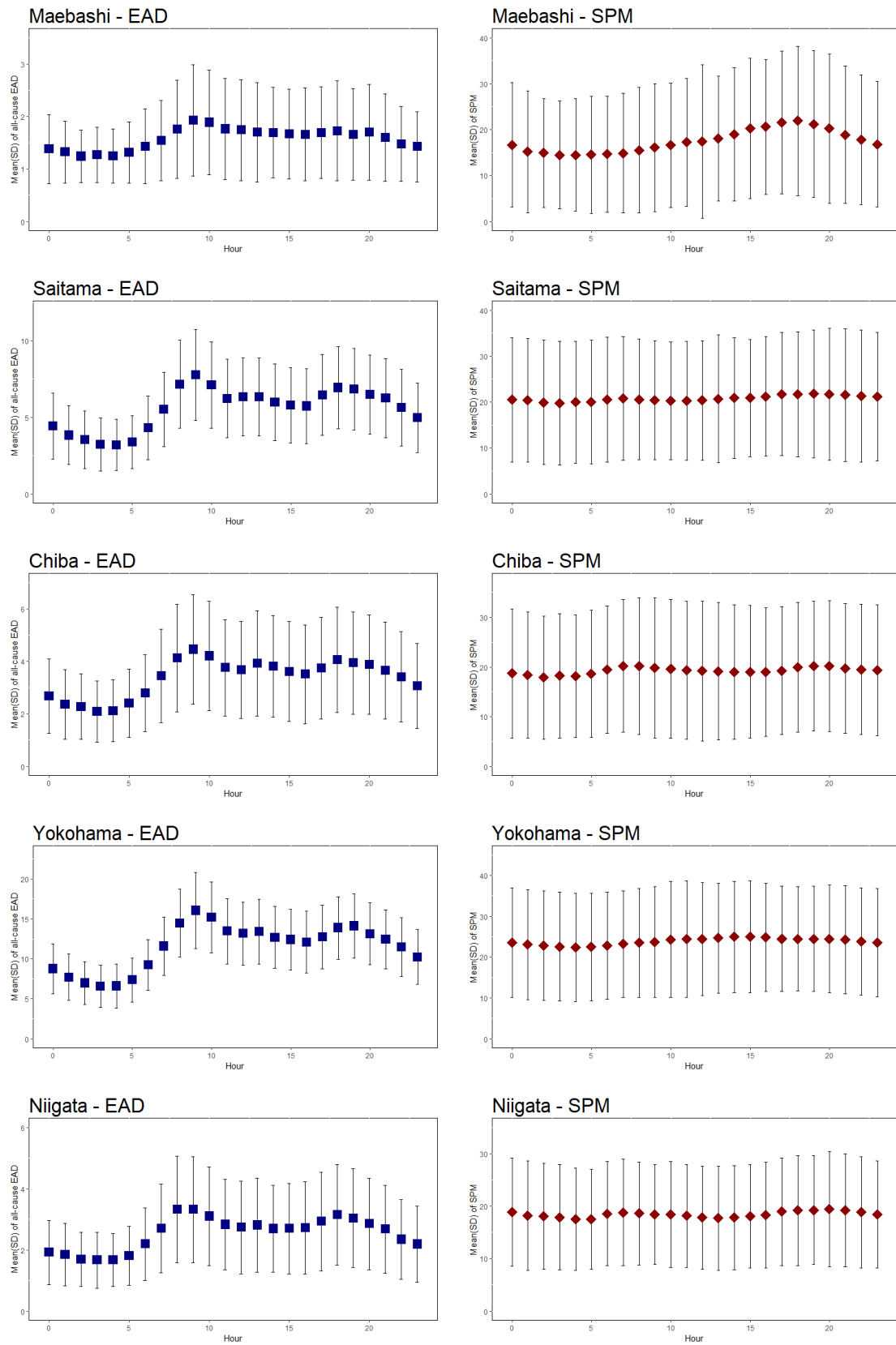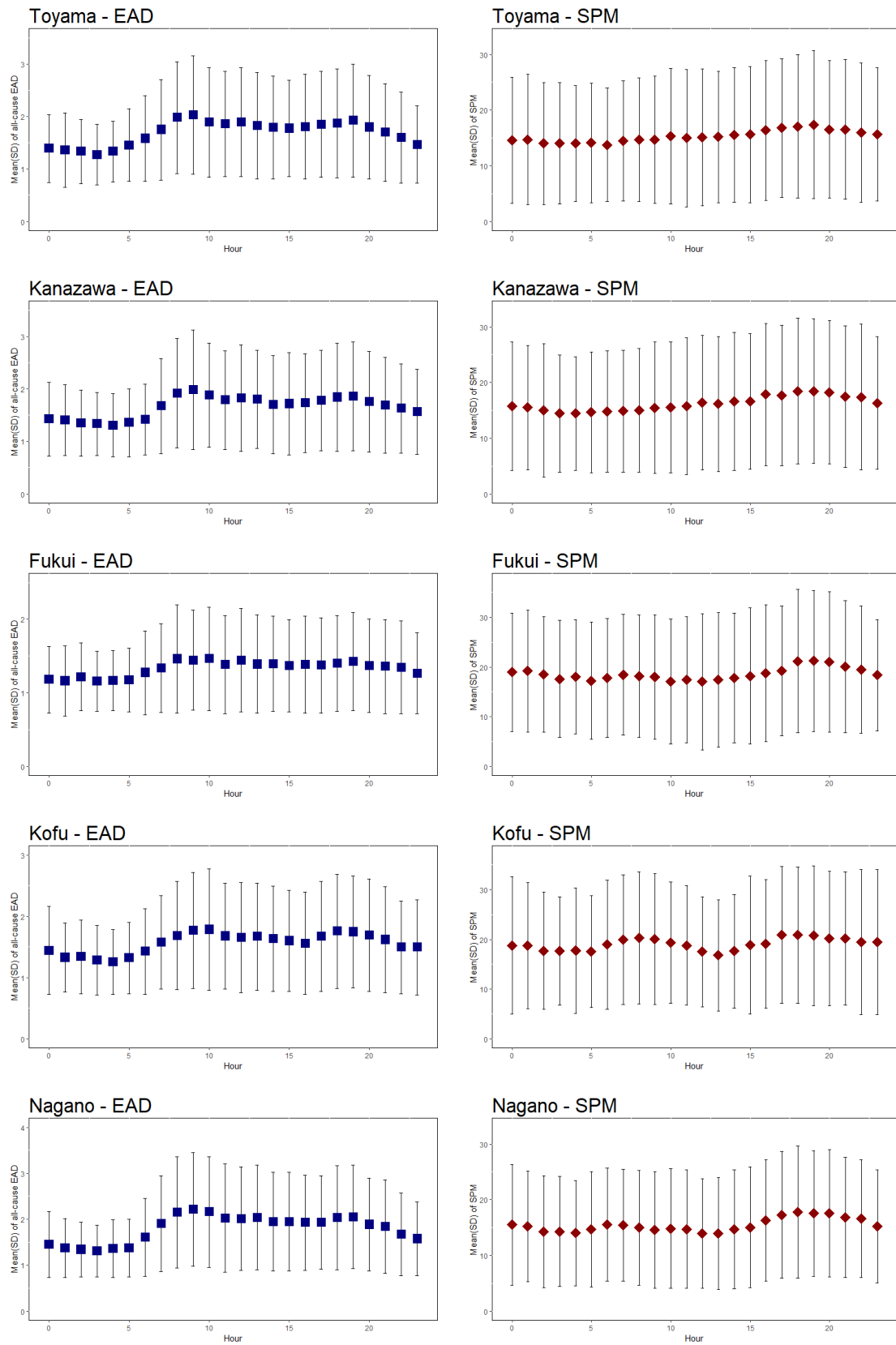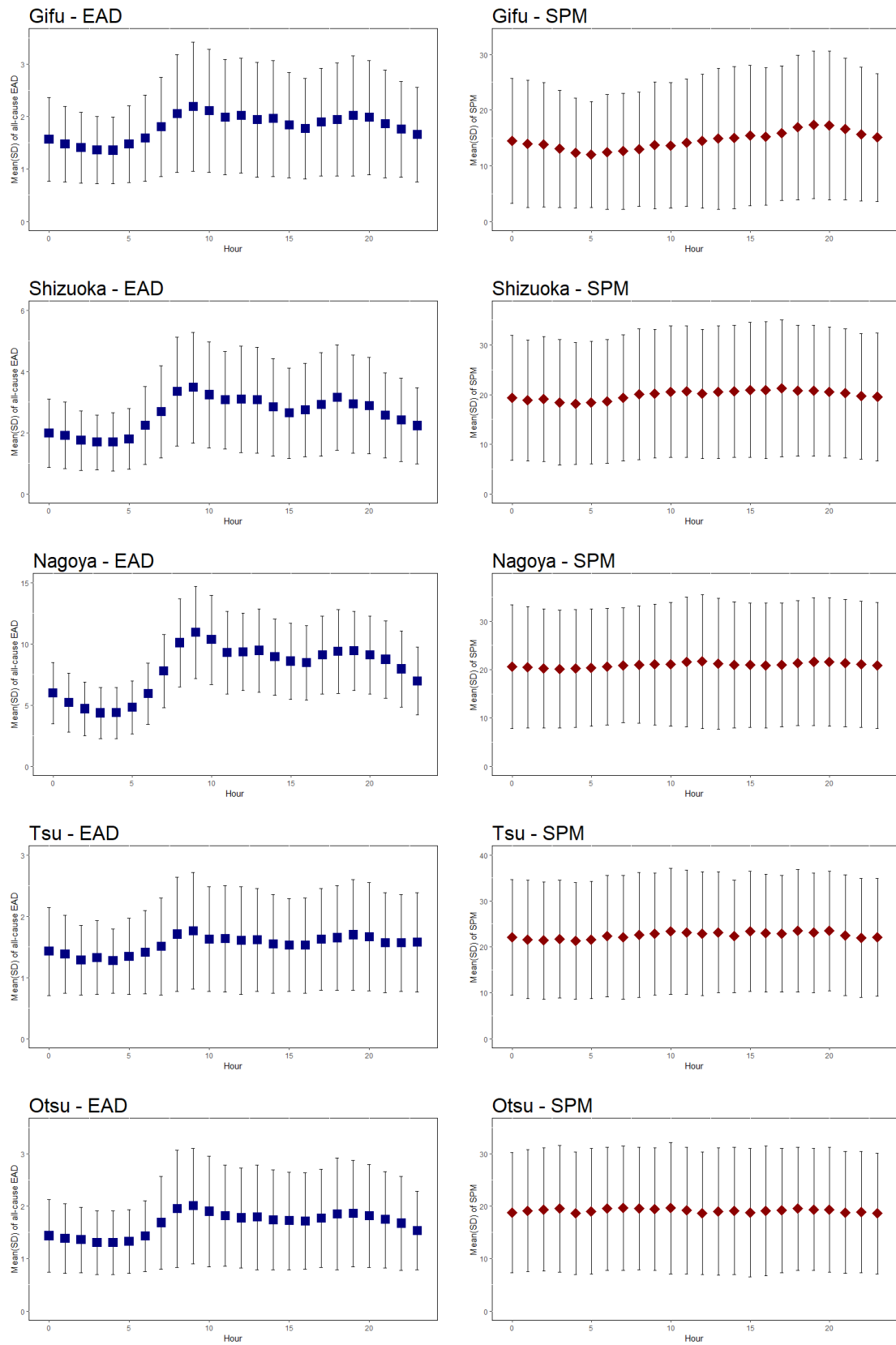
Akita - EAD

