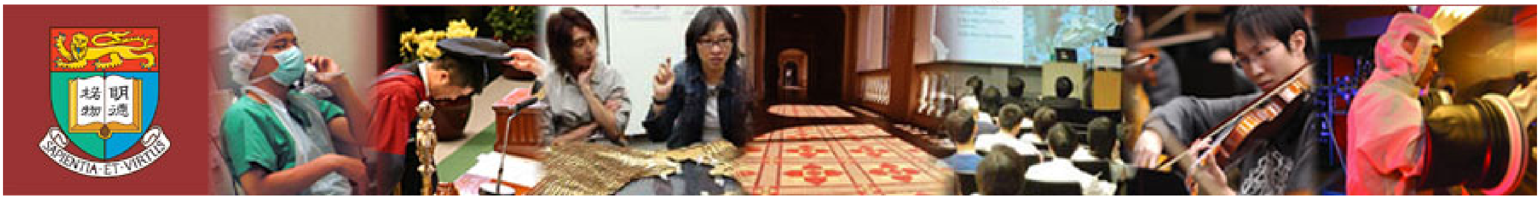

Title	**Is standard deviation of daily PM2.5 concentration associated with respiratory mortality?**
Author(s)	**Lin, H; Ma, W; Qiu, H; Vaughn, MG; Nelson, EJ; Qian, Z; Tian, L**
Citation	**Environmental Pollution, 2016, v. 216, p. 208-214**
Issued Date	**2016**
URL	**http://hdl.handle.net/10722/227793**
Rights	**This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.**

Is standard deviation of daily $PM_{2.5}$ concentration associated with respiratory mortality?

Hualiang Lin [a,1], Wenjun Ma [a,1], Hong Qiu [b], Michael G. Vaughn [c], Erik Nelson [c], Zhengmin Qian [c,*], Linwei Tian [b,*]

[a] *Guangdong Provincial Institute of Public Health, Guangdong Provincial Center for Disease Control and Prevention, Guangzhou, China*

[b] *School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong, China*

[c] *College for Public Health and Social Justice, Saint Louis University, Saint Louis, MO 63104, US*

Correspondence to: Zhengmin Qian, College for Public Health and Social Justice, Saint Louis University, 3545 Lafayette Avenue, Saint Louis, MO 63104, US. Email: zqian2@slu.edu; Fax: 314-977-3234; or Linwei Tian, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong, China; Email: linweit@hku.hk

[1] Hualiang Lin and Wenjun Ma contributed equally to this work.

ABSTRACT

Studies on health effects of air pollution often use daily mean concentration to estimate exposure while ignoring daily variations. This study examined the health effects of daily variation of $PM_{2.5}$. We calculated daily mean and standard deviations of $PM_{2.5}$ in Hong Kong between 1998 and 2011. We used a generalized additive model to estimate the association between respiratory mortality and daily mean and variation of $PM_{2.5}$, as well as their interaction. We controlled for potential confounders, including temporal trends, day of the week, meteorological factors, and gaseous air pollutants. Both daily mean and standard deviation of $PM_{2.5}$ were significantly associated with mortalities from overall respiratory diseases and pneumonia. Each 10 ug/m^3 increment in daily mean concentration at lag 2 day was associated with a 0.61% (95% CI: 0.19%, 1.03%) increase in overall respiratory mortality and a 0.67% (95% CI: 0.14%, 1.21%) increase in pneumonia mortality. And a 10 ug/m^3 increase in standard deviation at lag 1 day corresponded to a 1.40% (95% CI: 0.35%, 2.46%) increase in overall respiratory mortality, and a 1.80% (95% CI: 0.46%, 3.16%) increase in pneumonia mortality. We also observed a positive but non-significant synergistic interaction between daily mean and variation on respiratory mortality and pneumonia mortality. However, we did not find any significant association with mortality from chronic obstructive pulmonary diseases. Our study suggests that, besides mean concentration, the standard deviation of $PM_{2.5}$ might be one potential predictor of respiratory mortality in Hong Kong, and should be considered when assessing the respiratory effects of $PM_{2.5}$.

Capsule: This study suggests that, in addition to daily mean concentration, daily standard deviation of air pollution, is also significantly associated with increased respiratory mortality.

Keywords: fine particulate matter air pollution; standard deviation; respiratory mortality; time series study

1. Introduction

Numerous epidemiological studies have consistently demonstrated that short-term exposure to ambient $PM_{2.5}$ (particles with an aerodynamic diameter less than 2.5 μm) is associated with increased respiratory health outcomes (Dominici et al. 2006, Peng et al. 2008, Johannson et al. 2015). The majority of these studies have investigated the effects of daily mean concentration of $PM_{2.5}$, more generally, the location parameter of $PM_{2.5}$ distribution (Darrow et al. 2009, Chen et al. 2015). There is limited information on the health effects of $PM_{2.5}$ variability, the scale parameter, and the possible interaction of the mean and variability.

