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<td><strong>Author(s)</strong></td>
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Is standard deviation of daily PM$_{2.5}$ concentration associated with respiratory mortality?

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$^1$ Hualiang Lin and Wenjun Ma contributed equally to this work.
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
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.
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 to 18:00) 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 $75^{th}$ 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 ($\text{Temp}_0$) and previous 3 days’ moving average ($\text{Temp}_{1-3}$) and
a df of 3 for current day’s relative humidity ($\text{Humidity}_0$). 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:

$$\log[E(Y_t)] = \alpha + s(t, \text{df} = 6/\text{year}) + s(\text{Temp}_0, \text{df} = 6) + s(\text{Temp}_{1-3}, \text{df} = 6)$$

$$\quad + s(\text{Humidity}_0, \text{df} = 3) + \beta_1 \cdot \text{DOW} + \beta_2 \cdot PH + \beta_3 \cdot \text{Influenza},$$

where $E(Y_t)$ is the expected respiratory mortality count on day $t$, $\alpha$ is the model
intercept, $s()$ indicates a smoother function based on penalized splines, $t$ represents
time, and $\beta$ 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 ($\text{lag}_0$) up to three lag days ($\text{lag}_3$)), 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: lag01, lag02, and lag03).

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/m³ increase in daily PM₂·₅ 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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Days</th>
<th>Mean±SD</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Min</td>
</tr>
<tr>
<td>Daily mortality count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall respiratory</td>
<td>5113</td>
<td>18.8±6.4</td>
<td>4</td>
</tr>
<tr>
<td>COPD</td>
<td>5113</td>
<td>5.0±2.6</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5113</td>
<td>11.7±5.0</td>
<td>0</td>
</tr>
<tr>
<td>Air pollution (μg/m³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM₂·₅ mean</td>
<td>5112</td>
<td>37.5±19.9</td>
<td>5.8</td>
</tr>
<tr>
<td>PM₂·₅ SD</td>
<td>5112</td>
<td>10.5±6.4</td>
<td>2.0</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Pollutants</th>
<th>PM$_{2.5}$ SD</th>
<th>PM$_{2.5}$ mean</th>
<th>NO$_2$</th>
<th>SO$_2$</th>
<th>O$_3$</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{2.5}$ mean</td>
<td>0.67**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO$_2$</td>
<td>0.61**</td>
<td>0.75**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SO$_2$</td>
<td>0.63**</td>
<td>0.59**</td>
<td>0.60**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O$_3$</td>
<td>0.17**</td>
<td>0.49**</td>
<td>0.35**</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>-0.18**</td>
<td>-0.36**</td>
<td>-0.43**</td>
<td>-0.08**</td>
<td>-0.08**</td>
<td></td>
</tr>
<tr>
<td>Humidity</td>
<td>-0.12**</td>
<td>-0.42**</td>
<td>-0.39**</td>
<td>-0.28**</td>
<td>-0.42**</td>
<td>0.25**</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Models</th>
<th>Overall respiratory morality</th>
<th>Pneumonia morality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model-single*</td>
<td>1.40 (0.35, 2.46)</td>
<td>1.80 (0.46, 3.16)</td>
</tr>
<tr>
<td>Day time</td>
<td>1.35 (0.21, 2.50)</td>
<td>1.40 (0.35, 2.46)</td>
</tr>
<tr>
<td>Model w/PM$_{2.5}$ Mean</td>
<td>1.39 (0.27, 2.52)</td>
<td>1.35 (0.21, 2.50)</td>
</tr>
<tr>
<td>Model w/SO$_2$</td>
<td>1.46 (0.39, 2.55)</td>
<td>1.39 (0.27, 2.52)</td>
</tr>
<tr>
<td>Model w/NO$_2$</td>
<td>1.21 (0.13, 2.32)</td>
<td>1.46 (0.39, 2.55)</td>
</tr>
<tr>
<td>Model w/O$_3$</td>
<td>1.44 (0.38, 2.52)</td>
<td>1.21 (0.13, 2.32)</td>
</tr>
<tr>
<td>Model w/ws</td>
<td>1.39 (0.34, 2.45)</td>
<td>1.79 (0.45, 3.15)</td>
</tr>
</tbody>
</table>
Tab. 1: 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.

| 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.

<table>
<thead>
<tr>
<th>Models</th>
<th>No. of days</th>
<th>ERR(%)</th>
<th>Lower(%)</th>
<th>Upper(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall respiratory mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-low</td>
<td>1708</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Low-high</td>
<td>852</td>
<td>0.58</td>
<td>-1.56</td>
<td>2.78</td>
</tr>
<tr>
<td>High-low</td>
<td>765</td>
<td>0.89</td>
<td>-1.43</td>
<td>3.27</td>
</tr>
<tr>
<td>High-high</td>
<td>1784</td>
<td>2.75</td>
<td>0.66</td>
<td>4.89</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Pneumonia mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-low</td>
</tr>
<tr>
<td>1708</td>
</tr>
<tr>
<td>Low-high</td>
</tr>
<tr>
<td>852</td>
</tr>
<tr>
<td>1.32</td>
</tr>
<tr>
<td>-1.41</td>
</tr>
<tr>
<td>4.12</td>
</tr>
<tr>
<td>High-low</td>
</tr>
<tr>
<td>765</td>
</tr>
<tr>
<td>0.88</td>
</tr>
<tr>
<td>-2.05</td>
</tr>
<tr>
<td>3.89</td>
</tr>
<tr>
<td>High-high</td>
</tr>
<tr>
<td>1784</td>
</tr>
<tr>
<td>2.93</td>
</tr>
<tr>
<td>0.29</td>
</tr>
<tr>
<td>5.64</td>
</tr>
<tr>
<td>RERI</td>
</tr>
<tr>
<td>0.73 (95% CI: -3.13, 4.54)</td>
</tr>
<tr>
<td>AP (%)</td>
</tr>
<tr>
<td>0.71 (95% CI: -3.05, 4.46)</td>
</tr>
<tr>
<td>Synergy index</td>
</tr>
<tr>
<td>1.34 (95% CI: 0.23, 7.93)</td>
</tr>
</tbody>
</table>

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
devation, 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.

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**Conflicts of interest and source of funding**

None declared.

**References**


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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 μg/m³ 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.