Akita - SPM

Yamagata - EAD

Yamagata - SPM

Fukushima - EAD

Fukushima - SPM

Mito - EAD

Mito - SPM

Tochigi - EAD

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Toyama - EAD

Toyama - SPM

Kanazawa - EAD

Kanazawa - SPM

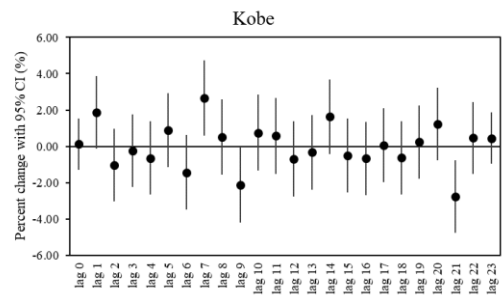Fukui - EAD

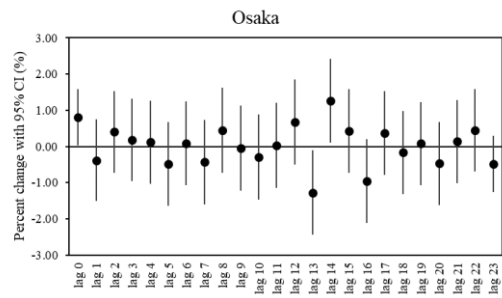Fukui - SPM

Kofu - EAD

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Nagano - EAD

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Saga - EAD

Saga - SPM

Nagasaki - EAD

Nagasaki - SPM

Kumamoto - EAD

Kumamoto - SPM