It is reasonable to hypothesize that daily variation of $PM_{2.5}$ might be independently associated with health outcomes. Consider the following hypothetical scenarios, where each day is divided into three equal periods and under the simplifying assumption that all covariates are held constant. Under this framework, suppose that the mortality count (on the logarithmic scale) is 100 when $PM_{2.5}$ concentration is 50 for each of the three time periods, and that the RR per 10 ug/m^3 increase in $PM_{2.5}$ is 2. In our first scenario, suppose that the $PM_{2.5}$ concentration is stable at 60 ug/m^3, resulting in a mortality count of 600 (100*RR*3 time periods =100*2*3=600). In the second scenario, suppose that the mean concentration is the same as the first scenario (60 ug/m^3), yet with large variability between the three time periods, 50, 60 and 70 ug/m^3, respectively. The mortality count would be 700 [100+ (100*2) + (100*4) =700], which is considerably larger than the mortality in the first scenario. These hypothetical scenarios suggest that variations in $PM_{2.5}$ throughout a given day should not be ignored as it may directly impact health outcomes.

Variability in air pollution is also manifest through peak concentration hours and lower concentration hours. Peak concentration is usually observed during day time, which may expose individuals to higher levels of air pollutants due to increased outdoor activities during the day time. A few recent studies reported that exposure to high levels of air pollution, with a lag time of a few hours, was associated with adverse health outcomes. For example, one study conducted in Japan reported that exposure to suspended particulate matter with a lag of 2 hours was associated with higher mortality risk among patients with hemorrhagic stroke (Yamazaki et al. 2007). Similarly, an experimental study showed that inhalation of diesel exhaust impairs the regulation of vascular tone 2 hours after exposure to air pollution (Mills et al. 2005). These studies imply that standard deviation might be a more straightforward indicator to address the acute health effects of air pollution.

The purpose of this study was to examine the effects of ambient air pollution, specifically, the daily variation and daily mean concentration of $PM_{2.5}$, and their interaction, on respiratory mortality in Hong Kong.

2. Materials and methods

2.1 Air Pollution Data

We obtained hourly air pollution data collected between January 1, 1998 and December 31, 2011 from the Environmental Protection Department of Hong Kong. Details of the air pollution monitoring have been described elsewhere (Qiu et al.

2012). In brief, there are 14 air monitoring stations in Hong Kong, each of which collected four major air pollutants (PM_{10}, NO_2, SO_2, and O_3). Hourly concentrations of $PM_{2.5}$ have been monitored in four stations (Tsuen Wan (TW), Tap Mun (TM), Tung Chung (TC) and Central (CL)) since 1998 (Fig. 1). We used the average of daily mean and variation of these four stations in the main model to approximate $PM_{2.5}$ concentrations for all of Hong Kong.

The daily mean concentration and variability in $PM_{2.5}$ was defined as the average concentration and standard deviation (SD) of 24-hour $PM_{2.5}$ concentration within one day for each station (Xu et al. 2014). We calculated daily mean and SD of hourly $PM_{2.5}$ concentration when at least 18 of the total 24 hourly measurements of $PM_{2.5}$ were available for a given station.

We also calculated daily mean concentrations of NO_2, SO_2 and 8-hour mean (10:00 to18:00) concentrations of O_3 using data from these four stations. Daily meteorological data for the same period, including daily mean temperature (°C), relative humidity (%) and wind speed (m/s), were also obtained from the Hong Kong Observatory.

2.2 Mortality Data

Daily mortality data, which covered all deaths in Hong Kong over the period of 1998-2011, were obtained from the Hong Kong Census and Statistics Department. They were coded according to the 9th revision (1998-2000) or 10th revision (2001-2011) of the International Classification of Diseases (ICD). Overall respiratory deaths (ICD-9: 460-519 or ICD-10: J00-J99, 519, excluding influenza), chronic obstructive pulmonary diseases (COPD, ICD-9: 491-492, and 496 or ICD-10: J40-J44), and pneumonia (ICD-9: 480-486 or ICD-10: J12-J18) were extracted to construct the corresponding time series. We excluded influenza because previous studies suggested that influenza epidemics may confound the associations between air pollution and respiratory mortality (Ren et al. 2006, Qiu et al. 2012). Therefore, daily hospital admissions for influenza were abstracted and used to identify influenza outbreaks, which were then treated as a potential confounder in the analysis (Thach et al. 2010).

2.3 Statistical methods

We examined the short-term association between daily mean and variation of $PM_{2.5}$ concentrations and respiratory mortalities using generalized additive models (GAM), and a quasi-Poisson link function was applied to account for over-dispersion in daily respiratory mortality (Zanobetti and Schwartz 2008, Stieb et al. 2009). We used a penalized smoothing spline to filter out seasonality and long-term trends in daily mortality, as well as temperature and relative humidity. We included day of the week and public holidays in the model as dummy variables (Schwartz and Morris 1995). To adjust for the potential confounding effect of influenza outbreaks, we entered a dummy variable for weeks with the number of influenza hospital admissions exceeding the 75th percentile in a year into the model (Wong et al. 2002).

