Temperature as a modifier of the effects of fine particulate matter on acute mortality in Hong Kong

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Abstract (Word count: 148)

Interactions between particulate matter with aerodynamic diameter less than or equal to 2.5μm ($PM_{2.5}$) and temperature on mortality have not been well studied, and results are difficult to synthesize. We aimed to assess modification of temperature on the association between $PM_{2.5}$ and cause-specific mortality by stratifying temperature into low, medium, and high stratum in Hong Kong, using data from 1999 to 2011. The mortality effects of $PM_{2.5}$ were stronger in low temperature stratum than those in high. The excess risk (%) per 10μg/m^3 increase in $PM_{2.5}$ at lag 0-1 in low temperature stratum were 0.94% (95% confidence interval: 0.65, 1.24) for all natural, 0.88% (0.38, 1.37) for cardiovascular, and 1.15% (0.51, 1.79) for respiratory mortality. We found statistically significant interaction of $PM_{2.5}$ and temperature between low and high temperature stratum for all natural mortality. Our results suggested that temperature might modify mortality effects of $PM_{2.5}$ in Hong Kong.

Keyword: Interaction; Fine particulate matter; Temperature; Mortality; Hong Kong

Capsule:

Statistically significant interaction of $PM_{2.5}$ and temperature between low and high temperature stratum was found for all natural mortality in Hong Kong.

List of abbreviations and their full forms

Abbreviations	Full form
$PM_{2.5}$	Particulate matter with aerodynamic diameter less than or equal to 2.5μm
PM_{10}	Particulate matter with aerodynamic diameter less than or equal to 10μm
NO_2	Nitrogen dioxide
SO_2	Sulfur dioxide
O_3	Ozone
TMR	Temperature-mortality relationship
SEC	Socioeconomic status
COPD	Chronic obstructive pulmonary disease
ICD-9	Ninth revision of the international classification of diseases
ICD-10	Tenth revision of the international classification of diseases
CVD	Cardiovascular Disease
RD	Respiratory Disease
dow	Days of the week
WHO	World Health Organization
CI	Confidence interval
GAM	Generalized additive model
ER	Excess risk
dfs	Degrees of freedom
ns	Natural spline

List of Tables and Figures

1. Introduction

Numerous epidemiological studies around the world have found short-term associations between exposure to ambient particulate matter (PM) and mortality (Ostro et al., 2008; Pope III et al., 2002; Wong et al., 2002a). These findings are consistent with many multicity studies conducted in western (Katsouyanni et al., 1997; Samet et al., 2000) and eastern countries (Chen et al., 2013; Wong et al., 2008b). Recently, research interest has been focused on the potential role of modifiers for ambient PM on adverse health outcomes. Some studies have investigated the modification of meteorological conditions on PM-associated mortality such as season (Kan et al., 2008; Peng et al., 2005; Wong et al., 2002a), demographic characteristics such as sex (Cakmak et al., 2006), socioeconomic status (SES) (O'Neill et al., 2003; Wong et al., 2008a), and pre-existing health status such as chronic obstructive pulmonary disease (COPD) (Bateson and Schwartz, 2004). Exploring potential modifiers of PM effects can aid to understand the underlying mechanism of PM triggered diseases, benefit risk assessment (Bellinger, 2000), and direct public policy making.

Temperature is an important modifier for PM, which has a great impact on mortality. Multicity studies have provided clear and convincing evidence that exposure to both hot and cold temperature was associated with increased risks of morbidity and mortality (Curriero et al., 2002; Ma et al., 2014). The independent effect of temperature on mortality has been extensively reported (Anderson and Bell, 2009; Xu et al., 2013; Zhou et al., 2014), but only a few studies have examined the effects of temperature modification on PM-associated mortality. Most of these studies identified significant interaction between PM and temperature (P<0.05), with stronger health

effects of PM in high temperature days for all natural (Qian et al., 2008; Ren and Tong, 2006,), and cardiovascular mortality (Li et al., 2011). Cheng and Kan (2012) found significant interaction (P<0.05) with higher PM effects in low temperature days (<15th temperature percentile) for all natural and respiratory mortality. However, one multicity study conducted in Italy (Stafoggia et al., 2008) reported non-significant interaction (P >0.05). Therefore, the findings of PM-temperature interaction on mortality are not consistent.

In Hong Kong, air quality is deteriorating with pollutant levels and the associated health hazards are similar to or even greater than those in other developing cities in South Asia (Wong et al., 2008b; Wong et al., 2002b). In addition, in contrast to multicity studies which reported stronger health effects of PM_{10} in warm seasons (Spring and Summer) than those in cool seasons (Autumn and Winter) (Peng et al., 2005; Stieb et al., 2002), a study in Hong Kong showed higher health effects in cool seasons (October to March) than those in warm seasons (April to September) (Wong et al., 2002a). Season may be a good proxy for temperature, but it is not a reliable indicator to classify low and high temperature days. Owing to the increasing of global warming and urbanization, it may induce misclassification.

Thus far no study has assessed the interaction between PM and temperature in Hong Kong for cause-specific mortality. So we aimed to evaluate the effect modification of temperature on mortality effects of fine particulate matter ($PM_{2.5}$). We first identified temperature cut-offs based on temperature-mortality relationships (TMRs) for cause-specific mortality to classify temperature into low, medium and high three strata, and then determined the extent to which the effects of $PM_{2.5}$ on mortality were

modified by these temperature strata.