Oita - EAD

Oita - SPM

Miyazaki - EAD

Miyazaki - SPM
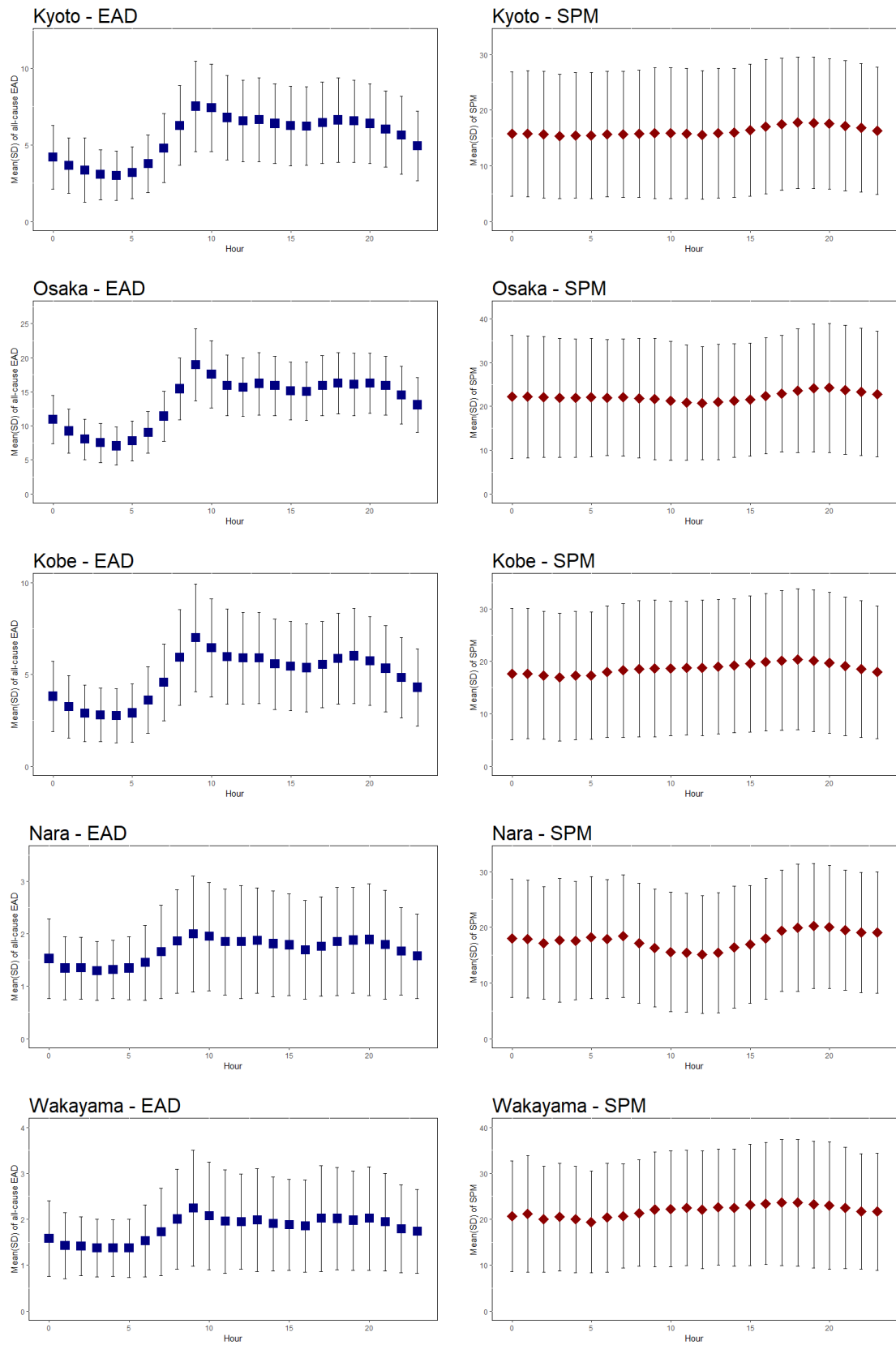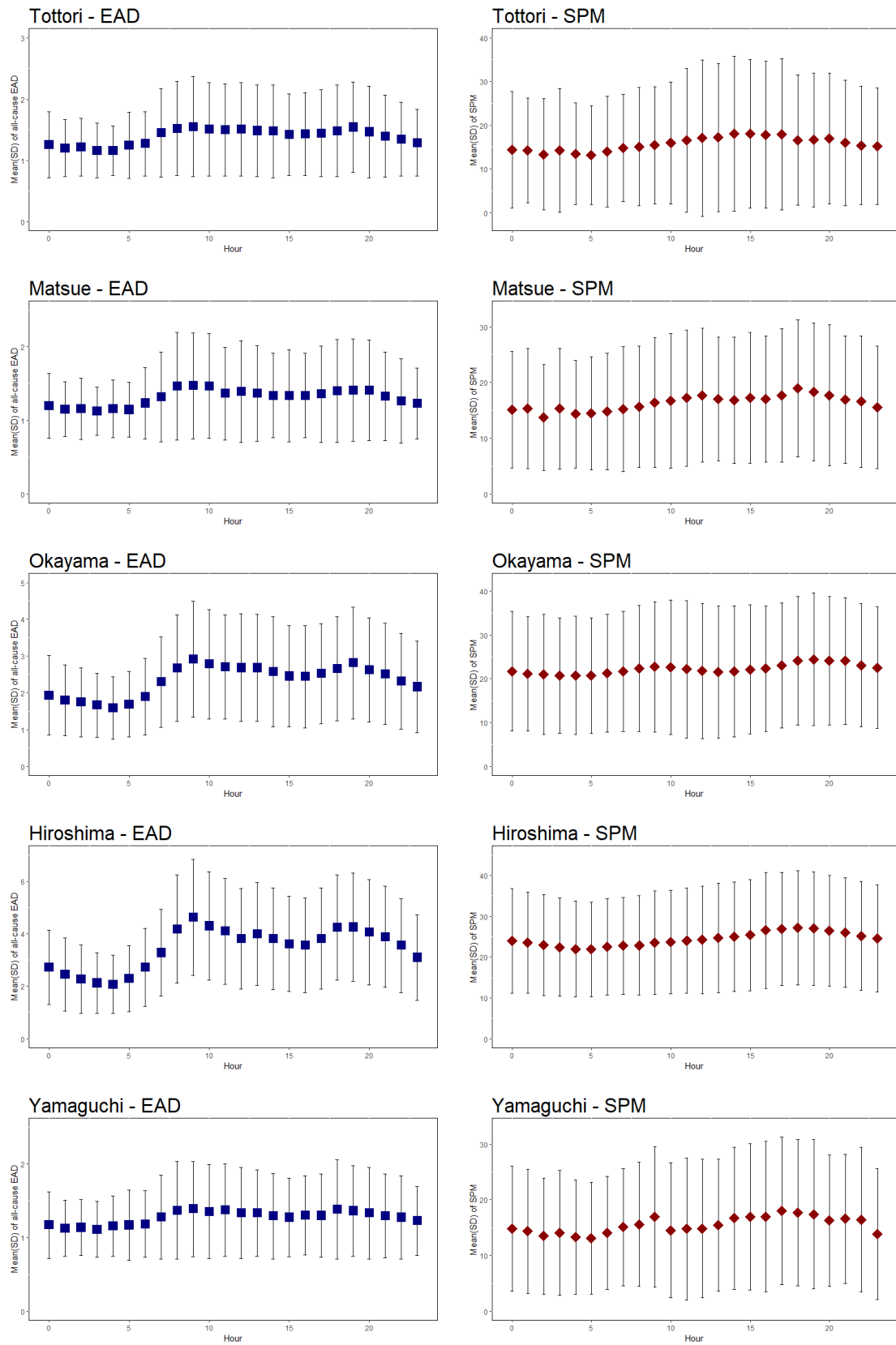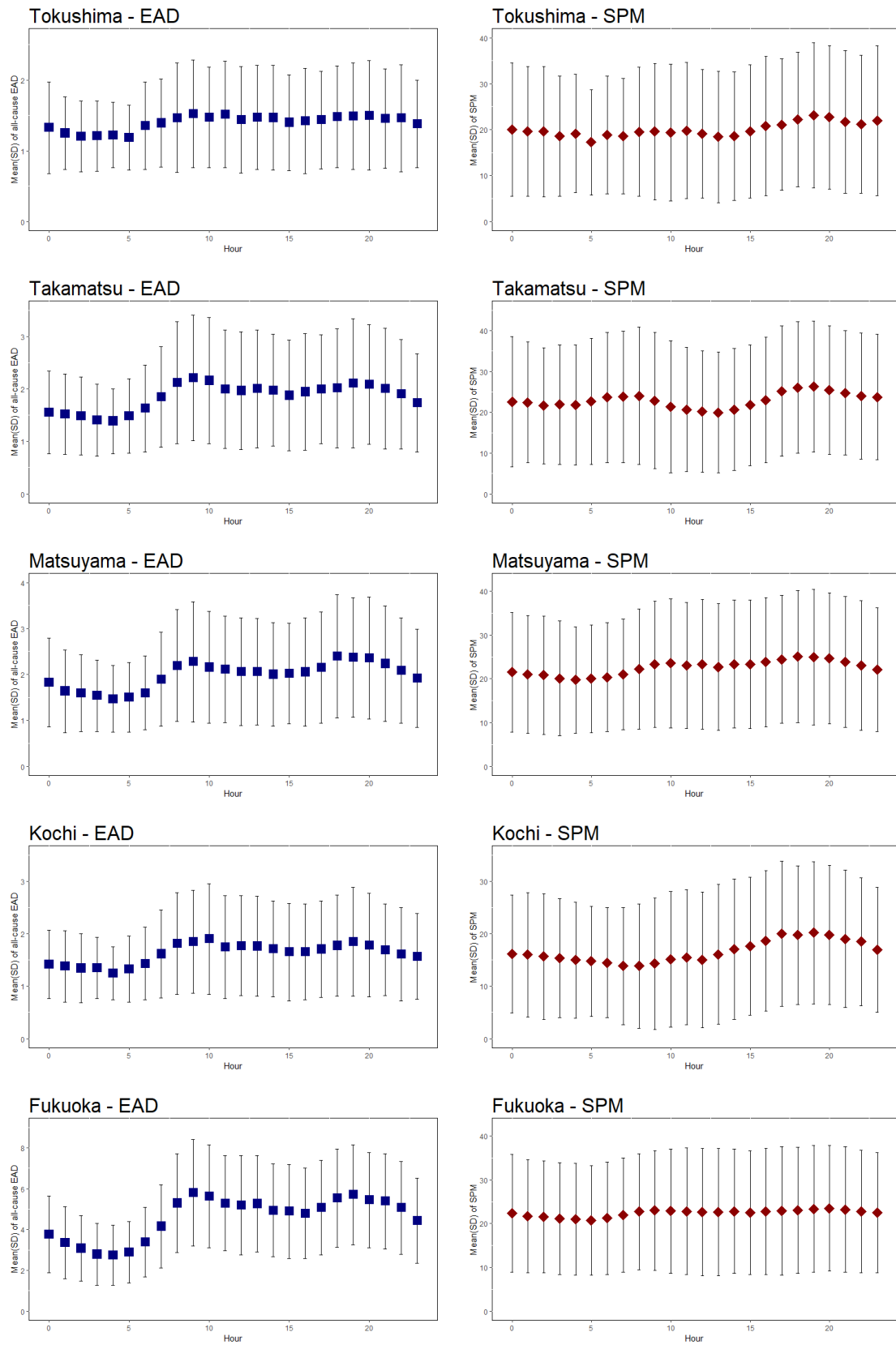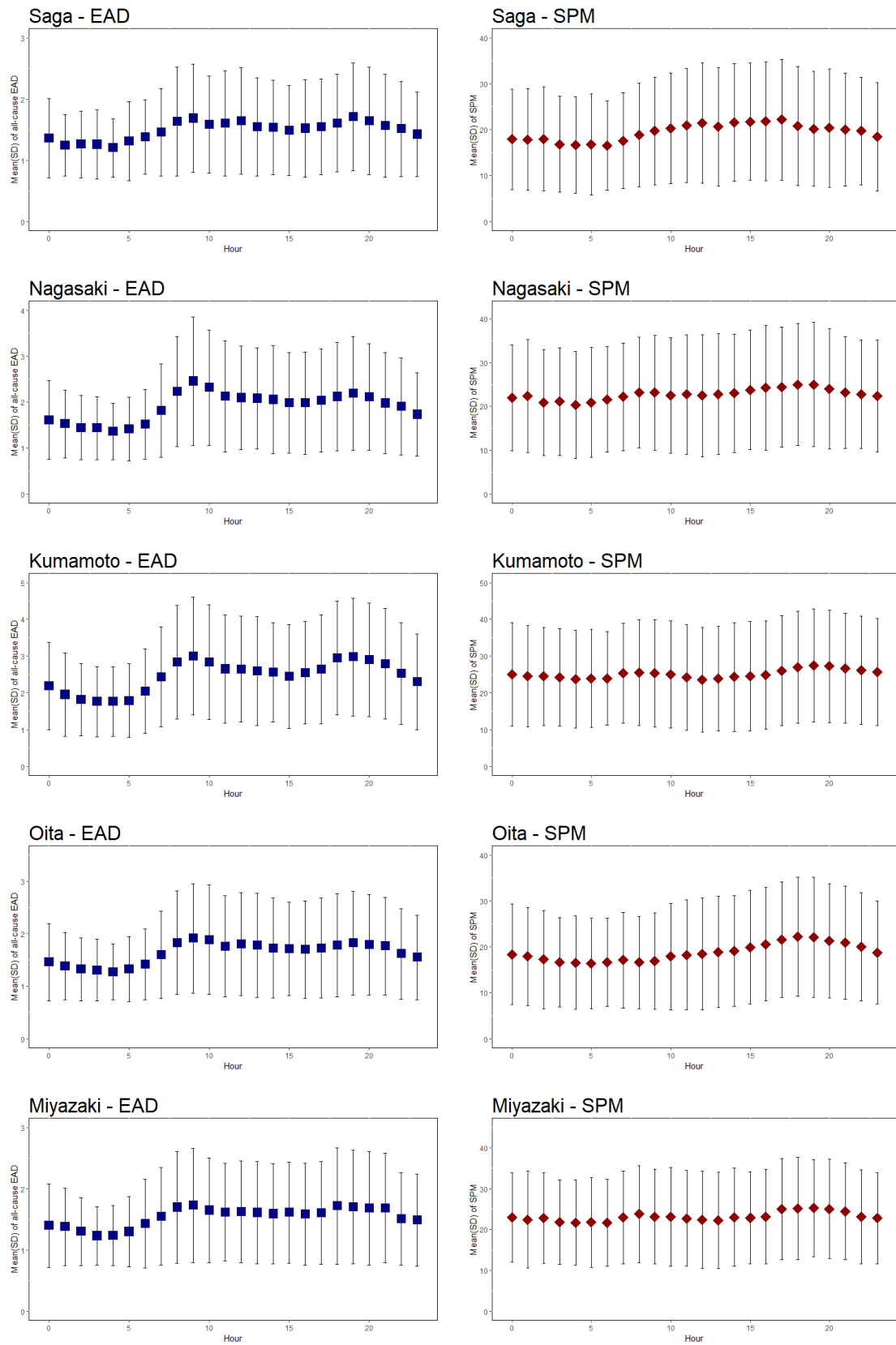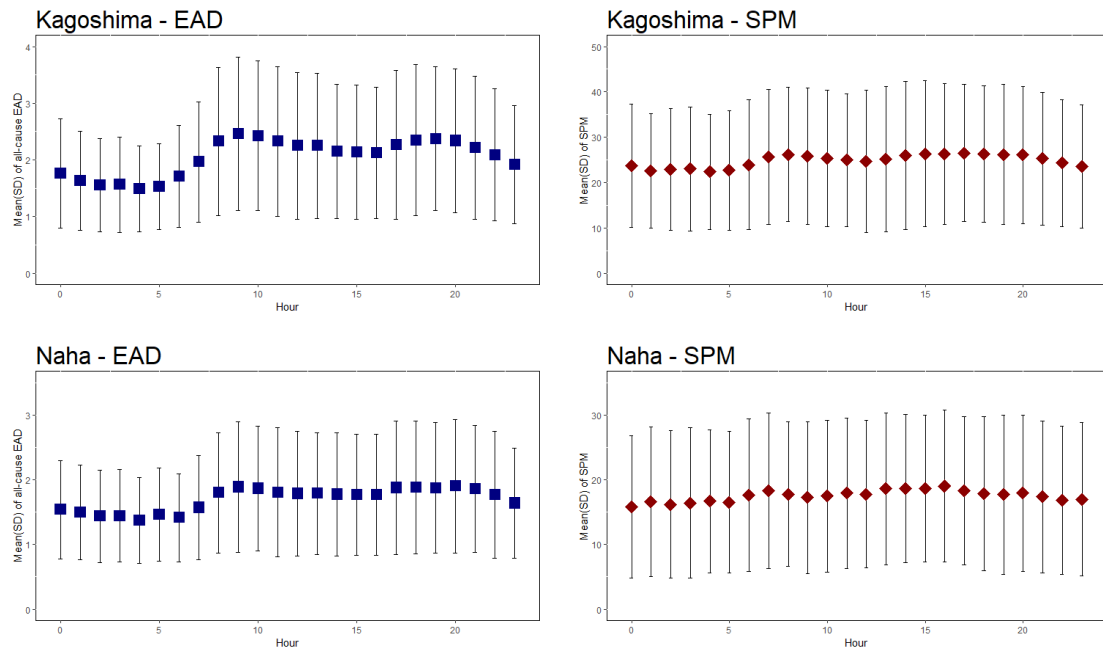
… (figure continued)