To reduce the potential concerns associated with multiple testing and model selection, we selected *a priori* model specification and degrees of freedom (df) for temporal trends and meteorological factors, as has been done by others (Bell et al. 2008, Peng et al. 2008, Tian et al. 2013). We used a df of 6 per year for time trends to filter out the information at time scales of 2 months, a df of 6 for mean temperature of current day temperature ($Temp_0$) and previous 3 days' moving average ($Temp_{1\text{-}3}$) and a df of 3 for current day's relative humidity ($Humidity_0$). For temperatures, 6 df was chosen to account for potential nonlinear relationship between temperature and mortality (Curriero et al. 2002). Briefly, we set up a core model to remove the long-term trends, seasonal variations and to adjust for time varying confounders as follows:

$$\log[E(Y_t)] = \alpha + s(t, df=6/year) + s(Temp_0, df=6) + s(Temp_{1-3}, df=6)$$
$$+ s(Humidity_0, df=3) + \beta_1{*}DOW + \beta_2{*}PH + \beta_3{*}Influenza,$$

where $E(Y_t)$ is the expected respiratory mortality count on day t, α is the model intercept, s() indicates a smoother function based on penalized splines, t represents time, and β is the regression coefficient.

After the core model was established, we included the $PM_{2.5}$ concentration in the model to analyze the association between daily mean and variation of $PM_{2.5}$ and mortalities from specific respiratory diseases.

We estimated the linear effects with different lag structures including both single-day lag (from the current day (lag_0) up to three lag days (lag_3)), as previous studies in China showed little evidence of association with a lag beyond 3 days (Kan et al. 2007, Lin et al. 2016). We also examined the respiratory mortality impacts of multi-day lags (moving averages for the current day and the previous 1, 2 and 3 days: lag_{01}, lag_{02}, and lag_{03}).

To justify the assumption of linearity between the logarithm of respiratory mortality and daily mean and variation of $PM_{2.5}$, we used a smoothing function to graphically examine the exposure-response relationship between daily mean and variation of $PM_{2.5}$ and respiratory mortality (Kan et al. 2007, Tian et al. 2014).

We further investigated the interaction between daily mean and variation of $PM_{2.5}$ in relation to respiratory mortality, the purpose of which is to check whether the effect of $PM_{2.5}$ variation can be ascribed to $PM_{2.5}$ mean, as there is a relatively high correlation between these two indicators. Each of these two factors was firstly classified into two levels (high and low) using the median value as the cut-point, and a new variable was then created to represent the combination of the two variables, which could be classified into four categories: low mean and low variation (LL), low mean and high variation (LH), high mean and low variation (HL), and high mean and high variation (HH). It is reasonable to expect that, if the effect of $PM_{2.5}$ variation is purely due to $PM_{2.5}$ mean, the effect of LH would be similar to that of LL, and the effect of HL would be similar to that of HH; otherwise, it may indicate that the effects of these two indicators were independent.

Our analysis suggested that they were independent (controlling for daily mean concentration of $PM_{2.5}$ did not change the risk estimates of daily $PM_{2.5}$ SD, as shown in Table 3), so we further examined their interaction using an additive model proposed by Andersson (Andersson et al. 2005), and calculated three measures of additive interactions: relative excess risk due to interaction (RERI), attributable proportion (AP) and synergy index (SI). When RERI and AP were equal to 0 and SI equal to 1, we considered that to be absence of additive interaction; while additive interaction was present if RERI and AP did not equal 0 and SI exceeded unity. Furthermore, an SI greater than 1 denoted a synergetic interaction, which implied that the joint effects of two factors in an additive model was greater than sum of their individual effects. On the other hand, if SI was smaller than 1, it implied an antagonistic interaction, indicating that in the presence of two exposures in an additive model, one factor decreased the effect of the other (Lundberg et al. 1996, Zhang et al. 2016).

2.4 Sensitivity analysis

A few sensitivity analyses were conducted to check the robustness of the findings. We used one alternative indicator for $PM_{2.5}$ variability, namely the standard deviation of $PM_{2.5}$ concentration at day time (7:00 am to 8:00 pm) as people usually have more outdoor activities and are exposed to the ambient air pollution during these hours. We also changed the degrees of freedom in the smoothing function of temporal trends. We also fit a model using a smoothing function (df=3) for wind speed to assess the impact of wind speed on the risk estimates. To check the potential exposure misclassification resulting from the pollution data, we did a sensitivity analysis by restricting daily mortality data to those residents who lived nearby Tsuen Wan Station, as this station has been suggested to be most representative of Hong Kong's overall air quality for the majority of the population (Qiu et al. 2012).