2. Materials and methods

2.1. Mortality data

Daily mortality data from 1999 to 2011 were collected from the Hong Kong Census and Statistics Department. Cause-specific mortality was coded according to the International Classification of Diseases (ICD) by the Department of Health, 9th revision (ICD-9) before 2001 and 10th revision (ICD-10) from 2001. In our study, mortality for all natural cause was coded as ICD-9:1-799 or ICD-10:A00-R99; cardiovascular disease (CVD) as ICD-9:390-459 or ICD-10:I00-I99; respiratory disease (RD) as ICD-9: 460-519 or ICD-10: J00-J98. The agreement between these two mortality ICD coding systems was over 90% in Hong Kong (Hong Kong Department of Health, 2005).

2.2. Pollutant and meteorological data

Daily 24-hour average concentration of air pollutants, including particulate matter with aerodynamic diameter less than or equal to 2.5μm ($PM_{2.5}$), particulate matter with aerodynamic diameter less than or equal to 10μm (PM_{10}), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2), and daily 8 hour (10:00-18:00 hours) average concentration of ozone (O_3) were collected by the Environmental Protection Department of Hong Kong from ten general monitoring stations, including Central and Western, Eastern, Kwai Chung, Kwun Tong, Sha Tin, Sham Shui Po, Tai Po, Tung Chung, Tsuen Wan, and Yuen Long. The ten monitoring stations are all general stations situated at an average of 20m above ground level. Data were regarded as missing if numbers of hourly concentration for one particular day were less than 75% (18 hours for $PM_{2.5}$,

76 PM_{10}, NO_2, SO_2, and 6 hours for O_3). For meteorological data, we extracted daily mean temperature in Celsius and relative humidity in percentage from the Hong Kong
78 Observatory.

80 *2.3. Statistical methods and data analysis*

2.3.1. Identifying temperature cut-offs

82 Two main steps were adopted in sequence to identify temperature cut-offs.

Step 1: identifying the best lag day of temperature

84 First, we built a core model for cause-specific mortality using quasi-Poisson generalized additive modeling (GAM). In the core model, we included dummy
86 variable for the day of the week (dow), a natural smoothing spline for time trend and relative humidity with four degrees of freedom, and daily admission numbers of
88 hospitalization due to influenza. The core model is shown as follows:

90
$$Log[E(Y_t \mid X)] = \mu + ns(time, df) + ns(relative\ humidity_t, df = 4) + dow_t + Influenza_t, \quad t = 1,\ldots n, \tag{1}$$

92 where t refers to the day of study; $E(Y_t \mid X)$ denotes expected daily death on day t; μ is the mean number of deaths; $ns(\bullet)$ denotes natural smoothing spline function; *df*
94 denotes degree of freedom; *dow* denotes day of the week; *Influenza* denotes daily admission numbers of hospitalization due to influenza; *n* denotes number of days.

96

We used the partial autocorrelation function (PACF) to guide the selection of degrees
98 of freedom (dfs). Specifically, we used 3 to 10 dfs per year for time trend for each disease category (all natural, cardiovascular, and respiratory mortality). We regarded

time trend was adequately controlled for if the absolute values of PACF coefficients were <0.1 for the first 2 lag days and no systematic patterns in the PACF plots were observed (Wong et al., 2008a). The PACF plots are shown in Supplementary Material.

Following selection of dfs for time trend for each disease category, we selected the best lag day to identify cool and warm temperature cut-offs. We adopted similar approach to a previous study of our group (Xu et al., 2013). Temperatures with log relative risk equal to zero in temperature-mortality relationship (TMR) would be selected as cut-offs. We used the average temperature of current and previous day (lag 0-1) to identify warm temperature cut-off. After including a smoothing temperature term with different lag days by natural spline function with four dfs in the core model, we selected the best lag day for cool temperature cut-off using the minimum generalized cross-validation (GCV). We found 14 lag days within two weeks before the day of death, including single lag days from lag 0, lag 1, lag 2, lag 3, lag 4, lag 5, and lag 6 and average lag days from lag 0-1, lag 0-2, lag 0-3, lag 0-4, lag 0-5, and lag 0-6, and lag 7-13.

Step 2: Classifying temperature strata

Temperatures below the cool temperature cut-off were defined as low temperature stratum, temperatures above the warm temperature cut-off were defined as high temperature stratum, and temperatures between cool and warm cut-offs were defined as medium temperature stratum.

2.3.2. Temperature-stratified generalized additive model (GAM)

We categorized temperature into three strata: low, medium and high using cool and warm temperature cut-offs. The model of GAM to estimate mortality effects of $PM_{2.5}$ in temperature strata is formulated as follows (Roberts, 2004):

$$Log[E(Y_t \mid X)] = \mu + ns(time, df) + ns(temperature_t, df = 4) + ns(relative\ humidity_t, df = 4) + dow_t + Influenza_t + \sum_{k=1}^{3} \beta_k PM_{2.5} T_{tk}, \quad t = 1, \ldots n, \tag{2}$$

where T_{t1}, T_{t2}, and T_{t3} are temperature stratum indicator variables corresponding to low, medium, and high temperature strata, respectively; β_1, β_2, and β_3 are effects of $PM_{2.5}$ on mortality in the corresponding temperature stratum. We used 2-day (lag 0-1) average concentration of $PM_{2.5}$ because the average of 2 days' pollution correlates better with mortality than a single day's exposure (data not shown).