Figure A1. Hourly distribution (mean ± standard deviation (SD)) of all-cause EAD (left) and ambient SPM (right) for each city.

Appendix A2
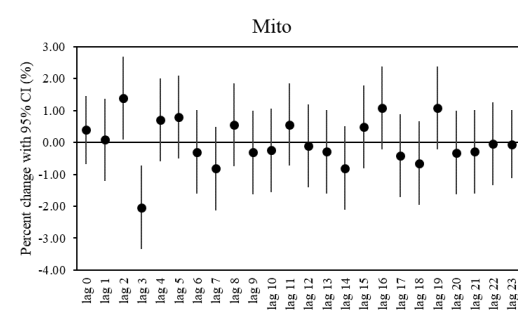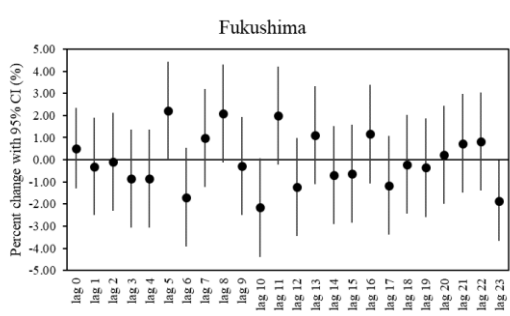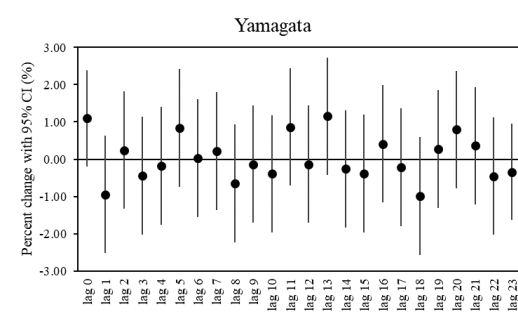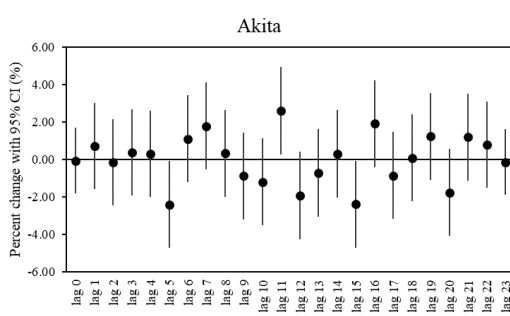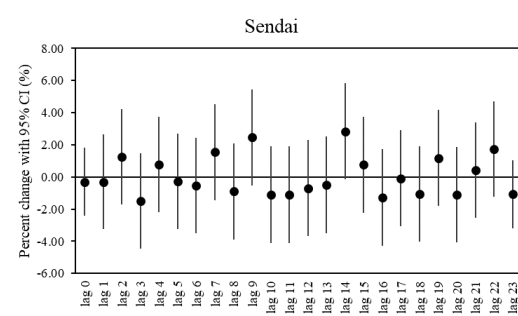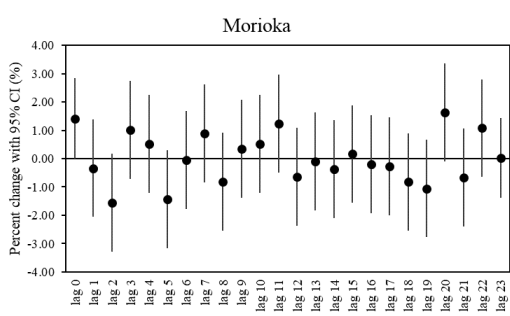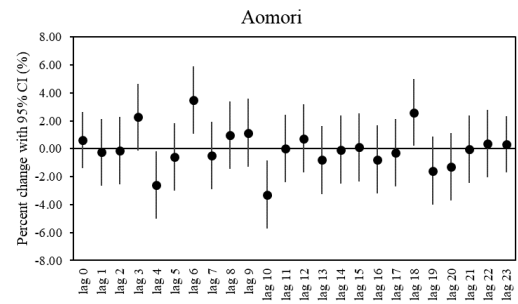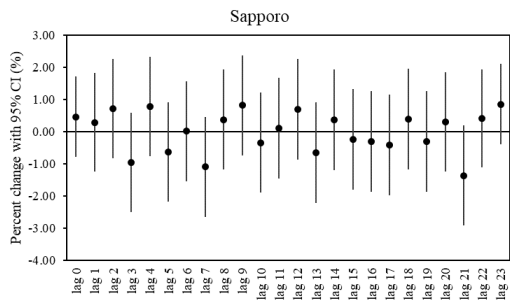
… (figure continued)