All analyses were conducted using the "mgcv" package in R. We reported the results as excess relative risk (ERR) in respiratory mortality for each 10 ug/m^3 increase in daily $PM_{2.5}$ variation. Statistical significance was defined as $p<0.05$.

3. Results

We recorded 95,857 deaths from respiratory diseases during the study period. Among them, 25,743 were from COPD and 59,713 from pneumonia. On average, there were 19 people died from respiratory diseases per day, 5 from COPD, and 12 from pneumonia.

Table 1

Summary statistics of daily respiratory mortality, air pollutants, and weather conditions in Hong Kong, 1998-2011.

Variable	Days	Mean±SD	Percentile				
			Min	P25	P50	P75	Max
Daily mortality count							
Overall respiratory	5113	18.8±6.4	4	14	18	22	58
COPD	5113	5.0±2.6	0	3	5	7	18
Pneumonia	5113	11.7±5.0	0	8	11	15	39
Air pollution ($\mu g/m^3$)							
$PM_{2.5}$ mean	5112	37.5±19.9	5.8	21.7	34.0	48.9	172.0
$PM_{2.5}$ SD	5112	10.5±6.4	2.0	6.0	8.5	12.8	92.2

NO_2	5112	55.5±20.4	7.7	40.2	53.6	67.9	152.4
SO_2	5112	17.6±11.0	0.1	10.5	15.1	22.6	121.5
O_3	5112	45.3±23.5	1.1	26.0	41.5	61.2	144.4
Meteorological factors							
Temperature (°C)	5113	23.5±5.0	8.2	19.5	24.7	27.8	31.8
Relative humidity	5113	77.9±10.3	27.5	73.2	79.0	84.7	98.1

Abbreviation: SD, standard deviation; Px, xth percentile; Min, minimum; Max, maximum.

During the study period, there were 190 days with missing information at TW station, 90 days at TM station, 456 days at TC station, and 44 days at CL station, accounting for 3.7%, 1.8%, 8.9% and 0.9% of the observation days, respectively. However, there was only 1 day for the entire study period where monitoring stations were unable to collect air pollution measurements. The daily mean and standard deviation of $PM_{2.5}$ concentration were 37.5 and 10.5 ug/m^3. Supplementary Figure s1 shows the time series of daily mean and standard deviation of $PM_{2.5}$ concentrations in Hong Kong during the study period. There were seasonal patterns for both mean and standard deviation of $PM_{2.5}$ with higher concentrations in the cold season. The daily mean concentrations of NO_2, SO_2 and O_3 were 55.5, 17.6, and 31.1 ug/m^3, respectively. The daily mean temperature and relative humidity were 23.5 °C and 77.9%, respectively.

Generally, the standard deviation of $PM_{2.5}$ was moderately to highly correlated with the mean concentration of $PM_{2.5}$ (correlation coefficient, r = 0.67) and was also correlated with other covariates (for example, r=0.63 for SO_2, and r = 0.17 for O_3). There were low to moderate correlations between other pollutants and weather covariates, except between SO_2 and O_3 (Table 2).

Table 2

Pearson correlation coefficients between $PM_{2.5}$ variation, air pollutants, and weather conditions in Hong Kong, 1998-2011.

Pollutants	$PM_{2.5}$ SD	$PM_{2.5}$ mean	NO_2	SO_2	O_3	Temperature
$PM_{2.5}$ mean	0.67**					
NO_2	0.61**	0.75**				
SO_2	0.63**	0.59**	0.60**			
O_3	0.17**	0.49**	0.35**	0.02		
Temperature	-0.18**	-0.36**	-0.43**	-0.08**	-0.08**	
Humidity	-0.12**	-0.42**	-0.39**	-0.28**	-0.42**	0.25**

**p< 0.01, * P< 0.05.

Fig. 2 shows the respiratory mortality effects of daily mean and standard deviation of $PM_{2.5}$ by lag time (in days) in the single pollutant models. We found that both mean and standard deviation of daily $PM_{2.5}$ concentration were significantly associated with increasing mortalities from overall respiratory diseases and pneumonia at most of the lag times examined; more acute effects were observed for

$PM_{2.5}$ deviation than $PM_{2.5}$ mean. For example, a 10 ug/m^3 increase in daily mean concentration of $PM_{2.5}$ at lag 2 day corresponded to a 0.61% (95% CI: 0.19%, 1.03%) and 0.67% (95% CI: 0.14%, 1.21%) increase in mortalities from overall respiratory diseases and pneumonia, respectively. And a 10 ug/m^3 increase in daily standard deviation of $PM_{2.5}$ at lag 1 day corresponded to a 1.40% (95% CI: 0.35%, 2.46%) and 1.80% (95% CI: 0.46%, 3.16%) increase in mortalities from overall respiratory diseases and pneumonia, respectively. In the models, we did not find any effects on mortality from COPD. In the two-pollutant models with adjustment for daily mean concentrations of NO_2, SO_2 or O_3, their effects changed very little and remained statistical significant (Table 3).