2.3.3. Temperature modified $PM_{2.5}$ on mortality

We tested for the statistical significance of differences between effect estimates of temperature strata (eg, the effect of $PM_{2.5}$ on high temperature vs low temperature stratum) by calculating the 95% confidence interval (CI) as

$$(\widehat{\beta_1} - \widehat{\beta_3}) \pm 1.96\sqrt{Var(\widehat{\beta_1}) + Var(\widehat{\beta_3}) - 2Cov(\widehat{\beta_1}, \widehat{\beta_3})} \tag{3}$$

where $\widehat{\beta}_1$ and $\widehat{\beta}_3$ are effects of $PM_{2.5}$ on mortality in low and high temperature stratum respectively, $Var(\widehat{\beta_1})$ and $Var(\widehat{\beta_3})$ are their respective variances, and $Cov(\widehat{\beta_1}, \widehat{\beta_3})$ is the covariance between $\widehat{\beta}_1$ and $\widehat{\beta}_3$ (Schenker and Gentleman, 2001).

We examined two-pollutant model by adjustment for each of the three air pollutants NO_2, SO_2, and O_3 in turn in 2-day average (lag 0-1) to check whether interactions

between $PM_{2.5}$ and temperature were robust.

2.3.4. Trend of temperature modification on $PM_{2.5}$

TMR can identify reliable cut-offs to classify temperature for each disease category. But in order to fully understand the trend and sensitivity of the effect modification of temperature on $PM_{2.5}$ for cause-specific mortality, we used a range of temperature percentiles as cut-offs. We increased the cool temperature cut-off from 5^{th} to 50^{th}, and warm temperature cut-off from 50^{th} to 95^{th} by 5-percentile increment, respectively. We then estimated health effects of $PM_{2.5}$ in both low and high temperature strata for each disease category.

All calculations were performed with R software (version 3.1.0) with 'mgcv' to fit GAM model. Our results were presented as excess risk in percent per $10\mu g/m^3$ increase of $PM_{2.5}$ concentration.

3. Results

3.1. Summary statistics of data

There was a total of 4,748 days from Jan 1, 1999 to Dec 31, 2011, with 456,317 deaths from all natural causes, of which cardiovascular disease accounted for 27.4%, and respiratory disease accounted for 19.4%. Table 1 shows the basic characteristics of cause of mortality, air pollutants, and meteorological conditions. On average, 96 all natural mortalities died per day in our study period, of which cardiovascular and respiratory accounted for 26 and 19 deaths, respectively. During the study period, the 24-hr mean values in $\mu g/m^3$ were $PM_{2.5}$: 36.9; PM_{10}: 52.1; NO_2: 57.3; SO_2: 18.7; and O_3: 44.9. The range of temperature varied from 8.2 ^oC to 31.8 ^oC with mean

temperature 27.1 ^{o}C in warm season (April to September) and 19.8 ^{o}C in cool season (October to March). Relative humidity (%) was relatively high, with mean value 77.8%. Daily all natural mortality counts, $PM_{2.5}$ concentration levels and temperature exhibited marked seasonal patterns with higher mortality counts and air pollution levels in cool seasons, than that in warm seasons (Figure 1). Daily cardiovascular and respiratory mortality counts and air pollutants (NO_2, SO_2 and O_3) are shown in Supplementary Material.

Table 1. Summary statistics for cause-specific mortality, air pollutants and meteorological conditions in Hong Kong, 1999 to 2011.

	Mean	SD	Percentile				
			Min	25th	50th	75th	Max
Cause of mortality (per day)							
All natural	96.1	16.4	49.0	85.0	95.0	106.0	168.0
Cardiovascular	26.4	6.8	6.0	22.0	26.0	31.0	56.0
Respiratory	18.7	6.3	3.0	14.0	18.0	22.0	52.0
Pollutant concentration ($\mu g/m^3$)							
$PM_{2.5}$	36.9	21.7	5.4	19.4	32.7	49.3	179.7
PM_{10}	52.1	28.3	7.9	30.0	47.2	68.8	573.0
NO_2	57.3	20.5	9.8	42.4	55.0	68.8	166.6
SO_2	18.7	12.6	3.0	10.6	15.7	22.7	135.2
O_3	44.9	27.5	3.6	23.2	38.6	60.9	196.0
Meteorological conditions							
Temperatures (^{o}C)	23.5	5.0	8.2	19.5	24.7	27.8	31.8
Relative humidity (%)	77.8	10.3	27.5	73.0	79.0	84.5	98.1

Abbreviations: SD: standard deviation; Min: minimum; 25th: 25th percentile; Max: maximum; $PM_{2.5}$: particulate matter with an aerodynamic diameter less than or equal to 2.5μm; PM_{10}: particulate matter with an aerodynamic diameter less than or equal to 10μm; NO_2: nitrogen dioxide; SO_2: sulfur dioxide; O_3: ozone.