Tochigi

Maebashi

Saitama

Chiba

Yokohama

Niigata

Toyama

Kanazawa

… (figure continued)

Fukui

Kofu

Nagano

Gifu

Shizuoka

Nagoya

Tsu

Otsu

… (figure continued)

Kyoto

Osaka

Kobe

Nara

Wakayama

Tottori

Matsue

Okayama

… (figure continued)

Hiroshima

Yamaguchi

Tokushima

Takamatsu

Matsuyama

Kochi

Fukuoka

Saga
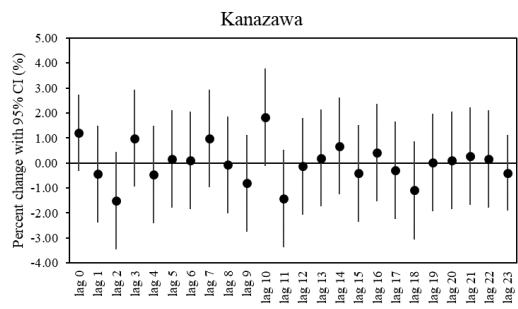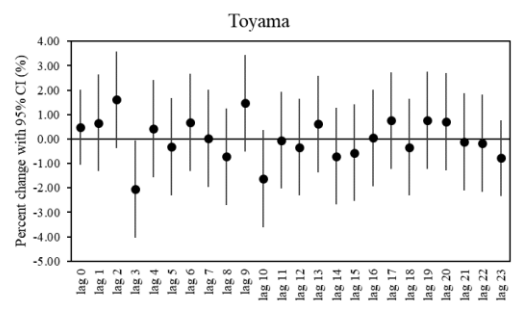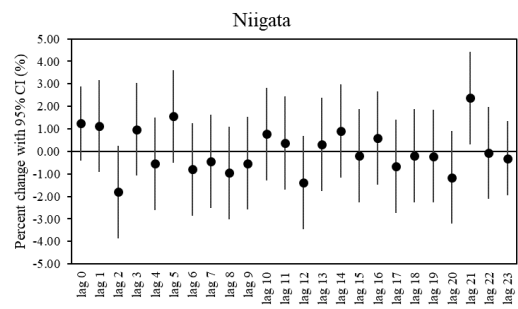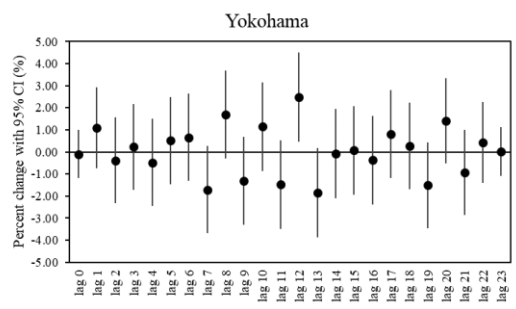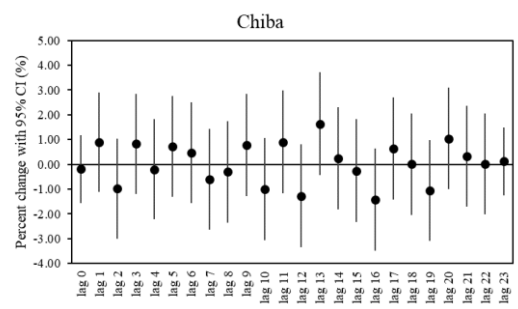