Table 3

ERR in mortality for an 10 ug/m^3 increase in daily standard deviation of $PM_{2.5}$ in different models.

Models	Overall respiratory morality	Pneumonia morality
Model-single*	1.40 (0.35, 2.46)	1.80 (0.46, 3.16)
Day time	1.35 (0.21, 2.50)	1.40 (0.35, 2.46)
Model w/$PM_{2.5}$ Mean	1.39 (0.27, 2.52)	1.35 (0.21, 2.50)
Model w/SO_2	1.46 (0.39, 2.55)	1.39 (0.27, 2.52)
Model w/NO_2	1.21 (0.13, 2.32)	1.46 (0.39, 2.55)
Model w/O_3	1.44 (0.38, 2.52)	1.21 (0.13, 2.32)
Model w/ws	1.39 (0.34, 2.45)	1.79 (0.45, 3.15)

Nearby TW	1.23 (0.32, 2.15)	1.39 (0.34, 2.45)
df=5/year	1.56 (0.51, 2.63)	1.23 (0.32, 2.15)
df=7/year	1.10 (0.04, 2.16)	1.56 (0.51, 2.63)
df=8/year	1.06 (0.01, 2.12)	1.10 (0.04, 2.16)

* Results obtained from single-pollutant models.

Abbreviations: ERR, excess relative risk; df, degree of freedom; "Model w/SO_2" means results from model with SO_2 being controlled for; "Model w/ws" means results from the model with wind speed being controlled for; "Nearby TW" means results from model with subjects around Tsuen Wan Station.

Fig. 3 shows the smoothing curves of the concentration-response curves for the effects of daily mean and standard deviation of $PM_{2.5}$ on mortalities from overall respiratory diseases and pneumonia. The concentration-response curves, while not perfect, suggested an approximately linear relationships.

In the sensitivity analyses, we used standard deviation of $PM_{2.5}$ at day time as an exposure indicator and produced comparable results: each 10 ug/m^3 increase in daily standard deviation of $PM_{2.5}$ corresponded to a 1.35% (0.21%, 2.50%) and 1.40% (0.35%, 2.46%) increase in mortalities from overall respiratory diseases and pneumonia, respectively. And when we controlled for daily mean concentration of $PM_{2.5}$, the risk estimates of daily $PM_{2.5}$ SD remained similar: the ERRs were 1.39% (95% CI: 0.27%, 2.52%) and 1.35% (95% CI: 0.21%, 2.50%) for mortalities from overall respiratory diseases and pneumonia, respectively. We used alternative degrees of freedom to adjust for temporal trends (5, 7 and 8 per year), with most of the results largely unaffected (Table 3). The model using only air pollution data from the TW station and the model controlling for wind speed both yielded results comparable to those from the main model. All these suggested that the association between daily $PM_{2.5}$ variation and overall respiratory diseases and pneumonia obtained from the main models was robust.

Table 4 shows the interaction between daily mean and standard deviation of $PM_{2.5}$ in relation to their effects on respiratory and pneumonia mortality. Despite the lack of statistical significance, the results suggested that there was some weak synergistic interaction between the two factors in regards to their association with overall respiratory mortality (RERI = 1.28, AP = 1.25, and SI = 1.87) and pneumonia mortality (RERI = 0.73, AP = 0.71, and SI = 1.34).

Table 4

The interactive effects between daily mean and standard deviation of $PM_{2.5}$ on respiratory mortalities in Hong Kong, 1998-2011.

Models	No. of days	ERR(%)	Lower(%)	Upper(%)
Overall respiratory mortality				
Low-low	1708	0	-	-
Low-high	852	0.58	-1.56	2.78
High-low	765	0.89	-1.43	3.27
High-high	1784	2.75	0.66	4.89

RERI	1.28 (95% CI: -1.72, 4.35)			
AP (%)	1.25 (95% CI: -1.73, 4.16)			
Synergy index	1.87 (95% CI: 0.21, 16.54)			
Pneumonia mortality				
Low-low	1708			
Low-high	852	1.32	-1.41	4.12
High-low	765	0.88	-2.05	3.89
High-high	1784	2.93	0.29	5.64
RERI	0.73 (95% CI: -3.13, 4.54)			
AP (%)	0.71 (95% CI: -3.05, 4.46)			
Synergy index	1.34 (95% CI: 0.23, 7.93)			

Abbreviations: ERR, excess relative risk; RERI, relative excess risk due to interaction; AP, attributable proportion.

Discussion

To our knowledge, this is the first study to report the association between daily standard deviation of $PM_{2.5}$ concentrations and respiratory mortality and its possible interaction with daily mean concentration of $PM_{2.5}$. Using 14 years of data with about 96,000 deaths in Hong Kong, our study suggested that, besides daily mean concentration of $PM_{2.5}$, standard deviation of $PM_{2.5}$ might be another respiratory health predictor; and it appears that these two factors might have some positive, but non-significant, synergistic interaction in terms of their effects on respiratory mortality. These findings provided additional insights into the deleterious respiratory health effects of air pollution.