186 **Figure 1. Daily observed all natural mortality, daily mean $PM_{2.5}$ concentration and daily mean temperature in Hong Kong, 1999 to 2011.**

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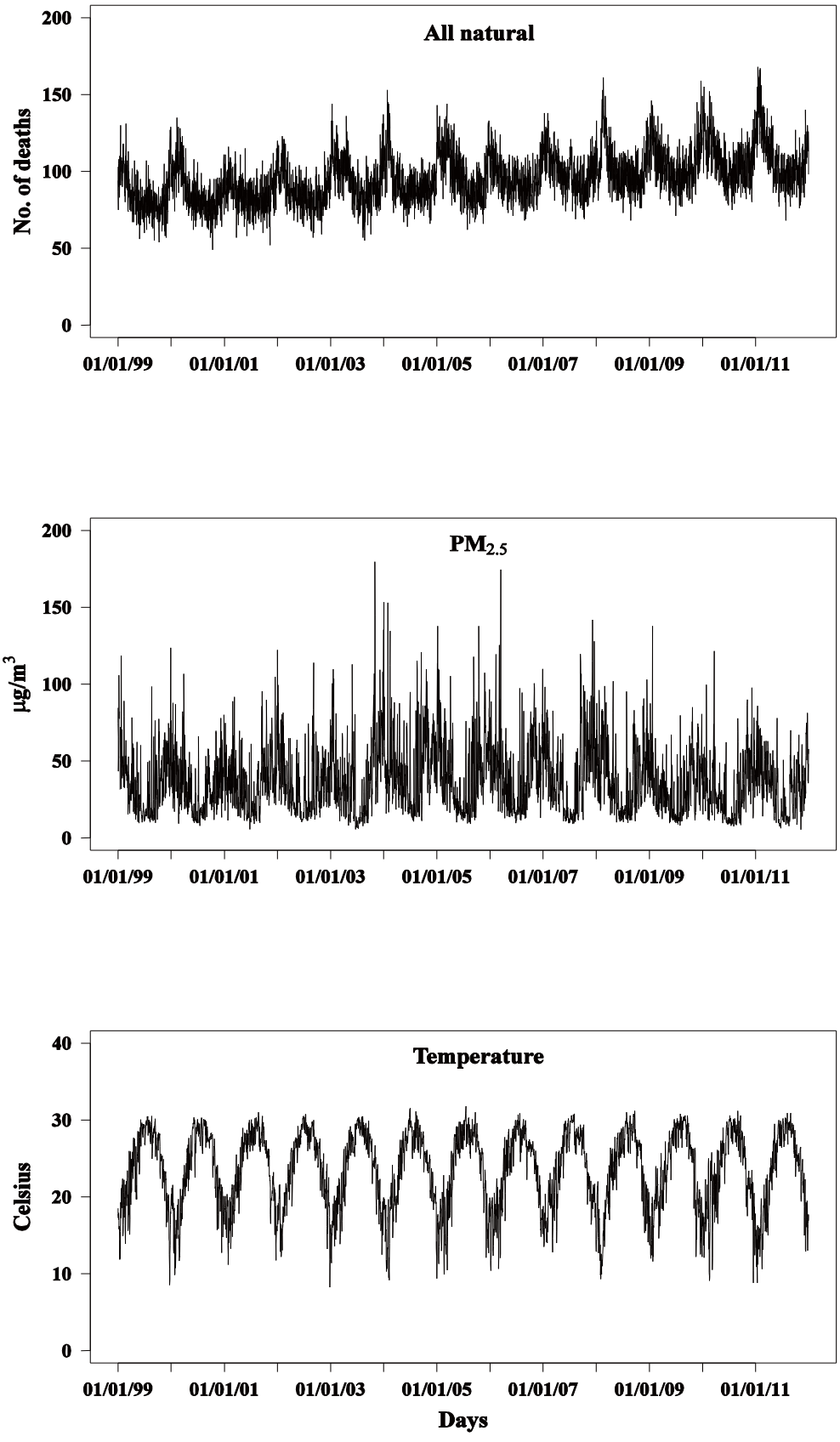


3.2. Spearman correlations

190 The Spearman correlation coefficients between air pollutants and meteorological conditions are reported in Table 2. The correlation coefficients between $PM_{2.5}$ and
192 other pollutants (PM_{10}, NO_2, SO_2 and O_3) were all high and positive, in particular the Spearman correlation between $PM_{2.5}$ and NO_2 (r >0.8). Temperature was negatively
194 correlated with $PM_{2.5}$, PM_{10}, NO_2, and O_3, but positively correlated with SO_2.

196 **Table 2. Spearman correlation coefficients between air pollutants and meteorological conditions in Hong Kong, 1999 to 2011.**
198

Variable	PM_{10}	NO_2	SO_2	O_3	Temperature	Humidity
$PM_{2.5}$	0.96	0.82	0.37	0.59	-0.48	-0.46
PM_{10}		0.79	0.35	0.61	-0.47	-0.50
NO_2			0.44	0.46	-0.48	-0.35
SO_2				0.01	0.08	-0.28
O_3					-0.08	-0.60
Temperature						0.14

200

3.3. Temperature cut-offs

202 For each disease category, we fitted the core model using PACF to guide the selection of degrees of freedom for time trend, and used minimum GCV to select the best lag
204 day for cool and warm temperature.