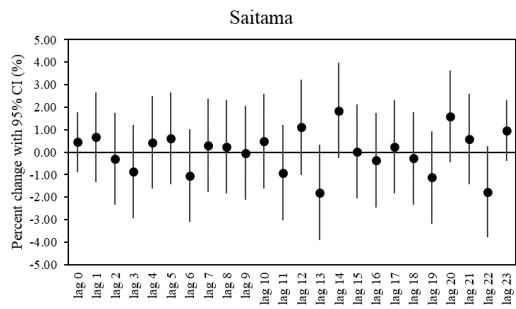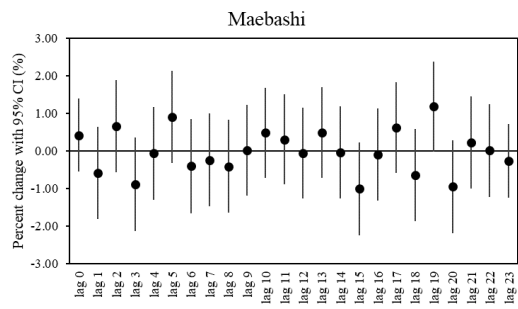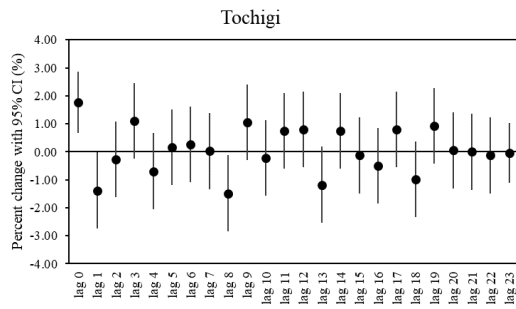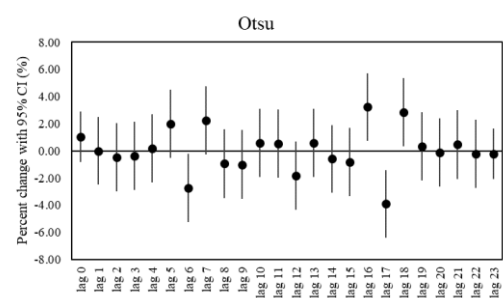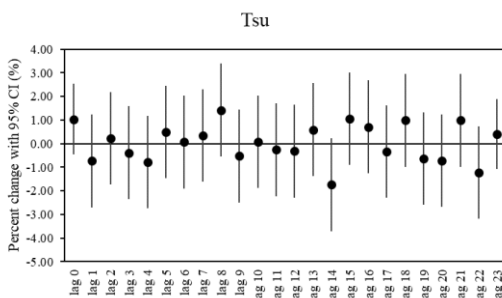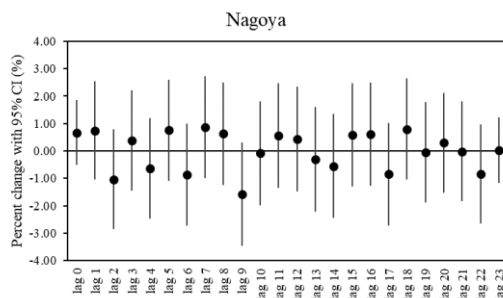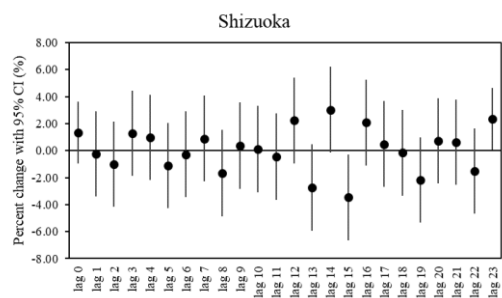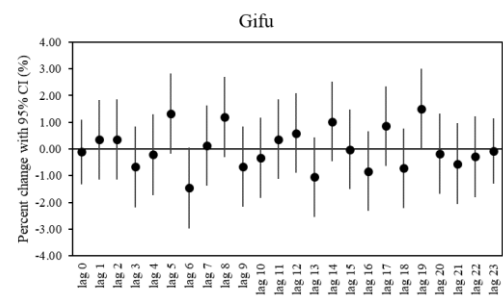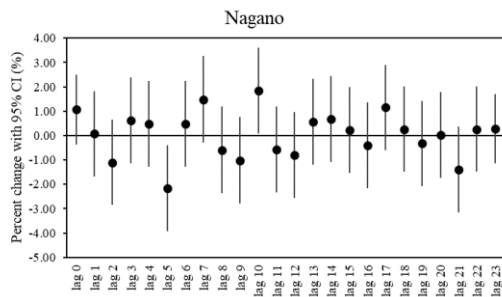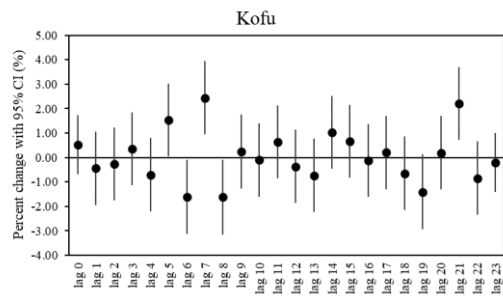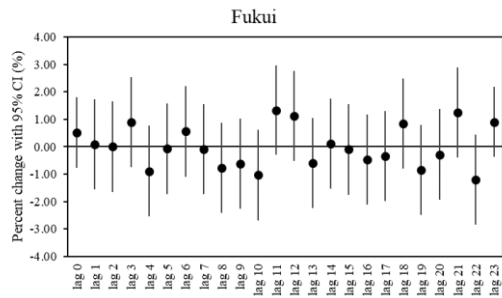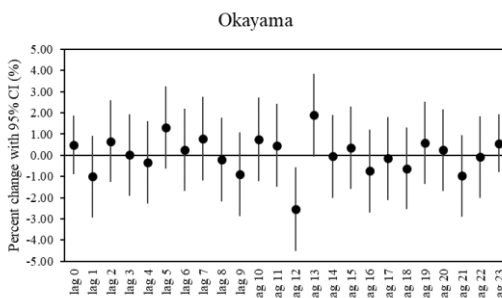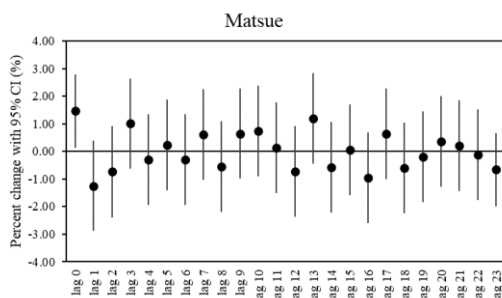