Similar to our study, a few studies have also reported that temperature variation within a short time period was associated with various adverse health outcomes (Zanobetti et al. 2012, Lin et al. 2013, Xu et al. 2014). Statistical theory also supports that the frequency of extreme events is more dependent on the variability than the mean values (Wordley et al. 1997). However, no such study has examined whether daily variation of air pollution is associated with human health (Madsen et al. 2012).

Our results of the association between daily variation of $PM_{2.5}$ and respiratory mortality, particularly pneumonia, could not be explained by their correlation with daily mean $PM_{2.5}$. We proposed a novel method to examine the individual effect of two moderately/highly correlated factors, which has not been previously reported. We also observed more acute effects of $PM_{2.5}$ SD (0-1 lag days) than those of $PM_{2.5}$ mean (2-3 lag days), and the model controlling for daily mean concentration of $PM_{2.5}$ showed a similar effect of daily standard deviation of $PM_{2.5}$, all these supported that the effects of $PM_{2.5}$ SD were not due to its correlation with $PM_{2.5}$ mean.

The effects of both daily mean and standard deviation of $PM_{2.5}$ on respiratory mortality changed very little after adjusting for various gaseous pollutants (NO_2, SO_2 and O_3). Consistent results were observed when using alternative model specifications, such as varying degrees of freedom for the smoothing functions for temporal trends and using air pollution information from a central representative air monitoring station. Taken together, this study suggested that both daily mean and variation of

$PM_{2.5}$ concentration could plausibly increase the risk of respiratory mortality, particularly pneumonia, and that adaptation of intervention strategies targeted solely to reduce mean concentration of $PM_{2.5}$ might be more successful at preventing poor health outcomes if measures are taken to reduce daily variation as well.

Our study further provided the first evidence of some weak, though non-significant, interaction between daily mean and standard deviation of $PM_{2.5}$ on respiratory mortality. Previous studies have mainly considered mean concentration of $PM_{2.5}$ when investigating the health effects and formulating air pollution control measures; this finding suggested that attention should also be paid to the daily variation of $PM_{2.5}$. The observed non-significant synergistic interactive effects suggested that people may suffer larger health impacts at days with higher values of both the mean and variation.

The adverse respiratory effects of larger variation in$PM_{2.5}$ concentration were biologically plausible. It was likely that during the days with higher standard deviation, people may have higher levels of exposure to $PM_{2.5}$ and inhale more particles. Some vulnerable subgroups may be less acclimatized to significant swings in $PM_{2.5}$ and thus led to more adverse health outcomes. Another possibility might be that increased daily variation of $PM_{2.5}$ concentrations may stress the ability of the respiratory system to adapt to extremely high levels of $PM_{2.5}$ concentrations, which happen frequently within a relatively short time period (which is more often observed in day time with more outdoor human activities, and thus more exposure to traffic exhausts). Such adaptation ability may be reduced in the presence of another illness, such as respiratory conditions. Recently, one Japanese study suggested that exposure to high levels of suspended particulate matter with a lag of 2 hours was associated with higher mortality risk among patients with hemorrhagic stroke (Yamazaki et al. 2007), and in one experimental study, inhalation of diesel exhaust was shown to impair the regulation of vascular tone 2 hours after exposure (Mills et al. 2005). The mechanisms for the observed positive interaction between daily mean and standard deviation of $PM_{2.5}$ concentrations remained largely unknown. However,, it is possible that, in Hong Kong, when both larger variations and higher daily mean concentrations of $PM_{2.5}$ occur simultaneously, the participants would be exposed to higher levels of ambient air pollution. This exposure would lead to enhanced acute mortality effects, especially for those who are the most vulnerable and susceptible, such as the elderly and those with chronic medical conditions. More studies are warranted to further investigate this research question. We found significant effects on mortalities from overall respiratory diseases and pneumonia, while no significant effect was detected for COPD. The underlying reasons remained unclear; it was possible that people with COPD had relatively fewer outdoor activities and were less affected by variation in ambient $PM_{2.5}$ concentrations. More studies are warranted to further investigate the underlying mechanisms.

This study had several strengths. Firstly, this study calls for consideration of daily variation of air pollution in future studies; based on a long time series data in Hong Kong, our study found a significant association between daily standard deviation of $PM_{2.5}$ and respiratory mortality, which has not been reported. Secondly, we proposed a novel and easy method to differentiate the effects of two correlated factors, which is often one concern in environmental epidemiological studies. Thirdly, this study explored the interactive effects of $PM_{2.5}$ mean and standard deviation on the risk of respiratory mortality, which further improved our understanding of the association between $PM_{2.5}$ and respiratory mortality. More importantly, findings from this study have some important public health implications. The variation of $PM_{2.5}$ concentrations should be considered as an important indicator in the future air pollution management and health protection measures. Practically, to reduce the daily variation of $PM_{2.5}$ concentrations, the air pollution controlling policies should pay more attention to vehicle emissions, which produced common cause of peak concentrations of $PM_{2.5}$ in Hong Kong (Cheng et al. 2006).