206 For all natural mortality, natural spline function for smoothing time trend with seven dfs per year was adequately controlled for long-term trend and seasonality, and
208 temperature at lag 0-6 was selected to identify cool temperature cut-off, temperature at lag 0-1 was selected to identify warm temperature cut-off; for cardiovascular
210 mortality, five dfs per year to control for long-term trend and seasonality, and temperature at lag 0-6 to identify cool temperature cut-off, temperature at lag 0-1 to
212 identify warm temperature cut-off; for respiratory mortality, six dfs per year to control

for long-term and seasonality, and temperature at lag 7-13 to identify cool temperature
214 cut-off, temperature at lag 0-1 to identify warm temperature cut-off.

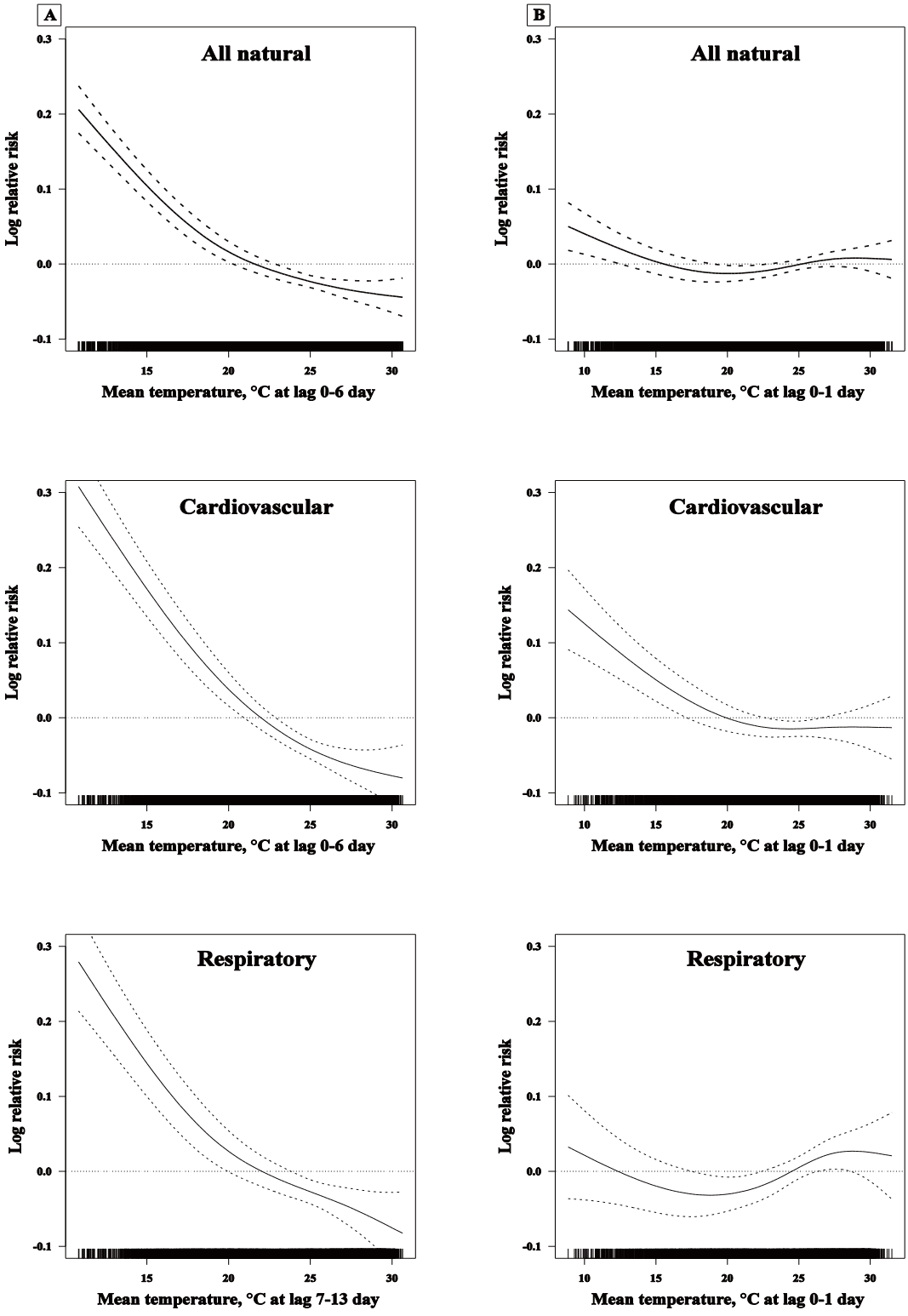
216 Figure 2 shows TMRs for cause-specific mortality. For TMRs to identify cool temperature cut-off, a reversed J-shape relationships between temperature and all
218 natural, cardiovascular, and respiratory mortality were all observed, with cool temperature cut-offs were 22 ^{o}C for these three disease categories. For TMRs to
220 identify warm temperature cut-off, we found a U-shape relationships between temperature and all natural and respiratory, but not for cardiovascular mortality. We
222 found warm temperature cut-offs at 25 ^{o}C for both all natural and respiratory mortality.