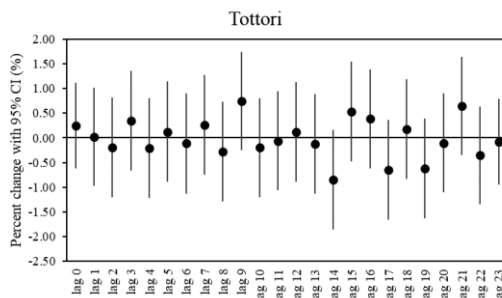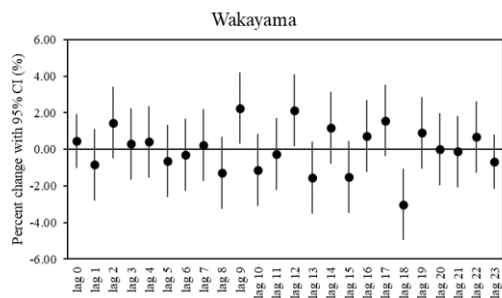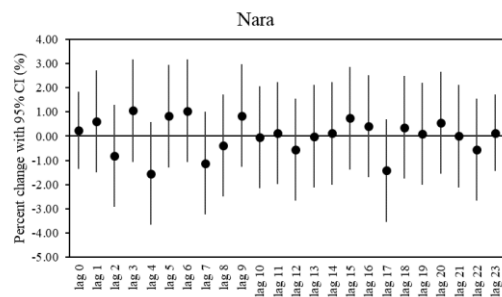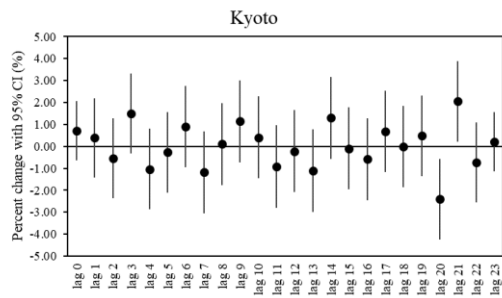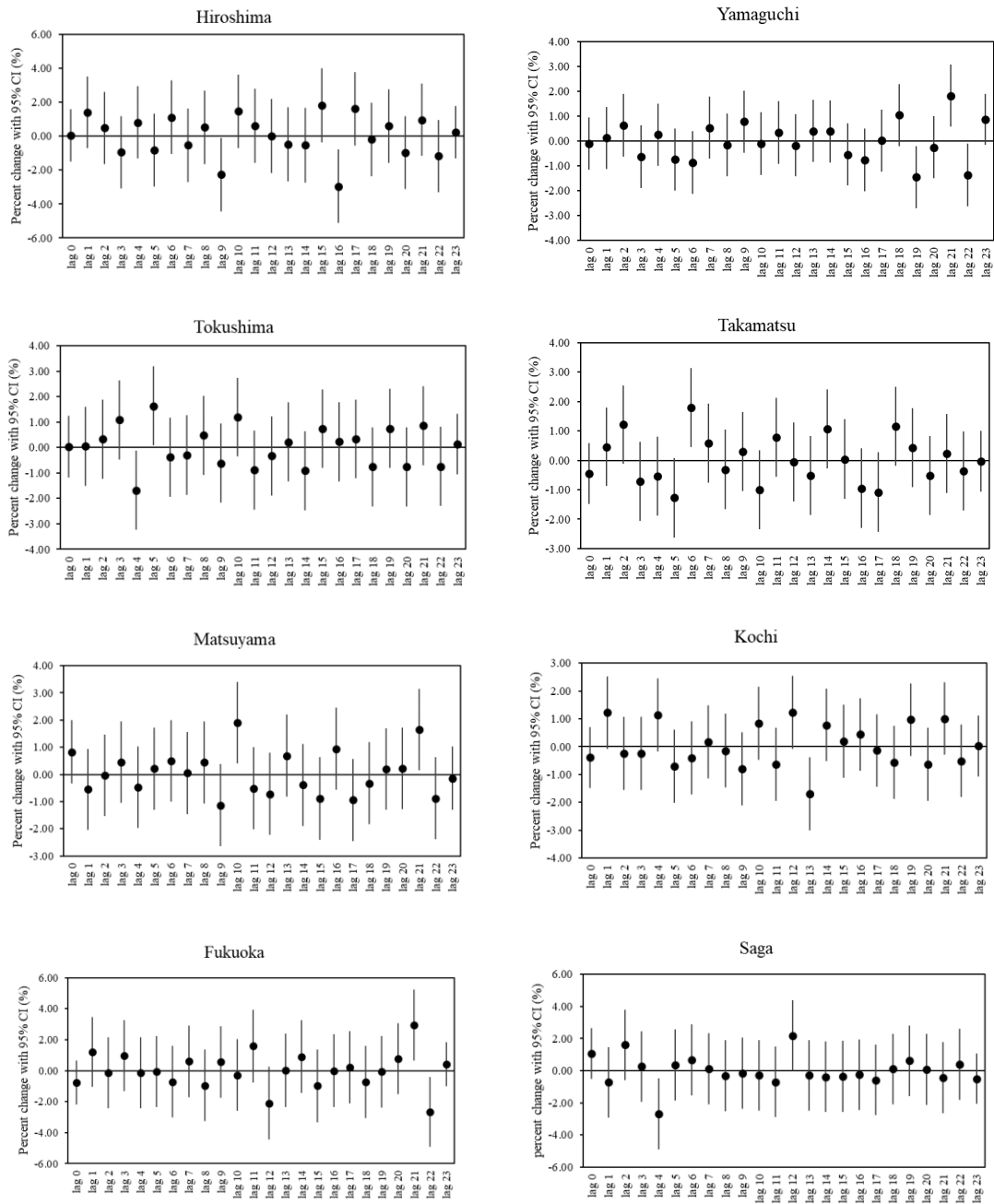
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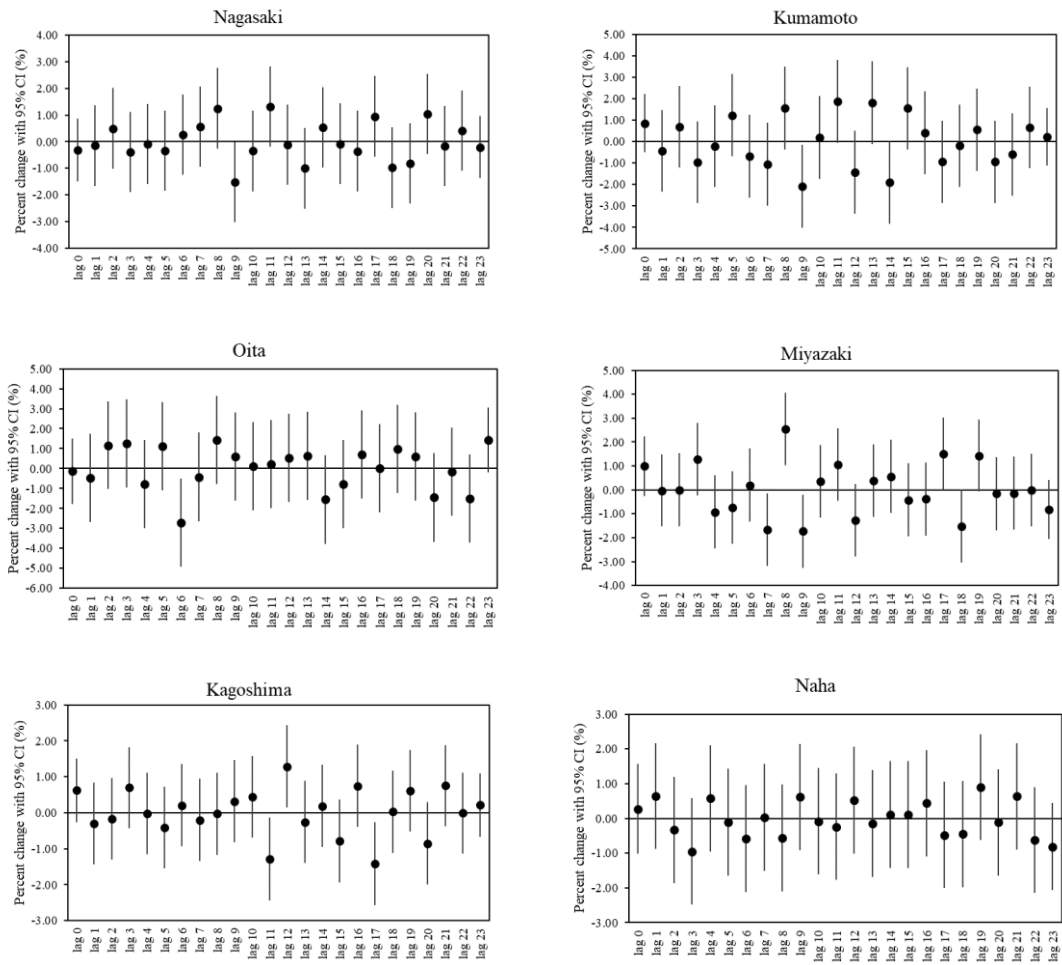

Figure A2. City-specific percent change of all-cause EAD associated with each 10 μg/m³ increase in ambient SPM (unconstrained distributed hour lag model).

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