We suggest more studies to investigate possible effects of $PM_{2.5}$ variation on other health outcomes and their interaction with $PM_{2.5}$ mean concentration in different environmental conditions.

At the same time, a few limitations should be noted. First, the ecological design of our study did not allow us to investigate the PM-mortality association at the individual level, thus hindering causal inference. Second, we used ambient air pollution data from fixed air monitoring stations to represent the population exposure, which might have resulted in exposure misclassification. Misclassification in causes of death were also possible due to diagnostic and coding transition, but there is evidence that the accuracy of diagnoses and causes of death certificates was high in the study area (Tian et al. 2013).

In summary, this study suggests that, in addition to daily mean concentration, the standard deviation of $PM_{2.5}$ might be one potential risk factor of respiratory mortality in Hong Kong; both indicators and their potential interaction should be considered when assessing the respiratory effects of $PM_{2.5}$, as well as formulating air pollution regulations.

Acknowledgements

The authors thank the Hong Kong Environmental Protection Department for providing air pollution monitoring data, and the Hong Kong Observatory for the temperature and humidity data.

Conflicts of interest and source of funding

None declared.

References

Andersson, T., Alfredsson, L., Källberg, H., Zdravkovic, S. and Ahlbom, A. (2005). Calculating measures of biological interaction. European journal of epidemiology **20**(7): 575-579.

Bell, M. L., Ebisu, K., Peng, R. D., Walker, J., Samet, J. M., Zeger, S. L. and Dominici, F. (2008). Seasonal and regional short-term effects of fine particles on hospital admissions in 202 US counties, 1999-2005. Am J Epidemiol **168**(11): 1301-1310.

Chen, R., Zhao, Z., Sun, Q., Lin, Z., Zhao, A., Wang, C., Xia, Y., Xu, X. and Kan, H. (2015). Size-fractionated particulate air pollution and circulating biomarkers of inflammation, coagulation, and vasoconstriction in a panel of young adults. Epidemiology **26**(3): 328-336.

Cheng, Y., Ho, K., Lee, S. and Law, S. (2006). Seasonal and diurnal variations of PM1. 0, PM2. 5 and PM10 in the roadside environment of Hong Kong. China Particuology **4**(06): 312-315.

Curriero, F. C., Heiner, K. S., Samet, J. M., Zeger, S. L., Strug, L. and Patz, J. A. (2002). Temperature and mortality in 11 cities of the eastern United States. American Journal of Epidemiology **155**(1): 80-87.

Darrow, L. A., Klein, M., Sarnat, J. A., Mulholland, J. A., Strickland, M. J., Sarnat, S. E., Russell, A. G. and Tolbert, P. E. (2009). The use of alternative pollutant metrics in time-series studies of ambient air pollution and respiratory emergency department visits. Journal of Exposure Science and Environmental Epidemiology **21**(1): 10-19.

Dominici, F., Peng, R. D., Bell, M. L., Pham, L., McDermott, A., Zeger, S. L. and Samet, J. M. (2006). Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA: The Journal of the American Medical Association **295**(10): 1127-1134.

Johannson, K. A., Balmes, J. R. and Collard, H. R. (2015). Air pollution exposure: a novel environmental risk factor for interstitial lung disease? CHEST Journal **147**(4): 1161-1167.

Kan, H., London, S. J., Chen, G., Zhang, Y., Song, G., Zhao, N., Jiang, L. and Chen, B. (2007). Differentiating the effects of fine and coarse particles on daily mortality in Shanghai, China. Environ Int. **33**(3): 376-384.

Lin, H., Tao, J., Du, Y., Liu, T., Qian, Z., Tian, L., Di, Q., Rutherford, S., Guo, L., Zeng, W., Xiao, J., Li, X., He, Z., Xu, Y. and Ma, W. (2016). Particle size and chemical constituents of ambient particulate pollution associated with cardiovascular mortality in Guangzhou, China. Environmental Pollution **208, Part B**: 758-766.

Lin, H., Zhang, Y., Xu, Y., Xu, X., Liu, T., Luo, Y., Xiao, J., Wu, W. and Ma, W. (2013). Temperature Changes between Neighboring Days and Mortality in Summer: A Distributed Lag Non-Linear Time Series Analysis. PloS One **8**(6): e66403.

Lundberg, M., Fredlund, P., Hallqvist, J. and Diderichsen, F. (1996). A SAS program calculating three measures of interaction with confidence intervals. Epidemiology **7**(6): 655-656.

Madsen, C., Rosland, P., Hoff, D. A., Nystad, W., Nafstad, P. and Næss, Ø. E. (2012). The short-term effect of 24-h average and peak air pollution on mortality in Oslo, Norway. European journal of epidemiology **27**(9): 717-727.