224

3.4. Temperature–stratified GAM and temperature modification on $PM_{2.5}$

226 Based on the identified temperature cut-offs, we stratified temperature into three strata: low, medium and high, and then used GAM to estimate the health effects of $PM_{2.5}$ for
228 these three temperature strata. In general, stronger mortality effects were found in low temperature stratum, followed by medium, and then high. For example, the estimated
230 excess risk (%) of $PM_{2.5}$ per 10 $\mu g/m^3$ increase for all natural mortality were 0.94% (95% confidence interval: 0.65, 1.24) in low temperature stratum, 0.90% (0.56, 1.26)
232 in medium, and 0.47% (0.18, 0.76) in high.

Figure 2. Temperature-mortality relationships of (A) Low temperature and (B) High temperature for all natural, cardiovascular, and respiratory mortality in Hong Kong, 1999 to 2011. Lag 0-1: average temperatures of current and lag 1 day; lag 0-6: average temperatures from current to lag 6 day; lag 7-13: average temperatures from lag 7 to lag 13. The density of the vertical bars on the x-axis shows the distribution of the temperature in Celsius.



Statistical significance differences (P<0.05) between low and high temperature strata were observed for all natural mortality, but not for cardiovascular and respiratory mortality. Table 3 shows the mortality effects of $PM_{2.5}$ in three temperature strata with and without adjustment for co-pollutant. Patterns of magnitude in change of mortality effects of $PM_{2.5}$ after adjustment for a co-pollutant (NO_2, SO_2 or O_3) were the same for all these three temperature strata, for which mortality effects of $PM_{2.5}$ showed little changes after adjustment for SO_2 or O_3, however, reduced markedly for all natural, cardiovascular, and respiratory mortality after adjusting for NO_2. Adjustment for a co-pollutant did not alter the overall conclusions about interaction between $PM_{2.5}$ and temperature for each disease category.

3.5. Trend of temperature modification on $PM_{2.5}$

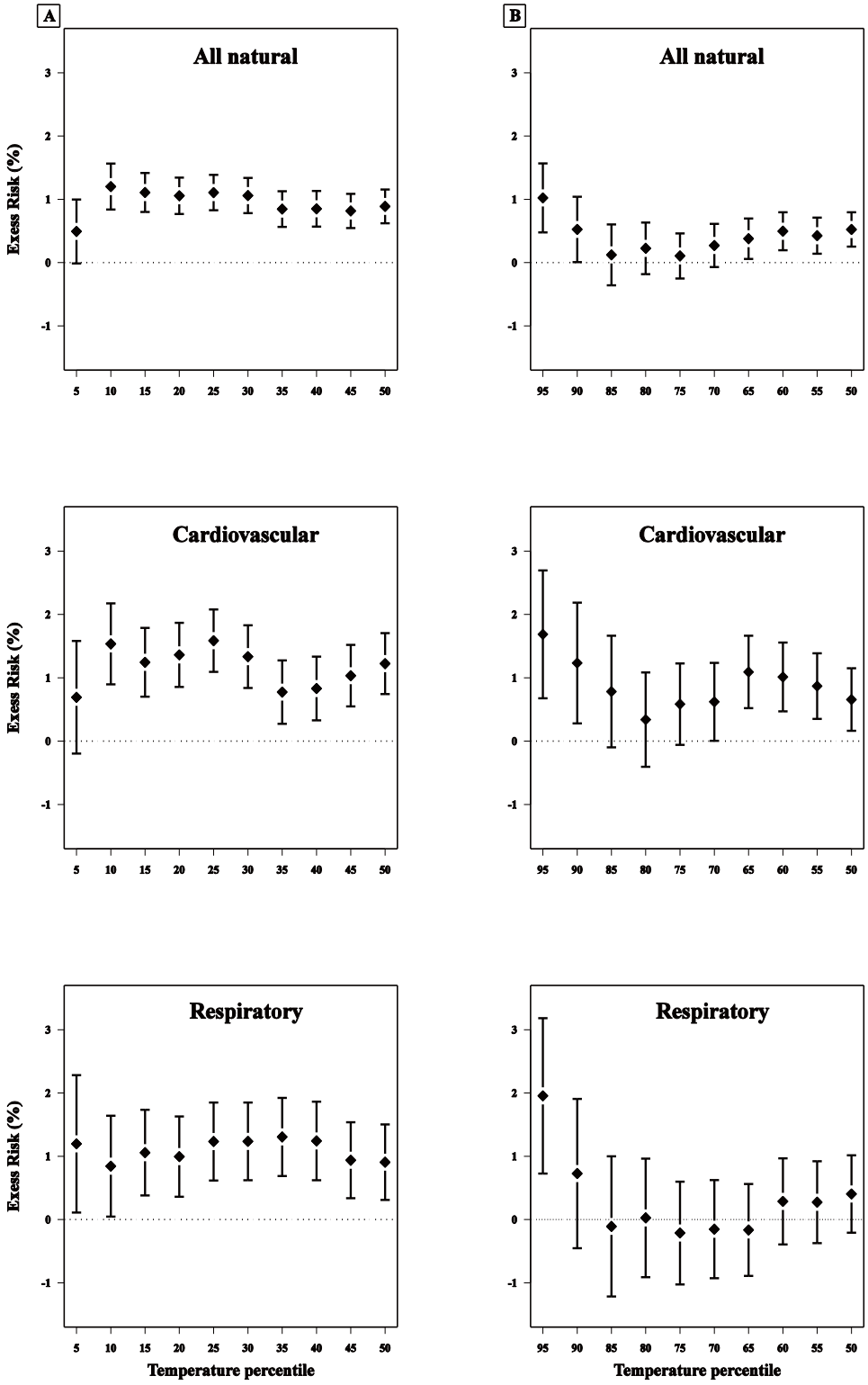
Mortality effects of $PM_{2.5}$ for each disease category in temperature strata defined by incrementing temperature percentiles are reported in Figure 3, where effect estimates are expressed as excess risk (%), and 95% confidence intervals, corresponding to a $10\mu g/m^3$ increase in $PM_{2.5}$ at average concentration of lag 0-1 days. The mortality effects of $PM_{2.5}$ in low temperature stratum were stronger than those in high temperature stratum. For low temperature stratum, although the mortality effects of $PM_{2.5}$ fluctuate, they were all statistical significant ($P < 0.05$), except for 5^{th} temperature percentile. For high temperature stratum, health effects of $PM_{2.5}$ were decreasing and reached their minimum at about 85^{th} highest temperature percentile and then increased with temperature decreasing.

Table 3. Estimated excess risk (%) and 95% confidence interval per 10μg/m^3 increase in $PM_{2.5}$ (lag 0-1) with and without adjustment for a co-pollutant.

Mortality	Temperature stratum		
	Low	Medium	High
All natural	< 22 °C	22 °C – 25 °C	≥ 25 °C
$PM_{2.5}$	0.94* (0.65, 1.24)	0.90 (0.56, 1.26)	0.47 (0.18, 0.76)
$PM_{2.5}$ + NO_2	0.37* (0.03, 0.71)	0.27 (-0.13, 0.67)	-0.34 (-0.73, 0.04)
$PM_{2.5}$ + SO_2	0.90* (0.58, 1.21)	0.86 (0.49, 1.23)	0.41 (0.07, 0.74)
$PM_{2.5}$ + O_3	0.87* (0.57, 1.17)	0.78 (0.42, 1.15)	0.25 (-0.11, 0.62)
Cardiovascular	< 22 °C	NA	≥ 22 °C
$PM_{2.5}$	0.88 (0.38, 1.37)	NA	1.03 (0.56, 1.50)
$PM_{2.5}$ + NO_2	0.05 (-0.56, 0.66)	NA	0.01 (-0.63, 0.65)
$PM_{2.5}$ + SO_2	0.96 (0.42, 1.51)	NA	1.14 (0.59, 1.69)
$PM_{2.5}$ + O_3	0.63 (0.10, 1.15)	NA	0.54 (-0.04, 1.11)
Respiratory	< 22 °C	22 °C – 25 °C	≥ 25 °C
$PM_{2.5}$	1.15 (0.51, 1.79)	0.39 (-0.40, 1.17)	0.26 (-0.38, 0.91)
$PM_{2.5}$ + NO_2	0.60 (-0.16, 1.35)	-0.24 (-1.14, 0.67)	-0.53 (-1.39, 0.34)
$PM_{2.5}$ + SO_2	1.10 (0.41, 1.79)	0.33 (-0.50, 1.17)	0.20 (-0.54, 0.94)
$PM_{2.5}$ + O_3	1.10 (0.45, 1.76)	0.31 (-0.52, 1.14)	0.12 (-0.69, 0.94)

All pollutants ($PM_{2.5}$, NO_2, SO_2, O_3) were using 2-day average (lag 0-1) concentration; *: significantly different from high temperature stratum; NA: not applicable because only one temperature cut-off was identified.

Figure 3. Estimated excess risk (%) of mortality and 95% confidence interval per 10μg/m^3 increase in $PM_{2.5}$ (lag 0-1) for temperature strata defined by temperature percentiles for (A) Low temperature stratum and (B) High temperature stratum. Low temperature stratum: temperatures < cool temperature cut-off; High temperature stratum: temperatures ≥ warm temperature cut-off.



4. Discussion

We tested for interactions between $PM_{2.5}$ and temperature for all natural, cardiovascular, and respiratory mortality in Hong Kong and estimated the mortality effects of $PM_{2.5}$ across three temperature strata. The mortality effects of $PM_{2.5}$ were much stronger in low temperature stratum than those in high temperature stratum. Interaction was statistically significant between low and high temperature strata for all natural mortality.

4.1. Temperature cut-offs identifying methods

For the analysis of interaction between $PM_{2.5}$ and temperature on cause-specific mortality, different analytical methods have been proposed. Ren and Tong (2006) employed bivariate response surface model to visually examine whether potential interaction exists between temperature and PM_{10}, and then fitted temperature-stratification parametric model with percentile-based temperature as cut-offs to define temperature strata, and then to estimate health effects of PM_{10} in different temperature strata. Li et al. (2011) also used bivariate response surface model, and then suggested using turning points of TMR as cut-offs to stratify temperature, and then to fit temperature-stratification parametric model. Temperature stratification uses fewer parameters and gives a simple, quantitative comparison of the mortality effects of PM in different temperature strata, which has been widely used by many studies (Morris and Naumova, 1998; Roberts, 2004). However, there is no consensus on the choice of temperature cut-offs. Some authors used percentile-based temperature threshold such as 1^{th} and 99^{th} (Wang et al., 2014), 5^{th} and 95^{th} (Qian et al., 2008), 15^{th} and 85^{th} (Cheng and Kan, 2012), and 50^{th} and 75^{th} (Stafoggia et al., 2008). This percentile-based method is based solely on the range of temperature, without

taking into consideration of cause-specific mortality. Our studies used TMRs of low and high temperature to identify cool and warm temperature cut-offs separately. Temperatures with log relative risk equals to zero in TMR were selected as cut-offs. The shape of TMR accounts for lag day of temperature. Further, the use of different lags to identify cut-offs for cool and warm effects according to their distinct lag pattern reduces the underestimation of thermal stress effect (Braga et al., 2001; Guo et al., 2011).