Mills, N. L., Törnqvist, H., Robinson, S. D., Gonzalez, M., Darnley, K., MacNee, W., Boon, N. A., Donaldson, K., Blomberg, A. and Sandstrom, T. (2005). Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. Circulation **112**(25): 3930-3936.

Peng, R. D., Chang, H. H., Bell, M. L., McDermott, A., Zeger, S. L., Samet, J. M. and Dominici, F. (2008). Coarse particulate matter air pollution and hospital admissions for cardiovascular and respiratory diseases among Medicare patients. JAMA: The Journal of the American Medical Association **299**(18): 2172.

Qiu, H., Yu, I. T., Tian, L., Wang, X., Tse, L. A., Tam, W. and Wong, T. W. (2012). Effects of Coarse Particulate Matter on Emergency Hospital Admissions for Respiratory Diseases: A Time Series Analysis in Hong Kong. Environmental Health Perspectives **120**(4): 572-576.

Ren, C., Williams, G. M. and Tong, S. (2006). Does particulate matter modify the association between temperature and cardiorespiratory diseases? Environmental

Health Perspectives **114**(11): 1690.

Schwartz, J. and Morris, R. (1995). Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. American Journal of Epidemiology **142**(1): 23.

Stieb, D. M., Szyszkowicz, M., Rowe, B. H. and Leech, J. A. (2009). Air pollution and emergency department visits for cardiac and respiratory conditions: a multi-city time-series analysis. Environmental Health **8**: 25.

Thach, T. Q., Wong, C. M., Chan, K. P., Chau, Y. K., Neil Thomas, G., Ou, C. Q., Yang, L., Peiris, J. S., Lam, T. H. and Hedley, A. J. (2010). Air pollutants and health outcomes: Assessment of confounding by influenza. Atmospheric Environment **44**(11): 1437-1442.

Tian, L., Ho, K. f., Wang, T., Qiu, H., Pun, V. C., Chan, C. S., Louie, P. K. and Ignatius, T. (2014). Ambient Carbon Monoxide and the Risk of Hospitalization Due to Chronic Obstructive Pulmonary Disease. American journal of epidemiology: kwu248.

Tian, L., Qiu, H., Pun, V. C., Lin, H., Ge, E., Chan, J. C., Louie, P. K., Ho, K. F. and Yu, I. T. (2013). Ambient Carbon Monoxide Associated with Reduced Risk of Hospital Admissions for Respiratory Tract Infections. Am J Respir Crit Care Med **188**(10): 1240-1245.

Wong, C.-M., Atkinson, R. W., Anderson, H. R., Hedley, A. J., Ma, S., Chau, P. Y.-K. and Lam, T.-H. (2002). A tale of two cities: effects of air pollution on hospital admissions in Hong Kong and London compared. Environmental health perspectives **110**(1): 67.

Wordley, J., Walters, S. and Ayres, J. G. (1997). Short term variations in hospital admissions and mortality and particulate air pollution. Occupational and environmental medicine **54**(2): 108-116.

Xu, Z., Hu, W., Wang, X., Huang, C. and Tong, S. (2014). The Impact of Temperature Variability on Years of Life Lost. Epidemiology **25**(2): 313-314 310.1097/EDE.0000000000000066.

Yamazaki, S., Nitta, H., Ono, M., Green, J. and Fukuhara, S. (2007). Intracerebral haemorrhage associated with hourly concentration of ambient particulate matter: case-crossover analysis. Occupational and Environmental Medicine **64**(1): 17-24.

Zanobetti, A., O'Neill, M. S., Gronlund, C. J. and Schwartz, J. D. (2012). Summer temperature variability and long-term survival among elderly people with chronic disease. Proceedings of the National Academy of Sciences **109**(17): 6608-6613.

Zanobetti, A. and Schwartz, J. (2008). Mortality Displacement in the Association of Ozone with Mortality. American journal of respiratory and critical care medicine **177**(2): 184-189.

Zhang, Z., Xie, X., Chen, X., Li, Y., Lu, Y., Mei, S., Liao, Y. and Lin, H. (2016). Short-term effects of meteorological factors on hand, foot and mouth disease among children in Shenzhen, China: Non-linearity, threshold and interaction. Science of The Total Environment **539**: 576-582.

Figure legend:

Fig. 1. Map of Hong Kong showing the locations of the air pollution monitoring stations.

Fig. 2. Percentage change in respiratory mortalities for per 10 ug/m^3 increase in daily mean and standard deviation of $PM_{2.5}$ at different lag days in single-pollutant models.

Fig. 3. Exposure-response curves for daily mean and standard deviation of $PM_{2.5}$ and mortalities for overall respiratory diseases and pneumonia. A natural spline smoother with 3 df was applied.

Fig. s1. Time series of daily mean and standard deviation of $PM_{2.5}$ concentration in Hong Kong, 1998-2011.