4.2. Interaction between $PM_{2.5}$ and temperature

We found greater mortality effects of $PM_{2.5}$ in low temperature stratum than that in high stratum for all natural and respiratory mortality. When compared with high temperature stratum, statistically significant interaction was found for all natural mortality. These findings were robust after adjustment for single co-pollutant of NO_2, SO_2, or O_3.

Our results are consistent with a study conducted in Shanghai, which found higher PM_{10} effects in low temperature stratum compared with medium and high temperature stratum for all natural, cardiovascular, and respiratory, and statistically significant interaction (P<0.05) was found in low temperature stratum, but not in high (Cheng and Kan, 2012). Possible reasons for statistically significant interaction of $PM_{2.5}$ and temperature between low and high temperature stratum in Hong Kong are: First, personal and ambient exposure to PM can vary across seasons because of changing of human behavior (Keeler et al., 2002). Residents in Hong Kong may be more likely to go outdoors and open windows in cool temperature days, whereas staying at home with air conditioner on in warm days. The change of activity may introduce higher

328 mortality risks of PM in cool temperature days, while reducing mortality risks of PM in warm days. Second, chemical compositions of $PM_{2.5}$ may vary in cool and warm
330 seasons. Yuan et al. (2013) found that local pollutants and non-local pollutants contributed different in cool and warm seasons. The reason may due to East Asian
332 Monsoon; the southwest monsoon brings clean oceanic air to Hong Kong in summer, while the northeast monsoon brings pollutants from inland in winter. Finally, because
334 of the inter-correlation among pollutants, higher $PM_{2.5}$ effects in low temperature stratum may be due to high level of other pollutants (Table 2). However, after
336 adjustment of co-pollutant, interaction of $PM_{2.5}$ and temperature between low and high temperature stratum remained statistically significant.

338

Although the underlying mechanism of the interaction between air pollution and
340 temperature for daily mortality is still unclear, several possible explanations have been advanced. Low temperature can cause physiologic stress, thus reducing
342 physiologic response ability to air pollution, making people more susceptible to air pollution. Williams et al. (1996) hypothesized that temperature below an optimal
344 temperature would have adverse impact on respiratory mucociliary function, which result in reducing its ability to clear pollutants. Brunekreef and Holgate (2002)
346 reported that air particles might increase inflammatory cytokines release, alter cardiac autonomic function to increase the risk of cardiopulmonary mortality. Therefore, an
348 interaction between $PM_{2.5}$ and temperature on mortality is biologically plausible.

350 *4.3. Temperature modification on causes of mortality*

The association between $PM_{2.5}$ and respiratory mortality is more affected by
352 temperature than the association between $PM_{2.5}$ and cardiovascular mortality. The

mortality effects of $PM_{2.5}$ decreased more for respiratory mortality than for
354 cardiovascular mortality as temperature increases (Table 3). Chemical compositions of $PM_{2.5}$ vary in cool and warm seasons may be the main reason. Yuan et al. (2013)
356 reported that vehicle exhaust, such as organic carbon (OC) and elemental carbon (EC), showed equal contribution in winter (16 November to 15 March) and summer (16
358 May to 15 September), but sulfate was 3-5 times higher in winter than in summer in Hong Kong. EC is more associated with cardiovascular mortality (Mar et al., 2000;
360 Peng et al., 2009), and sulfate is particular associated with respiratory mortality (Dai et al., 2014). With temperature increasing, the proportion of sulfate contributes less to
362 $PM_{2.5}$, which results in substantial decrease in the health effects of $PM_{2.5}$ on respiratory mortality, while the health effects of $PM_{2.5}$ on cardiovascular mortality
364 remain unchanged because of stable proportion of vehicle exhaust in $PM_{2.5}$ all over temperature range.

366

4.4. Study strengths and limitations

368 There are two major strengths in this study. First, we examined temperature modification on $PM_{2.5}$ using two shifting cut-offs from 50^{th} temperature percentile to
370 5^{th} for cool and to 95^{th} for warm to define three temperature strata in order to find trends of mortality effects of $PM_{2.5}$, which has not thoroughly studied previously.
372 Second, the availability of 13 years data with 4,748 consecutive days increases the statistical power to detect possible interactions. Some limitations of our study need to
374 be addressed. Data on meteorological conditions and air pollutants were based on the daily average of whole Hong Kong instead of individual data, so measurement error
376 may be present.

5. Conclusions

We found consistently higher $PM_{2.5}$ effects in low temperature stratum for all natural and respiratory mortality in Hong Kong. We identified statistically significant interaction of $PM_{2.5}$ and temperature between low and high temperature stratum for all natural mortality. Our findings provide evidence to support the effect modification of temperature on the association between $PM_{2.5}$ and cause-specific mortality.

Conflict of interest

The authors declare they have no competing financial interests.

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